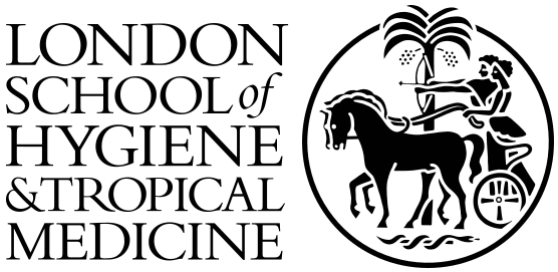

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TEMPORAL STUDIES OF CANCER OCCURRENCE AND APPLICATIONS OF THE AGE-PERIOD-COHORT METHOD TO TRENDS IN EUROPE

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Dedicated to my parents Joe and Eileen Bray. My love and thanks.

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Abstract

This thesis examines the utility of temporal studies of cancer in practice, particularly from the perspective of analyses of the three underlying time components, age, period of event and birth cohort. This enquiry encompasses a review of temporal studies and routine data sources, as well as a more critical appraisal of the strategies available for APC analysis and presentation. Specific methods are then applied to trends in cancer incidence and mortality in Europe.

The central aims of the thesis are:

1) to comprehensively review the graphical and analytical approaches available, particularly in relation to APC modelling and their usage in current practice;
2) on the basis of 1), to provide broad but sensible guidelines for the analyses of time trends;
3) on the basis of 2), to practically demonstrate the utility of time trends and the APC model;
4) to consider the benefits and limitations of systematic approaches applied to time trend studies.

The recommended strategies are used as guiding principles for a detailed analysis of trends in incidence and mortality rates of three cancers (cervix, endometrium and testis) in European populations. The analyses of these neoplasms – purposely selected given their differing temporal and aetiological profile as well as their means of prevention – provides a platform to demonstrate the utility of APC analyses and the specified recommendations in practice. This motivates a discussion of the difficulties inherent in such studies and the consequences of introducing systematic approaches to the analyses of cancer trends.

Table of contents

List of Tables and Figures

Declaration of own work

I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook. I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people.

Signed:..... Date: 20 January 2006...

Full name: **Freddie Ian Bray**.....

1 Introduction to topic and rationale for thesis

Investigations of the changing temporal patterns of incidence of, and mortality from, particular diseases are standard tools in epidemiological science and public health surveillance. Long-term data from vital sources enables a quantification of the evolution of population-based rates over time and may provide clues as to the underlying determinants. Trend analyses may establish novel hypotheses or provide confirmatory evidence of existing ones. In keeping with epidemiological inferences in general however, systematic measurement errors, potential confounders and the role of chance must be investigated as plausible explanations for a particular temporal pattern. Changing rates over time lend supporting evidence to inferences regarding causality should the temporal patterns relate, allowing for a sufficient time lag, to the (suspected or known) distribution and prevalence of one or several risk factors [1]. Time trends studies at the population level are an essential component in the implementation and evaluation of preventative strategies aimed at the primary, secondary and tertiary level.

There has been a transformation in the range and sophistication of the techniques applied to temporal data during the last few decades and some of these developments are discussed in this chapter. Historically, graphical inspections of disease rates often emphasised variations according to age and calendar time only. Temporal analyses broken down by a third component, the *birth cohort*, have become a conventional and standard mode of analysis only relatively recently – this in spite of origins dating back to the 19th century (in actuary and demography) – and the publication of several breakthrough mortality studies in the early and mid-20th century.

The emerging importance of generation-specific analyses has certainly been aided by theoretical developments of the *age-period-cohort* (APC) model and knowledge of the inbuilt mathematical limitations of the methodology. The use of statistical models to augment visual approaches to trends in disease rates from vital sources can be traced back to several key papers in the 1920s and 1930s. However, the methodological developments that began in the early-1970s were to be the major force for numerous applications in many areas of research. The generalisation of a family of linear models that provided maximum likelihood estimates via a weighted least squares algorithm [2] provided important practical applications to disease counts via the use of log-linear modelling approaches [2-4]. Complementing the theoretical developments was the availability of software [5,6] dedicated to fitting such models on computers powerful enough to handle the intensive computations.

In the study of temporal patterns of cancer, the increasing availability (and accumulation) of incidence and mortality data from vital sources has been a major driver in demonstrating the

validity of such techniques. The combined efforts of cancer registries in standardising procedures and data definitions have been particularly important in establishing the quality and comparability of cancer incidence data.

This thesis considers the study of time trends of cancer in the context of epidemiological and preventative research, outlining the specific complexities that may obscure interpretation at the data collection, analysis and presentation phases, both in theory and in practice. In section 1.1 of this introductory chapter, the specific objectives of the thesis are set out. The rationale of trends analyses and their application to cancer control is discussed in 1.2. Some preliminary comments on the data sources, the analysis and the presentation of trends is given in 1.3 and the properties of trends according to age, period and cohort dimensions of time outlined in 1.4. The history of *age-period-cohort*, or *generation* studies, is sketched in 1.5. The final section provides a preamble to the forthcoming chapters and their specific objectives in relation to the objectives of this research.

1.1 Objectives of thesis

This thesis examines the utility of temporal studies of cancer in practice, particularly from the perspective of analyses encompassing the three underlying time components, age, period of event and birth cohort. A primary aim is to provide some recommended procedures for temporal analyses and to gauge to what extent a systematic approach can be adopted in studies involving numerous populations and/or cancer sites. A truly systematic study could be considered one that takes a unified approach to data preparation, analysis and presentation of the results, so enabling a comparison and interpretation of results in an objective and parsimonious manner, potentially leading to insights into the disease derived from the variability in trends between and within subgroups.

In this thesis, trends in cancer incidence and mortality are investigated using data obtained from European population-based cancer registries and the WHO mortality databank data, respectively. The objectives are to:

- review methods available for the study of cancer trends and provide guidelines on this basis, particularly in relation to the use of APC models, informed by a review of current practice in the literature;
- demonstrate the practical utility of temporal analyses in monitoring cancer trends in terms of providing clues as to the factors that drive them, informing the debate surrounding prevention strategies;
- describe the benefits and limits to systematic approaches in practice.

In order to fulfil these objectives, some basic recommendations will be made on reviewing the graphical and modelling strategies available in the analysis of time trends. On the basis of these, a detailed analysis of European trends in three cancers motivates discussion of the utility of the APC model in practice, as well as some consideration of the role of systematic approaches in temporal studies of cancer.

1.2 Review of temporal investigations 1: applications to cancer control

Time trends of cancer rates provides an opportunity to measure how the risk of cancer in defined populations is changing, and more fundamentally, give pointers to the underlying determinants of the observation and a means to formulate, implement and further develop preventative strategies. Changes in the evolution of cancer incidence rates over time allow, in the absence of artefacts, consideration of plausible mechanisms of, and changes in, environmental exposures, time-lagged by an approximation of the latency period. Hypotheses may be more readily generated when changes in trends are observed over a relatively short timeframe rather than over a number of decades [7], although a rapid detection of changing trends is not easily achieved for most cancers [8].

Genetic factors only have a minor impact on time trends of cancer, unless there are sufficiently large migrational influxes and exoduses in the population under investigation [7]. Such demographic events would be readily identified, and in addition, would impact on the trend rather slowly relative to environmental determinants [9].

As discussed in more detail below, there are several approaches to cancer control [10]: the removal of the causes themselves before cancer develops either by general or specific measures (primary prevention); the detection of pre-invasive lesions or cancers at an early stage that are amenable to treatment (secondary prevention); therapy and care directed at preventing death from the disease (treatment) and alleviating pain and suffering (tertiary prevention / palliative care). The monitoring of secular trends plays a direct role in assessing the need for cancer control measures, and in continually evaluating implemented programmes.

Situation analyses of mortality trends have been exploited as a means to critically assess progress against cancer in recent decades [11,12]; the ensuing debate regarding the relative merits of different approaches to cancer control has remained at the top of the health agenda, particularly in the U.S. Predictions of future cancer burden have also become established as tools in the planning of health policy and the strategic allocation of future resources, and in measuring the success (or failure) of specific interventions [13].

1.2.1 Primary prevention

Primary prevention in a general sense is the protection of health by personal or communal means [14]. There are numerous applications of this level of prevention in controlling cancer, and indeed they embody the third revision of the European Cancer Code, a set of recommendations for the individual designed to reduce cancer occurrence in the community (in this case, the member states that collectively make up the European Union). The code advocates the avoidance of smoking, obesity and excessive sun exposure, prudent consumption of alcohol, the undertaking of daily physical exercise and increasing fruit and vegetable consumption, while reducing animal fat intake [15]. Primary prevention also includes the field of chemotherapy for which well-designed randomised trials may be utilised to demonstrate the effect of chemical substances on cancer risk [16].

Secular analyses of cancer trends in rates offer inferences regarding the possible introduction or removal of causes of cancer over time within a defined population, and as such have direct application to consideration of the longer-term impact of primary prevention strategies. The incidence rate is the correct indicator for measuring the impact of prevention, although mortality can be used as a surrogate for cancers where (often poor) survival rates have remained largely unchanged over time. Lung cancer is one such example, and further represents an important example of the promise of primary prevention. Not only is the disease the most common form of cancer worldwide [17], with cumulative risk approximately 10% in males in certain Eastern European countries and among black men in the U.S. [18], lung neoplasms are among the most preventable – at least 90% and 50% of lung cancer male and female cases respectively are attributable to tobacco smoking in Europe [19].

Time trends of lung cancer incidence and mortality have played a crucial role in validating smoking as the primary cause of the disease [20]. The recorded rise in rates and subsequent fall in some populations has reflected the maturity of the smoking epidemic in different countries. As has been noted by Lopez however, there are limitations to inferences in relating the impact of tobacco consumption to lung cancer trends [21]. The lack of availability of comparable information on tobacco smoking (in terms of data coverage and the methodology applied in its collection), and insufficiency of detail (e.g. by age and sex) hampers examinations of the interrelationships.

Yet the relation between tobacco consumption and lung cancer probably represents the best "cause to effect" example in cancer epidemiology, while reasonably comparable datasets on various characteristics of tobacco consumption trends are becoming increasingly available [22]. Most neoplasms have a multifactorial aetiology with very few single associations as powerful as the effects of smoking on lung cancer. Moreover, there is frequently insufficient

comprehension (and quantification) of the contribution of individual factors in explaining temporal observations, while data on the established determinants are often unavailable, or lack the requisite level of detail. Therefore, assessing the impact and prospects for prevention via the inspection of incidence trends is, for most cancers, often at best an informed speculation.

Nevertheless, there are some informative examples that relate the changes in putative risk factors to corresponding cancer trends in England and Wales. A general monograph on cancer incidence and mortality trends included a comprehensive chapter on trends in putative and known risk factors for cancer [23], while a recent article on trends in female cancers interrelated trends in several risk determinants, in an attempt to better explicate the trends in breast, endometrial and ovarian cancer occurrence [24]. The prospects of primary prevention of cervical, endometrial and testicular cancer will be revisited in Chapters 4 through 6, respectively.

1.2.2 Early diagnosis and screening

Cancer screening is the application of a test or enquiry, to identify individuals at sufficient risk of mortality (or serious morbidity) to benefit from further investigation or direct preventative action among those who have not sought medical attention on account of related symptoms. It is considered an effective strategy in reducing cancer mortality as neoplasms often undergo several pre-invasive changes before they become biologically relevant and clinically detectable. The monitoring of screening effects via trends analyses of incidence and mortality rates is of major importance for cervical, breast and prostate cancer for which screening has, for differing reasons, become commonplace in some countries. Monitoring trends of colorectal cancer incidence and mortality rates will become increasingly important as supporting evidence from randomised trials emerges as to which method (or methods) to apply in the test, as organised programmes are implemented, and there is a need to evaluate their effectiveness. The evaluation of screening in relation to trends in breast and prostate cancer are briefly described below. A thorough analysis of cervical cancer trends in relation to screening in Europe comprises Chapter 4.

1.2.2.1 Breast cancer

An international working group recently considered that there was sufficient evidence for the efficacy of screening women aged 50–69 by mammography in reducing breast cancer mortality [25]. The bulk of the evidence came from a number of large scale randomised trials showing that, in women aged 50-64, the early detection of invasive lesions via mammography at regular intervals could reduce breast cancer mortality by around 30% [25].

Supporting empirical evidence of its effectiveness came from time trends studies – declines in mortality were observed where screening had been introduced.

The main evidence that decreases were partially attributable to screening were studies in Northern Europe and Australia describing the anticipated increases in the incidence of early stage and *in situ* breast cancers, followed by decreases in advanced cancers, leading to subsequent reductions of mortality. Quantification of the contribution of screening has been notoriously problematic for breast cancer however. It has been estimated that about one-third of the overall 21% reduction in breast cancer mortality in the U.K. was due directly to screening by 1998 [26], although some have considered this an insufficient time lag for the benefits of screening to emerge [27]. Further, the observed declines in mortality in the U.K (a 25% reduction by 2000) started in 1986, before screening was introduced. In addition to mammography, a number of improvements in combination have probably led to the observed declines [28], and include the establishment of treatment protocols, improved chemotherapeutic options and better therapeutic guidelines [26].

1.2.2.2 Prostate cancer

Incidence rates of prostate cancer are influenced by the diagnosis of latent cancers both by prostate specific antigen (PSA) screening of asymptomatic individuals, and by detection of latent cancer in tissue removed during prostatectomy operations, or at autopsy. Where PSA testing has been prevalent, recorded incidence is very high, as seen in the U.S and several Nordic countries. The distribution of mortality rates is less affected by early diagnosis of asymptomatic cancers. Mortality is affected by case fatality as well as incidence, and survival is significantly greater in high-risk countries – five-year relative survival rates for men diagnosed 1995-2001 is 99.8% in the U.S. [29], a figure probably affected by lead and length time biases reflecting the upsurge in latent cancers that PSA has detected.

In evaluating the effectiveness of PSA using temporal analyses, the prostate cancer mortality rates in the U.S. have been historically of most interest, given the large underlying male population and the extent to which PSA testing has become prevalent. Based on current data from the SEER program, the overall all-race mortality rates based has been steadily declining from 1993 up to the latest year available, 2002 [29]. While there are promising leads, no risk factors are established [30], and these, in any case, could not account for the mortality declines. That the decrease might reflect advances in treatment in combination with PSA-related early detection has been the subject of much debate [31]. Supportive of a partial screening effect were the PSA-associated characteristics of the incidence trends of late-stage prostate cancer after 1992 [32] and the initial decline in the death rate due to a decline in late-stage cancers [33]. However a simulation of the effects of

lead time found the observed decrease were better explained by factors other than screening [34]. Other doubts come from mortality data in areas where PSA testing has been uncommon, where declines in prostate cancer death rates in such countries have been observed [35]. Two randomised clinical trials currently underway in Europe [36] and the U.S. [37] will provide additional information, within the next five years. These include the benefits and harms of screening, and will possibly answer whether PSA (and digital rectal examination) can reduce prostate cancer mortality.

1.2.3 Treatment and cancer care

As discussed above, the beneficial effects of treatment on breast and prostate cancer have made quantification of the respective effects of screening via mammography, and the PSA test in reducing mortality at the population level, very difficult to ascertain. The mortality rate is considered the appropriate measure for such an enquiry, as comparisons of survival rates over time may be less meaningful in this context, given that improvements in survival may be a result of early diagnosis and treatment in combination [38].

Trends in cancer mortality rates have also been the focus in determining the impact of cancer treatment relative to cancer prevention. As is discussed in the next section, an interpretation of the U.S. cancer mortality trends has led to a widely-publicised view that treatment, as a form of cancer control has been failing. Yet there have been a number of pivotal breakthroughs in oncology in recent decades [39], particularly with regards therapy for several forms of cancer that commonly affect younger persons aged under 45 [40]. The favourable trends in mortality following the introduction of novel therapies has lent support to their efficacy at the population level [41]. The examples of time trends studies below describe, in a European context, the need for adequate resources and effective management in providing optimal care.

Hodgkin lymphoma (HL) is considered one of the most curable forms of cancer. As with other haematological malignancies, survival has improved markedly with time [42], in response to the continued development of more effective chemotherapy in the last three decades [43]. Time trends of mortality reflect these improvements, and while incidence tends to be stable or decreasing in many populations [8], mortality trends have been falling since the 1960s in most European countries [44]. The exception is Eastern Europe, where a considerable delay in the decline of mortality from HL, and a lesser order of magnitude of the rate of decrease, is clearly observed, pointing to insufficient resources in the recent past, as well as inefficiencies in the organisation and management of the disease [44].

The treatment of acute leukaemias includes chemotherapeutic regimens which can cure up to 80% of childhood, and 40% of adult cases of acute lymphoblastic leukaemia [45]. The death rates from all types of leukaemia in Europe in younger age groups are similar to those of HL, both in terms of the trends and their interpretation. Declines in death rates are observed in most countries since the 1960s, although the corresponding falls in Eastern Europe declines are of a lower order of magnitude, and seen later than elsewhere [46].

Another success story, the introduction and development of chemotherapeutic regimens for the treatment of testicular germ cell tumours is examined in detail in Chapter 6 in relation to its impact on trends in testicular cancer mortality in Europe.

1.2.4 Assessing progress against cancer

Since Nixon signed the U.S. National Cancer Act in 1971 to provide "a total commitment of Congress and the president to provide the funds for the conquest of cancer" in the U.S., cancer control, metaphorically at least, has been on a war footing. Establishing whether a society is "winning" or "losing" the "battle" against cancer, and the relative merits and prioritisation of primary, secondary and tertiary prevention, have received much attention (in the U.S. in particular). Trends in cancer mortality rates have been at the forefront of the debate; the direction of trend has been considered by some as *the* indicator of progress, pointing towards success or failure in controlling cancer, and informing the need to redress the balance of allocation of funding to preventative and treatment-orientated research.

Bailar and Smith's paper in the New England Journal of Medicine in 1986 [11], an assessment of the "progress against cancer", based on trends in cancer mortality in the U.S. 1950-82, may be considered as igniting the debate. Their report was a somewhat pessimistic assessment of cancer control in the U.S., highlighting the failure of cancer control strategies to reduce the long-term mortality burden, and specifically, the need to shift research efforts away from treatment – given its perceived lack of impact on the mortality trend – to prevention. The conclusions were largely drawn from the fact that the overall age-adjusted mortality rates for all cancers combined had not changed appreciably over three decades. As the authors concluded: "by making deliberate choices among the measures, one can convey any impression from overwhelming success against cancer to disaster." Indeed, several authors were critical of some aspects of the study and a number of subsequent papers sought to readdress the issue. Sir Richard Doll, in his assessment of progress in Europe, indicated that while mortality from all cancers was the correct outcome, the use of the all-age adjusted rate was "profoundly wrong", in that it outweighs the effect of recent progress with the "prevalence of carcinogenic agents in the distant past, which are irrelevant" [40]. Any progress among young people, therefore, as would have been seen in

the age-specific rates, would have been masked on combining age groups, and the notable successes (in high resource settings) of therapeutic improvements for several relatively uncommon cancers, as discussed above, largely ignored.

A decade later in the same journal, Bailar and Gornik, using mortality data from 1970-94, and including this time a stratification of the trends into younger (0-54) and older age groups (55+) – concluded with a not dissimilar message to previously – that the favourable trends in the most recent years were largely through means of primary prevention and early detection rather than treatment [12]. Such an interpretation was vociferously challenged by Kramer and Klausner of the U.S. National Cancer Institute, who suggested theirs was a defeatist approach to progress. Further, they commented that Bailar's paper failed to allow for future breakthroughs in treatment or the variable prospects for cancer prevention, the difficulties in implementation of primary prevention, and the heterogeneity of cancer as a disease [47], claims refuted subsequently by Bailar and Gornik [48]. Deliberations on progress against cancer, and the capability of different strategies to control the disease on the basis of past, present and anticipated future mortality trends will undoubtedly continue in both scientific and political arenas well into the future, as witnessed by several recent news reports in the cancer literature [49-51].

1.2.5 Predicting future cancer burden

The planning of services is an integral component of cancer control programmes [52]. Predictions may inform us of the extent to which the determinants of the disease, and interventions, planned or unplanned, are likely to impact on the frequency of cancer in the years that follow. The specific objectives of predicting future cancer burden are dependent on the users of the information [13,53]. Health care providers need accurate and routinely-updated estimates of the future number of cancer patients in allocating finite resources to prevention, treatment and palliative care. Investigation of the root determinants of the underlying trends is critically important in translating predictions to policy evaluation. Artefacts related to the data source and coding issues, the possible effect of interventions, and the aetiological profile of the cancer type all need to be investigated.

Incorporating exposure data in making predictions may be considered amongst the best approaches; these are difficult to implement however, given the present lack of understanding of the factors that drive most cancer trends, as well as a lack of availability of such data where determinants are established. This necessitates the use of more simple techniques that usually involve simple extrapolations of trends in the recent past into the future. Projections can include supplementary data where available, and have been applied in predicting future lung cancer mortality on the basis of various scenarios regarding future

smoking habits [54,55]. Where necessary, predictions may also include information on specific interventions, such as screening activity: projections of breast cancer incidence in the Nordic countries in 2010, for instance, incorporated information on the impact of national mammographic screening programmes [56].

1.3 Introduction to the components of time

1.3.1 Data collection, analysis and presentation

As Estève notes, each of the stages of data collection, analysis and presentation bring their own set of problems to the study of cancer trends [57]. The appropriate measures for such analyses often come from existing sources of data, such as population-based cancer registries, which collect, store, and analyse information on all new cases of cancer in well-defined populations. National offices are responsible for the collation of information on the causes of death of its inhabitants, compiled, for instance, at the international level in the WHO mortality databank. Incidence and mortality relate to the frequency of the disease – other attributes can also be studied temporally, and survival rates measure the impact of cancer on patients, while prevalence, a more complex function of occurrence and duration of the disease, estimates the number of persons alive and requiring some aspect of care within a health system.

The relative merits of cancer incidence or mortality data in time trends studies and their complexities in interpreting trends have been much debated [58-60]. Changing completeness of registration, improving diagnostic methods, and inaccurate population estimates at the sub-national level may cause artefactual changes in incidence rates. Mortality data, though more extensive in availability than incidence, depends on the accuracy of the cause of death information, which may be subject to change with calendar time. In addition, mortality rates are poor measures of trends in risk (e.g. as surrogates of incidence) if there have been improvements in prognosis (case fatality) over time. Often the joint description of incidence, mortality and survival serves to confirm and clarify our understanding of the underlying disease processes. Comprehensive understanding of artefactual influences is a prerequisite however, and these are discussed in Chapter 2.

1.3.2 Age, period and birth cohort

Quantitatively, the most important time-related factor is age. Cancer incidence rates usually increase with age, and for epithelial cancers, the risk increases at approximately the 5^{th} to 6th power of age [61]. Ageing characterises the cumulative exposure of the body to carcinogens over time, and the accumulation of the series of mutations necessary for the unregulated cell proliferation leading to cancer [62].

Rates may also differ over calendar time and between different generations (birth cohorts) of individuals. The modern Lexis diagram provides a graphical representation of the demographical relationship between age and chronological calendar time. In the diagram, the lifetime of a group of individuals can be represented by a third time dimension, a straight line beginning on the time axis at the time of the person's birth, and continuing diagonally upwards, ending at the age and time point representing the event of interest e.g. cancer diagnosis or death. Lexis diagrams trace the experience of a cohort within a particular age interval or the experience of a cohort over a lifetime. Cohort effects may relate to birth itself, or may approximate factors related to birth by exerting influences that are shared in the same group as they age together.

An examination of cancer rates according to birth cohort may provide valuable insight into the nature and intensity of disease-correlated exposures that vary across successive generations, and given that many forms of cancer have a rather long induction phase, plays a vital role in corroborating evidence of the role of putative aetiological factors from other types of epidemiological study. A changing distribution and prevalence of environmental risk factors would tend to affect particular generations of individuals in the same way as they age together, and in some instances, may exert particular influence on earlier stages of carcinogenesis development, given the causes of cancer may take several decades to emerge.

Period effects are characterised by an immediate or fixed-delayed change in the incidence rates for all age groups [63], and thus may act as surrogate measures of events that quickly change rates with the same order of magnitude across all affected age groups under study. More frequently, they transpire from changes in classification criteria or the availability of new diagnostic tests, although the introduction of a powerful carcinogen or a screening intervention (affecting all study age groups) may also show up as a period effect. With respect to cancer mortality, the effect of interventions (e.g. advances in treatment affecting all study age groups) is likely observed as a period-related influence on mortality. However, as Hobcraft observes, the effects of period and cohort are weak proxies for events that we cannot measure directly [64].

While valuable information can be gleaned about temporal risk patterns from an analysis restricted to age-standardised rates over calendar time, strictly speaking, summary rates are only accurate as measures of risk in the absence of an interaction between age and calendar time, indicative of the presence of strong birth cohort effects [65]. Graphical descriptions of age-specific patterns according to period and cohort are an integral part of temporal analyses, and a careful visual inspection will usually provide some insight into the

importance of each time component, and possibly, its relative contribution to the observed temporal pattern.

A more formal quantification of the relative importance of the three time effects involves statistical modelling via the APC model [63,66-68] (see Chapter 3). Despite its increasing use, there are inherent limits to the approach as a result of the identifiability problem – the fact that knowledge of any two factors implies knowledge of the third, making one of the factors redundant [69].

1.4 Review of temporal investigations 2: a short history of cohort analyses

The analysis of disease events across the axes of calendar time and age has a long history in demography. Lexis described a graphical representation of the life history of subjects according to birth cohort (the abscissa) and age (the ordinate) [70]. The original diagram thus represented an age-cohort, rather than the age-period space to which the Lexis diagram represents today. The modern interpretation of the Lexis diagram, described in some detail by Case [71], displays subjects arranged by calendar year of event and age at time of event on the same unit scale, with each cell corresponding to a year of birth, the diagonal tracing the experience of subjects born in the same year, whom are under observation until either the end of follow-up, the event of interest occurs, or they are lost to follow-up. In the commonly tabulated system used for vital rates, a synthetic birth cohort over a 10-year range is derived from the combined experience of subjects in a five-year age group over a five-year period. Cohorts are identified by their central year of birth, with years other than the central year contributing to two overlapping cohorts.

The first use of the term *cohort* is attributed to Frost in a letter written to a colleague in 1935 [72]. The note was published posthumously alongside his landmark paper that discussed some insights that could be attained by visually examining age-specific death rates from tuberculosis according to *cohorts,* members of a community who share the same birth period, rather than simply in the usual cross-sectional way [73]. The present day usage of cohort extends beyond the closed or hypothetical sense of the term used by Frost. In modern epidemiology, a *cohort study* can be defined as "any study in which groups of people with defined characteristics are followed up to determine incidence of, or mortality from, some specific disease, all causes of death, or some other outcome" [72], and *cohorts* "closed populations defined and bound by their entry, often but not necessarily at birth" [74]. The term *age-period-cohort analysis* is often used to describe temporal studies that include birth cohort analyses, to distinguish it from the generic usage of cohort in prospective studies [75].

The arrival of birth cohort analyses however, preceded the work of Frost by a decade; two actuarial papers were published [76,77] stressing the importance of considering overall mortality rates that characterised generations born in a particular year rather than deaths occurring in a calendar year. The authors noted that rather similar age mortality curves were obtained on inspection of the diagonals in a cross tabulation of age and calendar year. An important study by Kermack and colleagues noted analogous observations by means of cohort analyses on all-cause mortality in Scotland and Sweden [78], hypothesising that early-life exposures had an impact on later adult mortality, particularly from birth to the age of 15. The paper has been described as innovative and of considerable importance in the deliberations as to whether environmental factors in early-life development materially influenced subsequent adult mortality [79].

Using data from the U.S., Frost's main contribution to promoting cohort analyses was to show that the peak in more recent cross-sectional age-mortality curves (in 1930) at later ages (50-60) compared to peaks in young children (0-4) previously (in 1880) and at the ages 20-40 in (1910) was an illusion – an examination of the same age curves by cohort indicated subjects comprising the 1930 curve passed through greater risks in the previous decades – the class of individuals whom were children in 1880 and who were aged 50-60 (if still alive) by 1930 [73]. In concluding, he noted that contemporary peaks of mortality in later life did not signify a postponement of maximum risk, but rather were the residuals of higher rates in early life. Frost acknowledges an earlier paper involving cohort analyses of tuberculosis mortality by Andvord [80], although generational influences on disease rates may have been known earlier [79,81]. Andvord's paper, published in a Norwegian journal using data from Denmark, Norway, Sweden and the U.S., suggested, not without some insight, that the age-curve by cohort enabled one to extrapolate the trends in younger cohorts through to older ages, thus enabling a prediction of future mortality [80].

It was not until the 1950s that the birth cohort approach to trend analyses was applied to rates of non-communicable diseases, such as cancer. Korteweg convincingly showed that a cross-sectional view of age curves of lung cancer mortality led to an erroneous interpretation; the age curves were artificially pushed down by the increase in lung cancer in younger age groups [82]. The consistent pattern of declining rates at relatively early ages for five consecutive periods between 1911 and 1945 was therefore not an observation that required a biological explanation.

Just as Frost and other researchers did before him, Korteweg argued that the correct way to view the mortality curves was in cohorts defined by date of birth: by doing so, the age-curves of lung cancer came to resemble the monotonically increasing "all sites except lung"

curve which, during that era, remained largely unaffected by the extraordinary effects of smoking that would subsequently impact on lung cancer rates [82]. Concluding, he remarked that the decline in lung cancer rates amongst the older age group was a consequence of "irritative factors" – an adopted term that, according to Sir Richard Doll, avoided the controversy of linking smoking as the principal cause [72]. The mechanisms that promoted lung cancer, Korteweg observed, acted particularly (but not exclusively) in younger people [82].

A number of generational studies of cancer incidence were published in the 1950s. Clemmesen and colleagues examined lung cancer incidence and mortality in European countries using a similar methodology [83]. Dorn and Cutler described the monotonic increase in lung cancer incidence by birth cohort in every age group using U.S. national survey data [84], while MacMahon extended Korteweg's observations to incidence trends in breast cancer [85] and to cancers of the digestive tract [86]. Much of the use of the earlier cohort analysis was reviewed by Case in a paper published in 1956 [71], who was particularly articulate in defining the role of the three time dimensions in the Lexis diagram, extending the discussion as to how to characterise the age mortality curve, and the possibility that adult disease rates were a product of early life.

Despite studies by Barrett, developing the cohort-based methods of earlier studies to descriptions of cancers of the cervix [87], bladder [69] and prostate [88], and applications such as the study of cohort trends in cervical cancer incidence trends in relation to rates of sexually-transmitted diseases [89], the techniques became largely neglected in the 1960s and 1970s [90]. In 1982, Muir suggested studies were needed that systematically examined trends, particularly by birth cohort [90]. It is interesting to note contrasting approaches to time trends compilations in that year – one volume of international time trends in cancer mortality contained only three chapters that applied cohort analyses [91], while in another volume on trends in incidence, they were included as part of the analyses in the majority of chapters [92].

A flurry of research arrived with the advent of theoretical and applied research into estimation of the independent effects of age, period and cohort via the APC model in the unavoidable presence of non-identifiability. It was Kermack and colleagues that first outlined the technical aspects of the estimation of relative mortality from tuberculosis using the decomposition of age and cohort effects in a multiplicative model [78]. In 1972, Barrett used a similar model in the study of cervical cancer mortality trends and discussed one arbitrary solution that incorporated all three effects, and the need to search beyond the linear trends [69,87,88]. From the 1980s, many novel solutions were offered as how should one present

the joint components in epidemiological settings [63,65-68,93-103], although much of the theoretical work had come earlier from workers in the sociological field [104-106]. A number of reviews and critiques of these techniques have been disseminated [107-112].

Two further compilations of international time trends of incidence and mortality were published in the early to mid-1990s [8,113]. The volumes varied in the editorial approach: Doll and colleagues documented and interpreted international trends in incidence and mortality by cancer site, allowing some flexibility in each site-specific chapter by leaving it to the expertise of the multiple authors to decide on the selection of data and the presentation format for a given cancer [113]. In contrast, the International Agency for Research on Cancer (IARC) monograph by Coleman and colleagues [8] was a strictly systematic attempt at the analysis of worldwide trends of the major cancers in four continents. The approach involved an algorithmic approach to APC modelling [57], and a fixed presentation style, with only a limited number of authors involved in the analysis and writing.

Other large studies with a systematic approach to the presentation of cancer trends in one population include the monograph by Roush *et al* examining incidence trends in Connecticut in the U.S., and a more recent book documenting incidence and mortality trends in England and Wales [23]. In addition, incidence and mortality trends are comprehensively examined in the U.S. published online as part of the SEER reviews series [114], although only the Roush *et al* publication embraced APC modelling.

Systematic overviews of cancer trends have also appeared in the medical and epidemiological literature, such as the series of articles examining mortality trends according to broad subgroups of cancer [115-119], for which a specific APC technique was used throughout [120]. The yearly updates of rates and trends in the U.S. in their "annual report to the nation" has recently involved the use of joinpoint analyses (see 3.2.3.2) to determine recent linear trends by calendar time [31]. Cohort analyses have not been a focus in this series however, although other reports on U.S. incidence trends have used a more sophisticated approach involving APC analyses [121].

1.5 Outline of subsequent chapters

Following on from this introductory chapter, Chapter 2 appraises the routine sources of data and their usage in temporal studies. The availability, quality and characteristics of incidence and mortality data are reviewed, and the synergy between the measures examined. Chapter 3 provides a critique of the numerous graphical and statistical methods available for analysing time trends of cancer data, with particular reference to the joint representation of age, period and cohort effects. The chapter rounds off with some observation and

recommendations with regards the analyses of time trends, and these techniques are employed in the study of trends in cervical cancer incidence (Chapter 4), endometrial cancer incidence and mortality (Chapter 5), and testicular cancer incidence and mortality (Chapter 6) in Europe. These chapters have been developed into a series of six research articles as part of a collaborative time trends project (Appendix 1). A declaration of the level of involvement of the author of this thesis in the planning, analysis and interpretation stages is given separately, as is due acknowledgement of collaborators involved (Appendix 2).

Finally, Chapter 7 discusses how the recommendations – based as they were following a review of the available methods – worked in practice. The Thesis ends with some concluding remarks on the role of the APC model and systematic approaches to analysis.

2 Routine sources of data: definitions, availability and data quality

While temporal investigations of cancer have important applications both in the planning and evaluating of public health strategies and in epidemiological research, they are a complex phenomenon to study, having substantial limitations and potential errors associated with them. Asides from the problems of analysis and presentation, discussed in depth in the next chapter, researchers wishing to critically interpret time trends must be aware of the characteristics of the incidence and mortality dataset specific to the cancer and population under investigation. They must be aware that artefacts (e.g. inaccuracies related to diagnosis or reporting) may have impacted on trends in addition to specific interventions of interest or hypothesised changes in the population prevalence of aetiological factors.

There are a number of artefacts associated with incidence rates that potentially affect trends should the extent of these biases change with time. Potential errors include: i) misclassification of a case as a resident or non-resident; ii) incorrect definition of an incident case of cancer; iii) duplicate registrations; iv) a failure to identify or diagnose true cancer cases; v) poor specification of diagnosis; vi) improvements in diagnostic procedures and vii) difficulties estimating populations at the national or sub-national level.

Mortality data is prone to erroneous death certification and changes in coding practice. If mortality trends are used as a proxy of incidence rates (as they often are, given their more extensive availability), a further bias is introduced for cancers where prognosis has improved with time, given that case fatality would not be constant.

The text that follows discusses the properties, availability and quality of cancer data from routine sources within Europe, and their utility (and limitations) in investigating time trends. The opening sections discuss incidence (2.1), mortality (2.2), and at a more cursory level, prevalence (2.3) and survival (2.4). Interrelationships between the indicators are discussed in 2.6.

As well as data from existing systems in Europe, there are a limited number of datasets that contain relevant exposure information at the population level, either collected for particular studies in repeated surveys, or in some countries, routinely, e.g. in national household surveys. Their availability in Europe and their limitations in temporal analyses are discussed in 2.7. Finally, the primary data sources and minimum inclusion criteria for the trend analyses that comprise Chapters 4 through 6 are set out in the final section, 2.8.

2.1 Incidence

Cancer incidence is the frequency of occurrence of new cases of cancer in a defined population over a given period of time. It can be expressed as the absolute number of cases

and is often used in this form in planning and prioritising resources for cancer control. For comparative purposes however, the quantification and comparison of risk necessitates the computation of *rates* of cancer. Ideally, we would estimate a rate by ascertaining, for every individual in the population, the risk of being diagnosed with cancer at a given age and specific point in time. The rate is sometimes described as the *force of incidence* or the *instantaneous incidence rate* [122] and requires that the designated period of time is infinitely small, approaching zero. As cancer is a relatively rare disease however, we must estimate the average rate of occurrence of new cases of cancer in a sufficiently large population over a sufficiently long time period. In this formulation, the denominator is the underlying person-time at risk from which the cancer cases in the numerator arose.

The term *rate* is often used interchangeably with the *risk* of developing a cancer, but, strictly speaking, risk is a proportion and describes the accumulation of the effect of rates over a given period of time e.g. the *cumulative risk* [123]. Cancer rates are nonetheless essential should we wish to make comparisons of risk in different groups. Observed changes in incident cases and deaths across time are particularly dependant on the ongoing demographic effects of ageing and population growth over time.

2.1.1 Data availability

Incidence data are produced by population-based cancer registries, whose remit is to collect and classify information on all new cases of cancer in a defined population, providing statistics on occurrence for the purposes of assessing and controlling the impact of cancer in the community [52,124]. The continuous recording of individuals with cancer followed several failed attempts at producing good quality cancer morbidity statistics. A series of cancer surveys between 1900 and 1910 in European countries based on questionnaires to physicians resulted in poor participation rates, while *ad hoc* analyses in the U.S. of ten metropolitan areas in 1937-38, 1947-48 and 1969-71 were eventually deemed undesirable, given that the outcome of the individual could not be followed [125]. Methodological enhancements in pilot studies in the 1930s brought about a more successful system that reported cases by name, eliminating multiple registrations and allowing the follow-up of individual patients.

The first systematic collection of incident cases was undertaken in Hamburg, Germany, in the 1930s, and funded by the Hamburg Public Health Department. The Danish Cancer Society founded the Danish Cancer Registry in 1942 and is today the oldest operating registry covering a national population in Europe. The other Nordic countries launched national population-based registries in the 1940s and 1950s, with the Swedish Cancer Registry being the most recent, established in 1958. The support for cancer registration

activities was greatly enhanced in 1946 by the recommendations of 12 international experts in the field of cancer control who advised the World Health Organization (WHO) to establish cancer registries worldwide with a view to comparability of a set of common standards. In 1966, the existing cancer registries formed the International Association of Cancer Registries (IACR) in order to uphold a common set of data definitions, as well as to promote communication and international collaboration between registries [126]. In a like manner, the European Network of Registries (ENCR) was established in 1989 to promote and coordinate the expanding cancer registration activities at the European level and to facilitate exchanges of ideas, cross-collaboration and research between registries. As of 2005, there were around 170 ENCR members (national or regional registries) in Europe collecting incident cases in 40 European countries.

Registries may cover national populations (e.g. the Nordic countries, The Netherlands and Slovakia) or certain regions within a country (e.g. Italy, Spain and France). The founding of registries has been a rather indiscriminate process over the last half century, dependent on official policy to support and fund such activities, or through individual initiatives by research-orientated clinicians and pathologists [35]. As a result, European cancer registries differ enormously with respect to the size of the population covered, the number of accumulated years of complete data available since the start of the endeavour, as well as, in the case of regional registries, their representativeness of the national profile of cancer burden and risk patterns.

2.1.2 Data quality

Population-based cancer registries produce timely information on the incidence of, and survival, from cancer in the community, and as such, form a unique and pivotal role in public health and epidemiological research. The effectiveness of registries relies profoundly on the quality control procedures in place, which can be broken down into three components: *comparability*, *completeness* and *validity* of the incidence data [127]. Comparability refers to the standardisation of practices concerning the classification and coding of new cases, and to the definition of incidence, such as rules for coding multiple primaries and incidental diagnoses. Completeness is the extent to which all of the incident cancers occurring in a target population are included in the registry database. There are numerous techniques used to evaluate registry completeness [127], including:

- methods that evaluate the data sources themselves (number of sources/notifications per case, percentage of cases histologically verified (%HV), and methods based on death certificates);

- methods that involve independent case ascertainment (rescreening of cases, capture-recapture methods, the mortality:incidence (M:I) ratio);
- historic data methods (stability of incidence over time, comparison of incidence in different populations, age-specific incidence curves).

Finally, validity or *accuracy* refers to the proportion of cases in the registry with a given characteristic that truly have that attribute, and depends on the precision of source documents and the level of expertise in abstracting, coding, and recording [127]. Again there are a number of approaches to its evaluation:

- diagnostic criteria methods (%HV), percentage of cancers for which no other information than a death certificate mentioning cancer can be obtained (%DCO);
- assessment of level of missing information (percentage with primary site unknown (%PSU), age unknown, histology unknown);
- re-abstracted record methods (comparison of recorded data with an 'gold standard' expert opinion e.g. for abstracted diagnosis, opinion of the clinician or pathologist that measures reproducibility between observers);
- internal consistency methods (internal validity checks for invalid codes or combinations, or unlikely combinations using the IARC computer program *Check* [128]).

Such analyses of registry performance are essential in providing credible time trends analyses in Europe, and a complementary local knowledge of the data collection procedures from the cancer registries themselves also minimise the likelihood of erroneous interpretation. The *Cancer Incidence In Five Continents* (CI5) series now in its eighth volume, and covering diagnoses of cancer 1993-97 in 186 registries in 57 countries [18], provides comparable data on the incidence of cancer in different geographical locations and distinct subpopulations (especially ethnic), as a source of reference for studies requiring information on international variations in cancer risk. It is also a good marker of the quality of an individual registry should it be included in the compilation, given that the editorial process includes the following quality assessments: stability of incidence over time, comparison of incidence in different populations, inspection of age-specific incidence curves including childhood cancers, %HV, M:I ratio, %DCO, % age unknown, and %PSU. Although CI5 has been more a publication focused more on geographical rather temporal comparability, inclusion of a registry in successive volumes is a reasonable indicator of consistency of high data quality over time.

More specifically, issues concerning data quality and other detectable artefacts in interpreting time trends have been comprehensively addressed by seminal papers by Saxén [59] and Muir *et al* [60], and more recently by Swerdlow *et al* [23]. The required provisos that ensure truly valid comparisons of cancer trends, as described by Muir *et al* [60], are worth repeating unabridged:

i. The definition and content of the cancer site being studied have not changed;

ii. The criteria of malignancy have not changed;

iii. The likelihood that a cancer will (ever) be diagnosed has not changed;

iv. The progress of cancer from inception to diagnosis is not modified by early detection or screening programmes;

v. Ascertainment of incident cases and deaths has been equally efficient throughout the period of study;

vi. Indexing in the International Classification of Diseases (ICD) has not changed;

vii. Accuracy and specificity of coding is consistent over time;

viii. Statistics are available at the level of detail required.

As the authors note, few, if any, data series would meet all of the above criteria, although the situation is perhaps not as discouraging as one might initially imagine. The influences of the above conditions differ appreciably according to the neoplasm under study, but in most instances, specific problems with a given site are recognised and the effects on the time trend, at least in terms of its likely consequence on the true underlying trend, reasonable well understood. Some factors that complicate assessments of incidence of certain cancer sites over time are discussed in brief below.

2.1.2.1 Changes in ICD classification

Changes in the content of the ICD rubric in consecutive revisions have had considerable effects on the evaluation of time trends; particularly affected have been cancers of the lung, pleura and liver. Others, such as rubrics for breast and laryngeal cancer have remained unchanged in the last four revisions [60]. The demand for a greater provision of detail in classification at the level of subsite in each successive volume has led to some problems with lack of comparability. Notably affected are cancers of the oral cavity and kidney, where, for example, subsites in the 9th revision are irretrievable from the less comprehensive codes in ICD-8.

2.1.2.2 Changes in the ICD index

Changes in the ICD index, the instructions used by coders to assign the correct code, have brought about the possibility of artefactual changes in the corresponding time trends. The assignments of carcinoids, neuroblastomas and sarcomas have all been affected. In the case of the index for mesotheliomas, mesothelioma of the peritoneum or pleura was assumed malignant in ICD8 and ICD9, while mesothelioma of unspecified malignancy was coded to 'neoplasm, connective tissue, benign' in ICD-7.

2.1.2.3 Changes in the definition of malignancy

The definition of what constitutes a tumour may change over time. The classification system of cancer is based on histomorphology, but malignancy is a clinical notion [59]. There has been an increasing likelihood of pathologists seeing evidence of malignancy in tissue samples through improving technology. For example, the rapid increase in cancers of the thyroid may, at least in part, be due to an increasing tendency to interpret papillary change as malignant. Benign neoplasms of the bladder have always been included in successive revisions of ICD, but with a better understanding of the biology of papilloma, some changes in the classification of tumour behaviour have emerged. Registry practices regarding the coding of invasiveness of bladder tumours have shifted accordingly.

2.1.2.4 Latent carcinoma

There is an increasing likelihood of incidental diagnoses of tumours that may not have progressed to invasion. The ICD does not make any provision for such cancers, and interpretation of the likes of prostate cancer incidence over time should be particularly guarded. Latent carcinomas of the prostate that are coded as malignant are substantially influenced by the frequency of transurtheral resections of the prostate (TURP) and more recently, opportunistic screening for prostate cancer via the PSA test.

2.1.2.5 Effects of screening programmes

Screening programmes modify the stage of progression at which cancer or pre-cancerous lesions are detected. Slow-growing tumours are therefore more likely to be diagnosed than under normal conditions. In the case of organised breast screening programmes, the classical model involves a temporary, artificial, increase in the observed incidence due to a prevalence round, as a result of the early diagnosis of malignancies that would have become clinically manifest in time [129]. This is subsequently followed by a reversion of the trend to its former state. Cervical screening should also induce a temporary increase in the observed incidence due to an amassing of prevalent cases, but there should, in the long-

term, also be a lasting reduction in rates of invasive cancer, as screening involves detection of pre-invasive disease.

2.1.2.6 Changes in medical practice

Changes in the tendency of patients to present for diagnosis, the availability and capability of medical services and the ability of the doctor to make diagnoses (based on their diagnostic efforts, aptitude and technological advances) can influence the likelihood of a cancer being diagnosed, as well as the accuracy and specificity of the recorded information [23]. Examples include an increasingly aggressive investigation of illness in the elderly, e.g. for brain tumours, a tendency towards greater specialisation in medicine, increasing use of treatment guidelines, networks and specialist referral.

2.1.2.7 Changes in population denominators

Age and sex-specific cancer incidence rates are obtained from the number of stratum-specific observed cases in a defined population and period, divided by the corresponding person-time (by convention, expressed in years), usually taken from population estimates. That these persons would have been counted as incidence cases if affected with the neoplasm in question is an assumption not strictly met using such crude demographic data as denominators, although its is waved for most cancers. There are some exceptions however, where an adjustment to the person-time would be desirable. An important example is the need for adjustment for prevalence of hysterectomy in the female population in the study of uterine cancer trends. An increasing proportion of women in some European countries have undergone a hysterectomy in the last thirty years and are consequently are at minimal risk of certain cancers, particularly endometrial cancer [130]. Unadjusted trends may therefore be attenuated relative to a more accurate temporal description that accounts for the prevalence of hysterectomy in each population.

2.1.2.8 Changes in registration efficiency and practice

As the registration process becomes more efficient, improving completeness of registration with time alongside a greater accuracy and specificity of data may produce artefactual changes in the incidence trends. Registries may vary in the rules adopted regarding the inclusion of neoplasms, for sites where there is difficulty in distinguishing between malignant, benign and unspecified tumours. The major concerns involve tumours of the brain and central nervous system as well as the bladder, although trends in melanoma of the skin and thyroid may also be affected. Trends in bladder cancer incidence are very difficult to interpret without precise information on how registries have dealt with papillomas over time. Saxén has shown that, on exclusion of papillomas of the bladder, much of the

variation in bladder cancer incidence rates in the Scandinavian countries was removed [59]. In general, changes in registry procedures are more likely to affect comparisons between registries, rather than trends in a single registry over time, provided such practices do not alter over time [113].

2.1.2.9 Changes in histological specification

The study of incidence trends according to histological subtypes is a relatively recent activity. The potential for insight over and above the traditional topography-only analyses is undeniable, given the evidence of heterogeneity in aetiology, screen detection and prognosis among histologies of certain tumours. Parkin *et al* put together a set of histological groups for 15 common cancers with an aim to reach some consensus between registries in classifying subtypes [131]. The main difficulties in comparing trends in histological groups between and within populations occur when the proportion of cases with unspecified histology is large, and has been observed to be changing over time; in such instances, the unspecified proportion usually decreases with time, as the specificity of known subtypes improves. The utility of trend analyses of histological subtypes, and the interpretational difficulties associated with their use, is revisited in Chapter 4, in the temporal study of the main histological subtypes of cervical cancer.

2.2 Mortality

Mortality provides a measure of the impact of cancer, and is expressed either as number of deaths occurring, or as a mortality rate: the number of deaths per 100,000 persons per year. Mortality data derive from vital registration systems, where usually a medical practitioner certifies the fact and cause of death. The International Classification of Diseases (ICD) provides a uniform system of nomenclature and coding, and a recommended format for the death certificate. Mortality is a product of the incidence and the case fatality ratio of a given cancer. Death rates estimate the average risk to the population of dying from a specific cancer, while fatality, the inverse of survival, represents the probability that an individual with cancer will die from it. Thus for stable trends over time, a case fatality ratio of 0.25 (equal to a survival of 0.75) would yield a mortality rate one-quarter that of incidence.

2.2.1 Data availability

Mortality data is usually available by year of death, five-year age group and sex, but its relative advantage over incidence stems from its more comprehensive availability at the national level; the WHO mortality databank holds mortality data for most countries in Europe, and for more extensive periods than that of incidence. Partly for this reason, temporal analyses of cancer mortality tend to be more common than those of incidence in

the medical and epidemiological literature. There are some potential difficulties interpreting mortality rates for some cancers, as discussed below.

2.2.2 Data quality

Mortality statistics are produced according to the underlying cause of death; although this may not equate with the presence of a particular tumour. Asides from artefacts related to registration practices, many of the factors that affect incidence apply equally to mortality data given that they both rely on the accuracy of the initial cancer diagnosis [132]. Comprehensive mortality statistics require that diagnostic data are available on decedents, which are transferred in a logical, standardised fashion to death certificates, which are then accurately and consistently coded, compiled and analysed. Death registrations require that the correct diagnosis is written on the death certificate and further that this diagnosis is then certified as the underlying cause of death [132].

Many studies have investigated the accuracy of death certificate diagnoses in vital statistics data, comparing cause of death entered on the death certificate with a reference diagnosis derived from autopsy reports [133], detailed clinical records [134], or cancer registry data [135]. Such studies have shown that the level of accuracy of the stated cause of death declined as precision in the diagnosis increased; although the total number of deaths from cancer of all types was only slightly underestimated, the distribution by site of cancer may be incorrect. A tendency to over-record non-specific diagnoses instead of the correct location (e.g. large intestine instead of rectum) has been noted, and accuracy is often lower in those dying at older ages. Grulich *et al* on analysing cancer trends in England and Wales 1970-90 in the age group 75-84 found the rise in all-cancer mortality in the elderly was in part due to increasing lung cancer mortality, but data artefacts were responsible for much of the increase in the other common specified cancers [136].

Percy *et al* [135] compared death certificates mentioning cancer as the underlying cause of death for almost 50,000 incidence cases, contrasting detection rates (proportion of death certificates conveying the same diagnosis as that made in life) and confirmation rates (proportion of cancer deaths for which the underlying cause was confirmed by hospital diagnosis). Over-reporting on death certificates was indicated when the detection rate was high relative to the confirmation rate, as was the case for neoplasms of the larynx and colon, and unspecified cancers of the uterus. Conversely, underreporting was observed (confirmation high relative to detection rates) for cancers of the cervix and corpus uteri, and rectal cancers. For melanoma and breast cancer, death certification was deemed more or less correct. There were also quite marked differences between different countries in the allocation of ICD-codes to death certificate diagnoses [137].

2.2.3 Impact of changing case fatality rate

Mortality data have been a useful surrogate for incidence patterns in aiming to describe changes in population risk. To be interpreted as such, one must assume a case fatality that is constant over the study period, and, where treatment has improved sufficiently to affect mortality rates, observed incidence and mortality trends may be at considerable variance. Mortality rates are therefore not a good representation of incidence rates for cancers where prognosis has improved over the study period.

2.3 Survival

The survival of a cancer patient is defined as the time that elapsed between diagnosis and death. The most basic measure of patient survival is the observed survival, with the five-year observed survival being the percentage of patients alive five years after the date of diagnosis. Not all deaths among cancer patients will however be due to the primary cancer in question. Deaths from other causes lower the observed survival rate and preclude comparison between groups where the probabilities of death in the general population vary. Relative survival avoids this problem of comparability, and is the observed survival in a patient group divided by the expected survival of a comparable group in the general population, usually with respect to age, sex and calendar period of investigation.

As with statistics on incidence, survival estimates are produced by cancer registries. To do so, they require follow-up of registered cancer cases, either actively or by matching death certificates against cancer notifications and assuming that unmatched cases are still alive. Population-based figures are becoming increasingly routinely available from registries and included in their annual reports. Survival comparisons at the European level have been made available through the EUROCARE studies. The most recently published (EUROCARE-3) was based on submitted data on patients diagnosed between 1990 and 1994 from 67 cancer registries in 22 European countries [138].

2.4 Prevalence

Unlike incidence, mortality and survival, which are established indicators in the cancer domain, an appropriate definition of prevalence is not universally accepted. Prevalence is a more complex measure of cancer incidence, fatality, and other influences operating in affected individuals prior to death or "cure". Total (or complete) prevalence is the number of persons in a defined population alive at a given time who have had cancer diagnosed at some time in the past. However, the resource requirements for treating newly diagnosed patients are very different from those for supporting long-term survivors. Thus, overall

prevalence is not particularly useful for health care planning purposes, especially as a large proportion of long-term survivors can be considered cured.

Partial prevalence, which limits the number of patients to those diagnosed during a fixed time in the past, is therefore a more useful measure of cancer burden. Prevalence for cases diagnosed within a certain number of years are likely to be of relevance to the different stages of cancer therapy, namely, initial treatment (within one year), clinical follow-up (two to three years) and cure (four to five years) [139]. There are some exceptions, primarily that of female breast cancer, for which the risk of death remains higher than the general population for many more years.

2.5 Staging information

Staging refers to the extent of disease in terms of an established and well-defined set of rules. It is an essential variable in clinical practice, both in the planning and evaluating cancer treatments, and in assessing likely prognosis. In epidemiology and public heath research, it is especially relevant in the evaluation of cancer control. Population-based cancer registries with adequate resources strive to record such information on every case, although in practice, there is often inadequate or inconsistent information in the records for staging in a proportion of the cases. The situation is broadly improving, although a tendency towards a declining proportion with unknown stage with time, may distort the stage-specific trends.

Where staging data may be considered of reasonable quality, an example of their fundamental importance has been in evaluating breast cancer mortality trends at the population level. An important aim in the U.K and the U.S., for example, has been to establish the underlying reasons for the observed drop in mortality that began during the 1980s and has subsequently continued [28]. Staging data may be used as a means to disconnect the main components of the period effect on mortality, mammographic screening and treatment, given screening should bring about an increase in early stage incidence among the screen-targeted age group, and a corresponding decline in the number of late-stage breast cancers.

The difficulties in deciphering breast cancer trends in populations where early diagnosis and treatment may both play a role serves as an example of the need for the co-evaluation of trends in mortality, incidence, and survival, stratified, where available, by stage. Although, one would ideally be informed by stage- and treatment-specific mortality rates of breast cancer, these are seldom complete and available in each of the periods under investigation [140]. There has been much debate surrounding inference of survival from breast cancer,

given the shift towards earlier diagnosis in some populations. The consequence is an increase in incidence and a survival time that is artificially prolonged by lead time; survival is improved by advancing the date of diagnosis without necessarily postponing the date of death. Mortality is not affected by such a bias.

There are however numerous examples where a joint analysis of the indicators has been instructive. In the U.S, Chu *et al* have evaluated trends in stage- and age-specific breast cancer incidence and survival alongside mortality in white females, concluding that screening and treatment were both implicated in the temporal pattern [141]. Significant decreases in both mortality and incidence in the age group 40-79 were observed, although modelling implied the large drop in mortality between 1989 and 1993 could not be entirely due to increasing screening activity. Localised incidence rates increased rapidly from 1982-87 but were stable or less rapidly rising thereafter. Regional disease rates decreased after 1987, suggested as a result of increasing use of mammography in the prior period. In contrast, the authors commented that improvements in therapy were likely responsible for the increasing three-year survival rates observed in cases diagnosed 1980-89 for both localised and regional disease, and in all age groups.

2.6 Incidence versus mortality

As has been noted above, there has been considerable deliberation on the relative merits of incidence, mortality and survival rates in cancer research generally, and in time trend analyses specifically [28,57,58,132,142-145]. The importance of determining artefacts and considering their contribution to observed cancer incidence and mortality trends have been comprehensively addressed by the papers by Saxén [59] and Muir *et al* [60], while many studies have investigated the accuracy of death certificate diagnosis [135,137,146,147]

Analysing trends in incidence may allow some insight into the possible changes in the prevalence and distribution of risk factors that drive the trend. Given its coverage and availability, the mortality rate has historically been a useful surrogate for incidence. The assumption of constancy over time in the fatality ratio may not hold for cancers where prognosis has been improving and novel effective therapies for a number of cancers were introduced from the 1960s. Mortality rates are certainly the best measure of disease outcome; in determining the beneficial effects of a specific treatment regimen at the population level, for example.

In the same epoch that survival was improving, so cancer incidence was sufficiently accrued (in Connecticut and the Nordic countries, for example) to allow detailed analyses of secular trends [113]. However, in their landmark study of environmental causes of cancer in the U.S.

published in 1981, Doll and Peto utilised mortality rather than incidence data, citing that incidence was the more complex to interpret and that two factors were largely responsible for their concern. In addition to the artefacts associated with changing efficiency of the registration process, Doll and Peto considered the effects of changing practice in classification of cancers associated with different rates of fatality and the spread of screening tools that detect cases earlier as having had a large impact on the record incidence of many cancer types. This neglect of available incidence data drew some criticism [148,149] although Doll *et al* have since reiterated their viewpoints [113].

There is a general consensus (including that of Doll and Peto) that a combined description of trends in incidence, mortality and survival often serves to confirm and clarify understanding of the underlying biological and epidemiological processes, as well as restate the relative strengths and weaknesses of each measure in interpretation [58,60,132,149]. Doll *et al* comment that incidence, while of great value, has not removed the need for mortality data, necessary – in combination with incidence – to detect improvements in therapy, and partly to verify the validity of incidence trends [58].

Asides from cancer occurrence data from vital sources, there are a limited number of datasets collected on risk factors that may be of some utility in elucidating cancer trends or clarifying epidemiological evidence. These are briefly discussed below.

2.7 Supporting data from health surveys

Increasing rates in lung cancer mortality in men in the last century were shown to closely approximate the upsurge in smoking prevalence in the underlying population several decades before. The relation between tobacco consumption and lung cancer is of course beyond doubt – the majority of cases would be avoided on elimination of cigarette smoking – particularly in countries where the habit has long been established [150,151]. Rather than being attributed to specific carcinogens however, many common cancers have a more complex, multifactorial aetiology. Moreover, there is often a lack of information on important population exposures for a given cancer, either in specific populations or over time.

Where such data are available, in sufficient detail and of reasonable quality, trends in exposure data may be compared to trends in disease to ascertain which are credible as risk factors in the study population. To better understand incidence and mortality trends in breast, endometrial and ovarian cancer in England and Wales, Dos Santos Silva *et al* presented the cancer-specific trends alongside changes in fertility and oral contraceptive use [152]. Increases in breast cancer incidence rates were rapid among successive generations up to the end of the 19th century, mirroring declining fertility. Slower increases

were observed for cohorts thereafter, with declines seen in consecutive generations born after 1920. On the basis of the exposure trends, it was speculated, among other possibilities, that the introduction and increasing use of oral contraceptives may have produced a long-lasting protective effect.

Comparisons of changing risk factors among several populations has the advantage that it is less prone to confounding than with a single population, given that unmeasured factors related to both exposure and changes in trends are less probable in several different populations, than would be the case be in just one [153]. More generally, ecological comparisons provide only weak evidence of associations, are potentially misleading, and are susceptible to certain problems and biases. One issue is the imposition of an appropriate time lag between exposure and cancer occurrence, which may be rather arbitrary. Furthermore, exposure information may not be available for the relatively distant past, and, where it is, the corresponding population data may comprise different individuals, given a wide enough interval between exposure and cancer. The main problem involves the weak assumption that trends in a particular exposure apply to all members in that population. There may be differences in the relationship at the individual level (within groups) and the group level (between groups) [153].

Several monographs on temporal trends have included chapters that describe available trends in common risk factors in the population of interest. Thus Rouch *et al*, in describing incidence of common cancers in Connecticut, U.S., provide tabular and graphical descriptions of trends in tobacco and alcohol consumption, as well as a number of dietary, reproductive hormonal and occupational factors state- or nationwide. Swerdlow *et al* presented an introductory chapter corresponding to an A-Z of trends in almost 60 risk factors to complement their study of cancer incidence and mortality trends in England and Wales [23].

In Europe, the availability of collections of risk factor data is rather limited. Data on trends in tobacco consumption is however well-covered by the reference volume *International Smoking Statistics* which comprises historical data from 30 developed countries, based on sales data from the Tobacco Research Council supplemented by survey data on smoking habits by age and sex [22]. A number of lifestyle factors have been collated at the European and international level and made available as online databases. Several risk factor surveys have provided valuable trends in exposures. The WHO MONICA Project (Multinational MONItoring of Trends and Determinants in CArdiovascular Disease) was established to monitor trends and determinants of cardiovascular diseases [154]. Population surveys for the main risk factors were conducted in geographically defined populations in 21

predominantly European countries. The related Health for All software package contains temporal data covering a number of maternal and child health indicators [155]. The WHO-CINDI Programme (Countrywide Integrated Noncommunicable Disease Intervention) was initiated in 1982 by the WHO Regional Office for Europe [156]. CINDI surveys have been conducted in defined regions in 26 European countries and include risk factors that are common to a number of chronic noncommunicable diseases, and include smoking and excessive alcohol consumption. Detailed data on dietary factors are available in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a cohort study of over 500,000 healthy, middle-aged men and women in 23 centres in 10 countries [157].

2.8 Data sources used in this thesis

A critical review of APC methods in Chapter 3 is put in practice in Chapters 4 to 6 using data available at the national or regional level for incidence, obtained with permission from members of the European Network of Cancer Registries (ENCR), the population-based cancer registries in Europe. Mortality data was extracted from the WHO Mortality Databank. Chapter 4 provides an analysis of trends in cervical cancer incidence by histological subtype; Chapter 5, an analysis of endometrial cancer incidence and mortality trends and Chapter 6 analyses trends in testicular germ call cancer incidence (by main histological subtype) as well as testicular cancer mortality.

Incidence and mortality analyses were carried out using Stata [158]. Details of the inclusion criteria are listed below; further details, additional inclusion and exclusion criteria, and pointers to data quality concerns are contained within the specific chapters under the heading *Data Sources*. The data were analysed and presented according to the United Nations (UN) classification of Europe; this definition classifies 38 countries into one of four areas [159], as shown in the map of Figure 2.1.

2.8.1 Incidence

ENCR members are asked to make regular submissions of incidence, mortality and population data to a central EUROCIM data bank held at the IARC [160]. The incidence data from each registry are converted to ICD-O-2 and subjected to a set of validity checks. No attempt is made however to impose any inclusion restrictions on the basis of quality, and all submitted registry datasets are included in the final EUROCIM database.

For the purposes of the analyses detailed in Chapter 4-6, incidence data was extracted from the EUROCIM by registry, topography (ICD-O-2), histology (ICD-O-2), year of diagnosis, and five-year age group. Corresponding data on person-years at risk, derived from population estimates supplied by each registry were also available in EUROCIM by year,

age and sex. To confine the analyses to data considered to be of high quality, a minimum requirement for a registry's inclusion in the analysis was their consecutive compilation in the last three volumes (VI-VIII) of CI5 [18,161,162]. This criterion was chosen as a general marker of each registry's data quality over time, given the editorial process involves a detailed assessment of the comparability, completeness and validity of the submitted incidence datasets.

For eight countries, a number of regional registries were aggregated to obtain an estimate of the national incidence trends. It was therefore assumed that the regional characteristics accorded with the national population profile, in terms of socioeconomic status, customs, and urban/rural mix, and so forth.

As the span of data available from regional registries varied, the aggregation aimed to maximise the registration period, while ensuring as many of the regional registries were involved in the national estimation. An attempt was made to ensure the same registries were used throughout the elected time period, although in practice, some registries did not cover the whole span. The possible systematic error induced by the sudden inclusion or removal of a registry with a shorter period of coverage than the designated study period was considered to be of less concern than the loss of that registry's contribution of data in its entirety.

A minimal span of recent data was required in order to apply the main statistical techniques in practice: each dataset was required to span at least 11 years to allow joinpoint regression (see 3.2.3.2), and a minimum of 15 years was required for APC analyses (see 3.3.1). The European countries involved, the area covered by cancer registration, and the years of registration available, are summarised in Table 2.1. Due to computation difficulties in dealing with small numbers, Iceland was not included in the APC analyses.

2.8.2 Mortality

National mortality data were extracted from the WHO mortality databank, which contains death data officially reported by WHO Member States, by topography (ICD-9), five-year age band, sex, and year of death. Population data were extracted from the same source. The only rules for inclusion were that countries were listed in the UN classification of European countries, and as for incidence, the span of data was at least 11 years (for joinpoint regression) and 15 years (for APC analyses). The countries and years for which national data were available are presented in Table 2.2.

Figure 2.1: Map showing the four European areas studied, as defined by the UN [159]

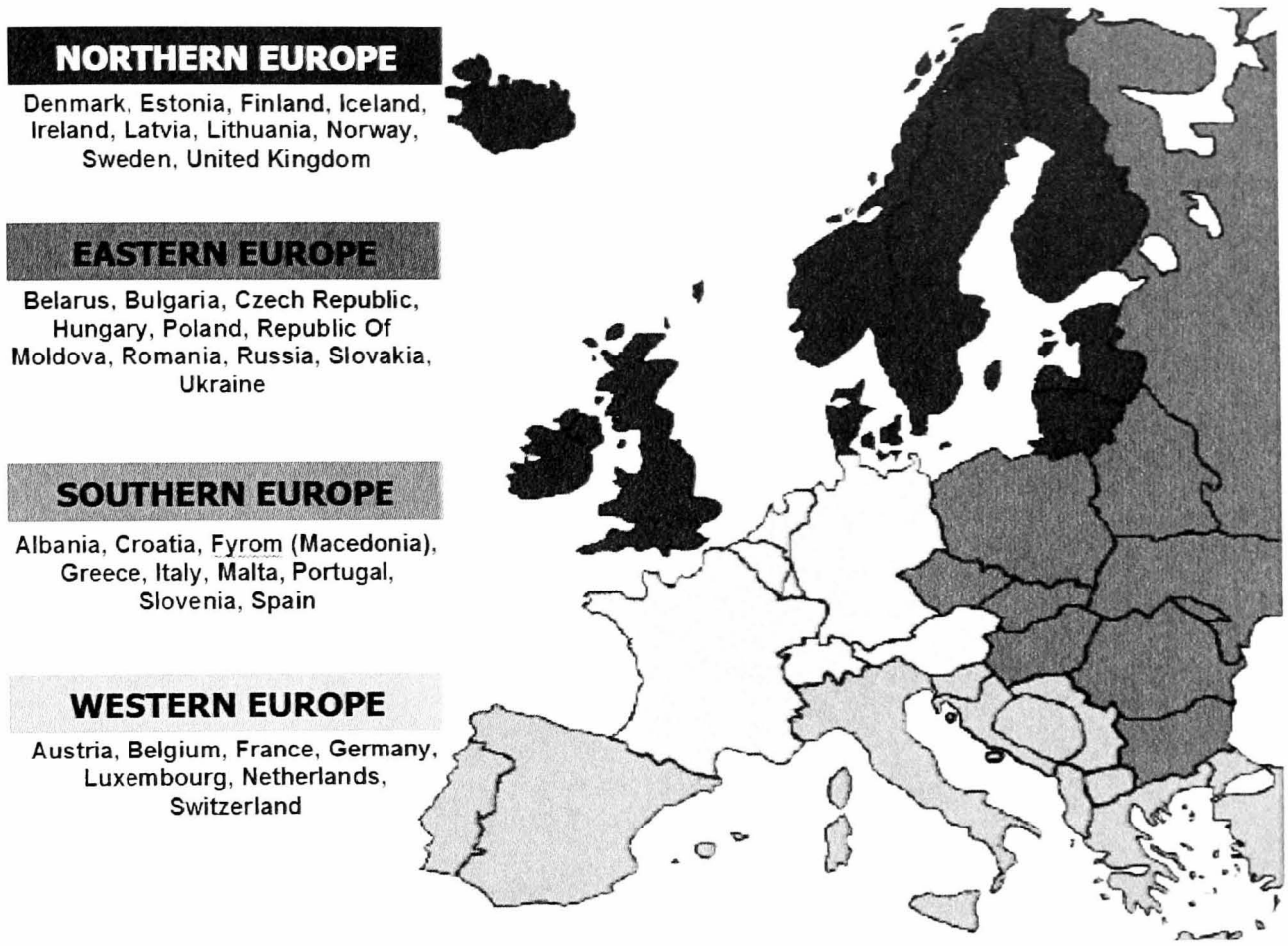


Table 2.1: Cancer incidence by registration status, where data were available for a span of years ≥ 11 (for joinpoint analyses) and ≥15 (for APC analyses)

European Area	Country	Joinpoint: Period available (year span)	Registration status (years available where regional)	APC: Period available (# five-year periods)
Northern	Denmark	1978 – 1998 (21)	National	1979-1998 (4)
	Estonia	1968 – 2000 (33)	National	1971-2000 (6)
	Finland	1953 – 1999 (47)	National	1955-1999 (9)
	Iceland	1955 – 2000 (40)	National	N/A
	Norway	1953 – 1997 (45)	National	1953-1997 (9)
	Sweden	1960 – 1998 (39)	National	1964-1998 (7)
	United Kingdom	1981 – 1997 (17)	England (1978-1997) Scotland (1978-1997)	1978-1997 (4)
Eastern	Czech Republic	1985 – 1999 (15)	National	1985-1999 (3)
	Poland	1986 – 1996 (11)	Cracow City (1978-1997) Lower Silesia (1987-1997) Warsaw City (1978-1997)	N/A
	Slovakia	1968 – 1997 (30)	National	1968-1997 (6)
Southern	Italy	1983 – 1999 (17)	Florence (1985-1997) Varese Province (1983-1997) Parma Province (1983-1997) Ragusa Province (1983-1997) Turin (1985-1997)	1983-1997 (3)
	Slovenia	1980 – 1997 (18)	National	1985-1999 (3)
	Spain	1978 – 1997 (20)	Tarragona (1980-97) Granada (1985-97) Murcia (1984-96) Navarra (1978-97) Zaragoza (1981-95)	1983-1997 (3)
Western	France	1978 – 1997 (20)	Bas-Rhin (1975-1997) Calvados (1978-1997) Doubs (1978-1997) Isere (1979-1997) Somme (1982-1997) Tarn (1982-1997)	1978-1997 (4)
	Germany	1981 – 1997 (17)	Saarland (1981-1997)	N/A
	Switzerland	1983 – 1997 (15)	Basel (1983-1997) Geneva (1983-1997) Neuchatel (1983-1996) St.Gall-Appenzell (1983-1997) Vaud (1988-1996) Zurich (1983-1996)	1983-1997 (3)
	The Netherlands	1974 – 1997 (24)	Eindhoven (1958-1997) Maastricht (1986-1998)	N/A

N/A: not applicable. Either there was <15 years available in the data series or, for the cancers analysed in this thesis, the underlying numbers were too sparse to provide reliable results on fitting the APC model.

Table 2.2: Cancer mortality data available for a span of years ≥ 11 (for joinpoint analyses) and ≥15 (for APC analyses)

European Area	Country	Joinpoint: Period available (year span)	APC: Period available (# five-year periods)
Northern	Denmark	1969 – 1999 (31)	1969-1998 (6)
	Estonia	1981 – 2002 (20)	N/A
	Finland	1969 – 2002 (34)	1970-1999 (6)
	Iceland	1969 – 2002 (34)	N/A
	Ireland	1969 – 1999 (31)	1969-1998 (6)
	Latvia	1969 – 2000 (32)	N/A
	Lithuania	1980 – 2002 (23)	N/A
	Norway	1981 – 2002 (20)	1969-1998 (6)
	Sweden	1969 – 2001 (33)	1969-1998 (6)
	United Kingdom	1969 – 1999 (31)	1970-1999 (6)
Eastern	Belarus	1981 – 2001 (19)	N/A
	Bulgaria	1970 – 2002 (33)	1970-1999 (6)
	Czech Republic	1986 – 2001 (16)	1986-2000 (3)
	Hungary	1970 – 2002 (33)	1971-2000 (6)
	Poland	1970 – 1996 (27)	1980-1994 (3)
	Republic of Moldova	1981 – 2002 (20)	N/A
	Romania	1970 – 2002 (32)	1981-2000 (4)
	Russia	1980 – 2002 (23)	N/A
	Ukraine	1981 – 2000 (18)	N/A
Southern	Croatia	1972 – 2000 (29)	1986-2000 (3)
	Greece	1969 – 1990 (22)	1969-1998 (6)
	Italy	1972 – 2002 (31)	1969-1998 (6)
	Malta	1972 – 1997 (26)	N/A
	Portugal	1972 – 1999 (28)	1980-1999 (4)
	Slovenia	1983 – 2001 (19)	N/A
	Spain	1972 – 2002 (31)	1974-1998 (5)
Western	Austria	1985 – 2002 (18)	1971-2000 (6)
	Belgium	1972 – 1999 (28)	1971-1995 (5)
	France	1972 – 2000 (29)	1969-1998 (6)
	Germany	1972 – 2002 (31)	1985-1999 (3)
	Luxembourg	1972 – 2000 (29)	N/A
	Switzerland	1985 – 2002 (18)	1970-1994 (5)
	The Netherlands	1969 – 2001 (33)	1970-1999 (6)

N/A: not applicable. For the cancers analysed in this thesis, the underlying numbers were too sparse to provide reliable results on fitting the APC model.

3 Methodological approaches to analyses of cancer trends

This chapter presents a summary and critique of the various approaches at a researcher's disposal in analysing time trends of cancer occurrence. In putting forward some recommendations for an appropriate analysis, emphasis is put on the need for approaches to data collection, analysis and presentation that maximise comparability, and a description of trends that makes full use of any *a priori* knowledge regarding the biology and epidemiology of the cancer under investigation in the study population. The review covers the following areas:

- The use of graphical descriptions as exploratory analyses:
    - Graphical depictions are a key fixture of temporal analyses. They necessarily involve choices regarding the form of the rate (e.g. standardised or stratified) and the particular time component (age, period or cohort) to plot against it. The selection of scale (e.g. arithmetic versus a log-transformation of the Y axis) and the dimensions of the graph (ratio of the Y to X axes) are often considered trivial matters; scaling however can accentuate or attenuate particular observations and some advocated rules for presentation are discussed.
- The use of models to quantify temporal change:
    - Simple methods that estimate relative and absolute changes over time are standard, but the magnitude of change depends on the form of model and the period of time considered. The degree of linearity in the underlying data will dictate how informative relative changes are. Recently, methods (and dedicated software) have become available for determining abrupt linear changes in the trend, which remove, to some extent, the arbitrariness involved in selecting an appropriate time period.
- The APC model: characteristics, the identifiability problem, and approaches to presenting the parameter estimates:
    - The relative straightforwardness of fitting APC models is at odds with the difficulties in providing an informed presentation of the model parameters, given the irresolvable issue of non-identifiability. Statisticians and epidemiologists have taken a keen interest in developing methods to circumvent non-identifiability since the late-1970s, and as a result, a wide-range of methods are presently available and used in practice. A critical review requires a suitable classification of approaches, and each method is

considered in terms of its degree of arbitrariness (and the extent to which a strategy connects to external knowledge available) and its complexity (in terms of both the method and its interpretation).

- A review of the application of APC models to cancer trends 2000-2004:
    - APC modelling has also become an established tool in practice. A thorough search and description of relevant articles in medical and epidemiological journals in recent years provides an opportunity to review current practices regarding the analysis of cancer trends.

The following text therefore assimilates and appraises the various techniques proposed, from graphical presentations (3.1) and the estimation of the rate of temporal change from simple linear models (3.2), through to more sophisticated analytic techniques using the APC model (3.3) and in particular, the various approaches to dealing with the non-identifiability problem (3.4). A review and critique of current literature is outlined in 3.5.

The broad aim of this chapter is to provide some recommendations for a researcher wishing to perform an analysis of temporal variations in cancer rates, and these are given in 3.6. The value of these guidelines in practice – obtained as they were from a mainly methodological perspective – will be put to test in later chapters.

3.1 Graphical presentation of trends and their attributes

As reviewed in the introductory chapter, early approaches to analysing time trends mainly focussed on graphical or tabular approaches that related age patterns to existing knowledge of disease biology. Despite the use of mathematical modelling of age and cohort as early as 1927 [78], general usage of APC models began during the last decades, and in the study of cancer, mainly since the 1970s, an early example being Barrett's analysis of cervical cancer [87].

Despite a shift of emphasis towards a modelling framework, graphical approaches remain an intrinsic part of good data analysis [163]. Exploratory data analysis (EDA), as originally set out by Tukey [164], is a philosophy as to how best to dissect a dataset; what should be investigated, how it should be undertaken, and how it is then interpreted. EDA uses mainly graphical techniques to analyse the dataset, as its main role is to open-mindedly explore. Graphs may often reveal the structural characteristics of the dataset, as well as open the possibility of gaining new or unsuspected insight into the data. In combination with the pattern-recognition skills that humans naturally possess, graphical descriptions thus provide unparalleled power to carry this out.

Unquestionably no statistical tests or estimations should commence without a thorough understanding of the underlying relationships between the variables in the dataset. Pre-analysis strategies may find coding errors or outliers in the raw dataset. Given the lack of a unique set of age, period and cohort parameters in the APC model, interpretation is aided by an understanding of the basic features of the observed trend data that graphical approaches provide. These relations may establish hypotheses regarding the nature of the trends, and may lend support to a particular approach to APC modelling that is more informative and less arbitrary.

Although some authors have offered some guidance in visually depicting trends in disease rates [165], such displays are usually heterogeneous in the literature, possibly reflecting the fact that the technical issues involved are not given high priority, leaving the graphical depiction a matter of individual preference. In consequence, there can be difficulties comparing results across studies; some guidelines towards a more systematic representation of trends may therefore be of some value in this respect, acting as a pointer for future temporal analyses.

The following sections consider what underpins a good graphical presentation, making some minimum recommendations to improve comparability and aid interpretation of temporal studies. The type (and level of detail) of the statistical measures portrayed is discussed in 3.1.1, and some of the key technical properties of the graph itself, the scale and ratio of the axes, are described in 3.1.2 and 3.1.3, respectively. The various ways to summarise rates plotted against, or stratified by age, period and cohort are reviewed in 3.1.4.

3.1.1 Age-adjusted rates

There are powerful reasons for adjusting for the effects of age when comparing cancer risk in populations over time. Age is a strong determinant of cancer risk. In general terms, the risk of epithelial cancers, which comprise nine-tenths of all human cancers worldwide, increase approximately as a fifth power of age [166], representing about a 1000-fold difference in cancer rates between young (aged 20) and old persons (aged 80). In addition, the demographic effects of ageing and population growth will continue to have a major impact in European countries, particularly within the next two decades [159]. Direct standardisation procedures yield the age-standardised rate [167] and cumulative risk [123], both of which absorb the schedule of age-specific rates, allowing comparisons of cancer risk over time in the same population using a single summary measure. In the former, a standard population with a fixed age distribution – such as the World standard of Segi [168], later modified by Doll [169] or the European standard [170] – is applied to the age-specific

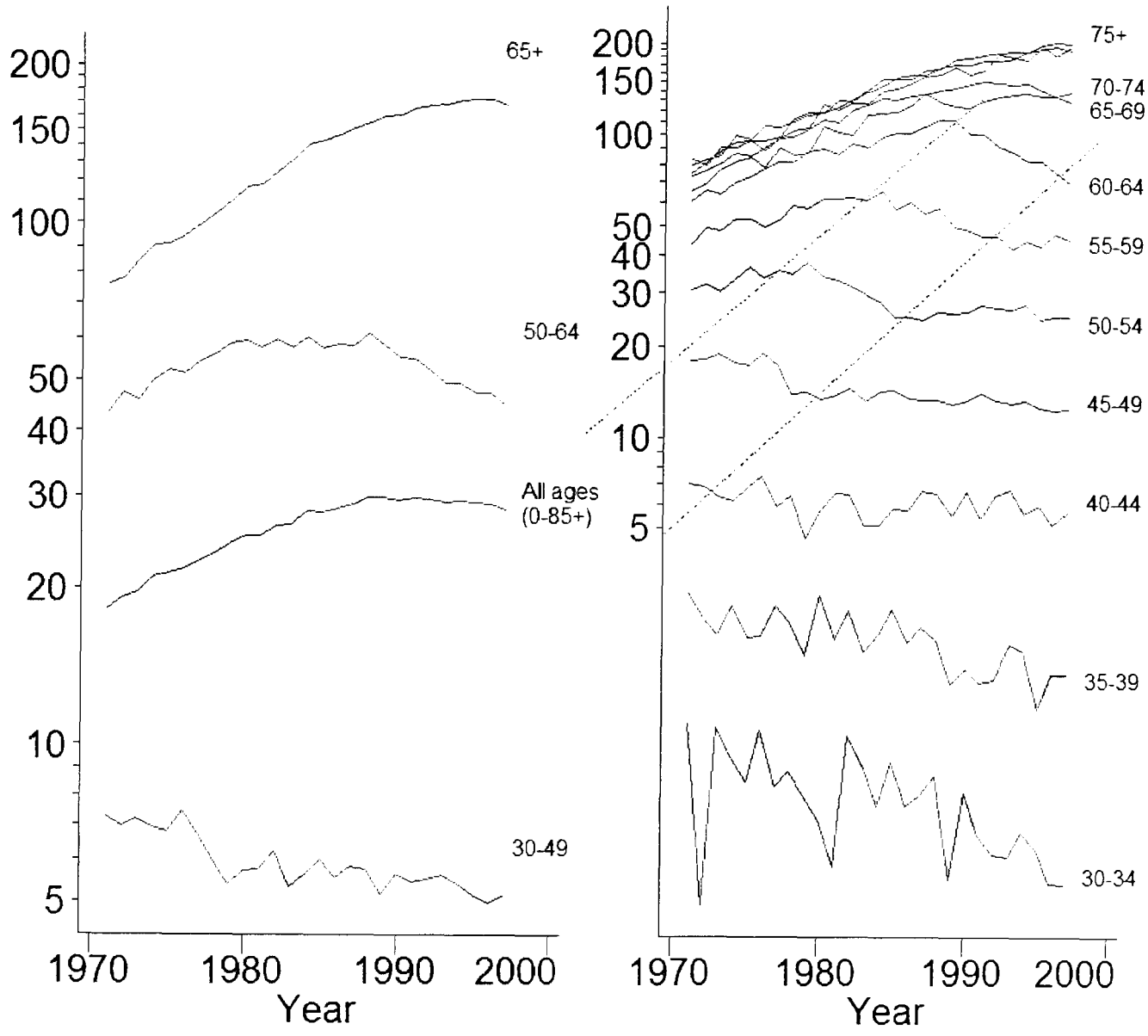
rates to obtain an expected summary rate if the population of interest had the same age distribution as the standard.

Trends in age-adjusted rates are often not the best way to examine cancer risk either geographically or temporally [123]. Strictly speaking, trends in this measure are only accurate in the absence of an interaction between age and calendar time. Trends in age-standardised rates by calendar period may thus mask important changes in the age-specific rates, particularly in the presence of strong birth cohort effects [171].

Figure 3.1 presents annual trends in lung cancer mortality rates in women in England 1971-1997 using three rate measures, the all-ages age-standardised rate, age-truncated rates (age groups 30-49, 45-64 and 65 or over) and five-year age-specific rates. The age-adjusted rate conveys the idea of a levelling off of lung cancer rates in all women by the late 1980s, but fails to give an accurate picture of the underlying trends for certain age groups. According to the truncated rates, there have been substantial declines in younger women aged 50-64 since this time, while rates in the youngest age group have been decreasing throughout the 30-year period. Generation-specific decreases become more evident when the mortality rates are plotted versus period by five-year age band, as depicted in the right-hand diagram of Figure 3.1 (see 3.1.4).

There can be no substitute to an inspection of age-specific rates in temporal analyses, as these serve to validate the use of age standardisation and provide valuable background information in interpreting results from more complex modelling procedures [171]. Trends in age-adjusted rates may be informative if they are used to facilitate a summary of the trends allowing a comparison across several populations, with the understanding that the underlying trends in age-specific rates form the foundation of the analysis. Valuable information can be gleaned from visual descriptions of the age-standardised rates over time across populations, such as the portrayal of incidence and mortality trends of various cancers in different countries with regions worldwide [35]. Age-truncated rates used in accordance with the epidemiological profile of the cancer under study, may succinctly summarise the major changes in the trends, with diverging trends by age group, suggestive of birth cohort effects and the need for a more detailed analysis of the time components.

Figure 3.1: Lung cancer mortality in women in England and Wales 1971-97. All-ages and truncated ASR (Europe) vs. calendar year (left diagram); five-year age-specific rates (30-84) vs. calendar year (right diagram) (source: WHO)



Graphical descriptions may be ambiguous if the rates are associated with excess random variation. In such instances, it is common practice to aggregate the number of events and person-years at risk over several years (commonly aggregates of 3 or 5 years). Alternatively, moving or rolling averages can be calculated, with the advantage of retaining (with the exceptions of the first and last point) single-year rates that are aggregated mean estimates centred around their midpoint, although disadvantaged by the fact that the average rates are no longer independent of each other. Aggregated rates tend to be smoother than the rolling mean alternative, and given they retain more information regarding the trend, may be the preferred option.

Indirect standardisation is used seldom in time trends studies, although age-standardised cohort ratios have been favoured by some epidemiologists investigating temporal studies of cancer mortality in England and Wales [23,89,172]. The approach requires age-specific and

birth year-specific data, and therefore the individual records of events. The age-standardised cohort mortality ratio (SCMR) summarises the risk of death in each birth cohort at the age they have attained in the study period relative to the expected mortality at the same ages in the population overall, adjusting for population structure between cohorts [23].

3.1.2 Semi-log vs. arithmetic displays

Two types of scale are in general use in plots of rates over time: the arithmetic (no transformation of either axis) and semi-logarithmic (logarithmic transformation of the ordinate). Both transformations are regularly applied in epidemiological literature to graphically portray disease rates over time.

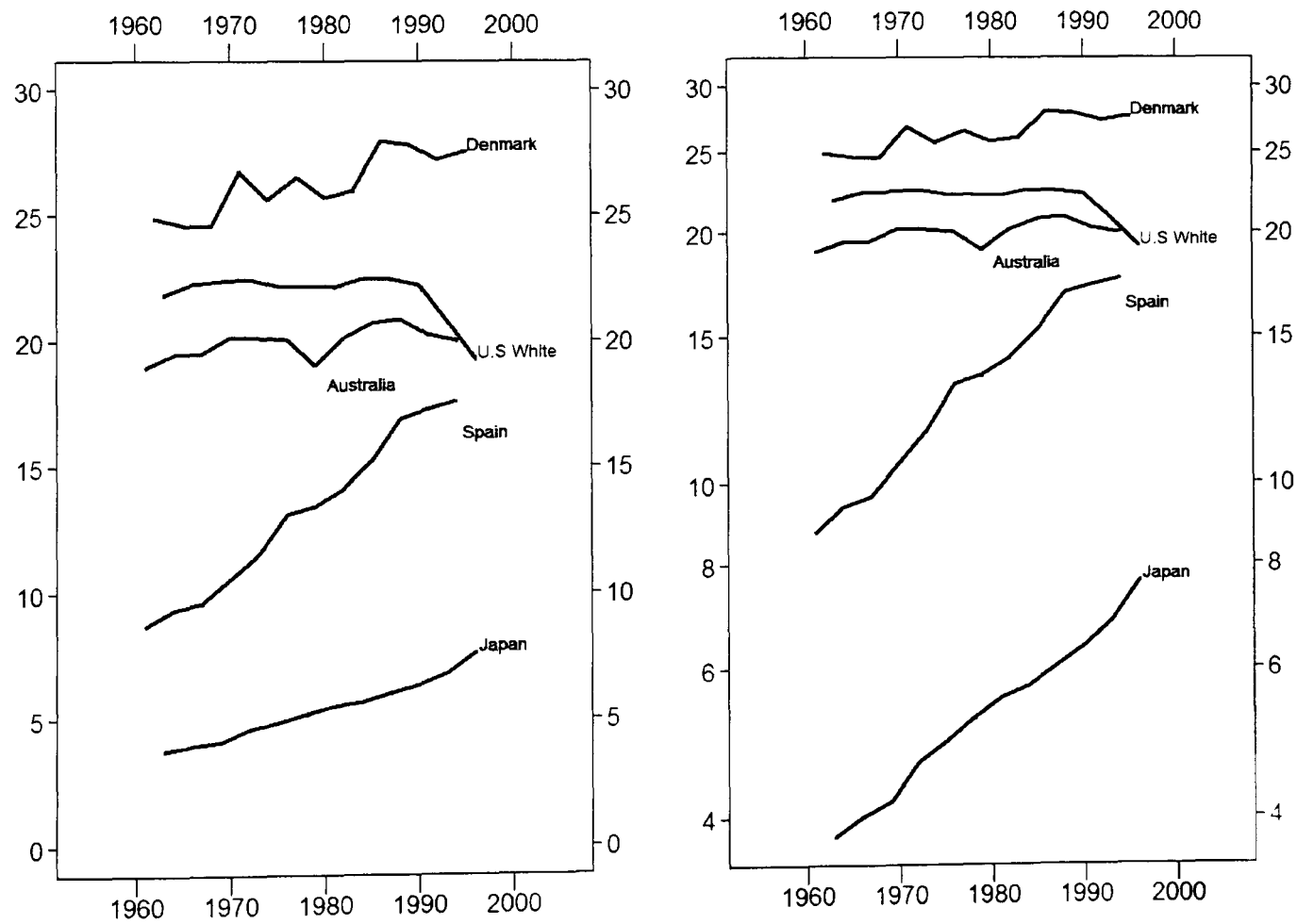
Arithmetic scales are appropriate where absolute rather than relative changes in magnitude are the main point of interest, for example when temporal trends of greater magnitude are considered to be of greater consequence when the absolute values are large. Examples in public health include the evaluation of operating costs for a vaccination programmes over time, the number of interval cancers in a screened population, or the predicted number of breast cancer cases as an indication of the resources required for treatment. The slopes of the trend line reflects absolute changes in the rate over time, and can be estimated by fitting a simple linear regression to the rate with time fitted as a continuous covariate (see 3.2.2).

There are two reasons why the semi-log display may be of greater utility in studies investigating changes in rates with time. Firstly, rates of very different order of magnitude may be plotted and visually interpreted. A visual interpretation of rates associated with few events alongside those with many is enabled, such as trends in five-year age-specific rates of lung cancer incidence in men aged 30-74, or the comparison of trends in rates of a rare versus a common cancer. Secondly, it should be considered important in epidemiological research to identify proportional changes in rates among populations where the baseline rates differ [165]. The semi-log display is particularly effective at depicting relative changes in risk over time in low risk relative to higher risk groups, providing evidence of similarities or differences in the trends between groups. Figure 3.2 illustrates the arguments by contrasting the use of the arithmetic and semi-log displays in portraying trends in age-adjusted female breast cancer mortality in five populations. The large and uniform increases in Japan (relative to the U.S., for example) are played down by the use of arithmetic scaling of the Y-axis, given the lower baseline rate. On a log scale, the two-fold increase in death rates in Japan is readily apparent, a much larger increase than observed in high-risk areas but similar to the rate of increase that was seen among Spanish women.

It remains true that both semi-log and arithmetic scales have interpretational advantages in certain circumstances; it has been argued, for instance, that use of the log scale may conceal important period or cohort effects, primarily in the older age groups when the rates are of a large magnitude [109]. In the temporal analysis of rates however, the log-transformed plot should generally be preferred, given its interpretational link with log-linear modelling, and the concept of multiplicative effects for which relative changes in rates with time for all ages can be viewed as a series of parallel lines.

Sufficiently detailed labelling of a log-transformed ordinate may also be important, in order that absolute changes over time can also be calculated and evaluated. The log-scaled ordinate may be labelled (or ticked) as deciles of each cycle e.g. from 0.1 to 1, 1 to 10,1 to 100, and so forth. If the rate of change is constant, the observed time trend will be a straight line on a semi-log display. Quantification of this regular trend, often described as the estimated annual percentage change (EAPC), can be obtained (together with an estimate of its precision) via log-linear modelling (see 3.2.2).

Figure 3.2: Age-standardised (World) mortality rates of female breast cancer in five countries 1960-97 examined on an arithmetic and a semi-log scale respectively (source: WHO)



3.1.3 Ratio of Y:X axis

Devesa *et al* [165] describe the potential differences in interpretation of the magnitude and direction of the time trend on altering the ratio of the Y- to X-axis. Fundamental is the degree to which a time-related increase or decrease will be evident. One sensible rule, the authors propose, allows a 1% change in the rate per annum to be detected by a 10° change in the slope. To determine the Y:X ratio, the span of the abscissa must be considered in relation to the range of values for the rate described on the ordinate. Assuming a semi-log transformation, the proposal works for a one-cycle ordinate (e.g. 1 to 10) and a 40-year abscissa plotted giving a Y:X ratio of 1:1 and a square graph. Alternatives such as a 2-cycle 40-year graph (Y:X ratio of 2:1) and a 3-cycle 20-year (Y:X ratio of 6:1) would visually represent the slope of the trends equivalently. The adoption of uniform scaling rules in recent studies by its proponent and collaborators has led to a degree of comparability among these studies not seen elsewhere in the trends literature (see also 3.5.3).

3.1.4 Graphical displays by age, period and cohort

3.1.4.1 Line charts: Korteweg's approach

The demonstration of the importance of the birth cohort phenomenon (when compared with cross-sectional trends on the same graph) is often attributed to Korteweg's study of lung cancer mortality trends in England and Wales [72,82]; but its roots are in earlier work such as Frost's examination of tuberculosis mortality in the U.S. [73], as discussed in Chapter 1.

The lung cancer graph associated with Korteweg, connected, as solid lines, the age-specific rates by period, and as broken lines, the rates in each cohort. This conveyed in a single diagram the idea that cohort influences were a more plausible explanation for the rising lung cancer rates than period of diagnosis. Given the strong tendency for risk of lung cancer to increase with age, the description of rates declining in later ages in each successive period seemed implausible and an effect produced by artefact. The cohort-specific representation however provided a more rationale explanation for the observed lung cancer trend, with rates uniformly increasing in successive generations regardless of age, therefore explaining the potential for an erroneous interpretation with the period display.

In an interview looking back at his career, Sir Richard Doll recently described the need to persuade the medical community of the causal link between smoking and lung cancer even after publication (with Sir Austin Bradford Hill) of their landmark report in 1950 [173]: "If smoking is the cause, we ought to find that wherever the disease was common, smoking should be common, and vice versa... And that's what we found when we looked round the world" [174]. The realisation of a regular age relationship and sharply rising death rates with

each generation and in successive generations would have helped to convince the unconverted of the carcinogenicity of tobacco [74].

3.1.4.2 Line charts: rates versus age by period, cohort

Portraying rate versus age by period *and* birth cohort in a single graph demonstrated both the importance of generational changes and the misrepresentation of the period curve as an indicator of an inconsistent degree of immunity at different ages, when applied to tuberculosis infection [73]. Rates at older age were artificially pulled down due to this age group passing through greater risk earlier in life (as picked up by birth cohort trends). The graphical display of lung cancer trends in this fashion is cited as a textbook example of temporal relations and differences between period and cohort [65,71,82], though for many other neoplasms, the relationships are less clear, and by necessity, graphs are usually plotted separately by period and cohort.

The first- and second-left graphs of Figure 3.3 depict observed (logarithm of) female breast cancer rates versus age by period (A by P) and versus age by cohort (A by C) respectively, based on mortality data from Japan [68]. When examining such period or cohort curves, there are a number of features that alert us to a particular interpretation [175]. Curves that appear to be placed on top of each other indicate that there is no increase in the regular time trend, with fluctuations the result of random variation. If there are steady increases in incidence by period or cohort, the lines will be relatively parallel, with the most recently diagnosed or the most recently-born generations, respectively, experiencing the highest rates.

A lack of parallelism in such curves however – indicative of increases or decreases affecting some age groups more than others – can lead to difficulties in interpretation of the temporal patterns. In Figure 3.3, the A by P and A by C plots display such characteristics, although some parallelism can be seen in younger age groups at diagnosis e.g. among those aged under 65 and more recent generations e.g. among those born after 1900. The interpretational difficulties with these displays leads to more informative plots of logged-rates versus cohort by age (C by A) and versus period by age (P by A), as discussed below.

3.1.4.3 Line charts: rates versus period and cohort, by age

The rate versus age graphs were perhaps more commonly utilised in early temporal studies, where interest was focused mainly on interpreting cross-sectional age curves to better understand the known biology of disease. More recent practice favours comparisons of plots of rates versus period and birth cohort, with lines connecting each age group, given that

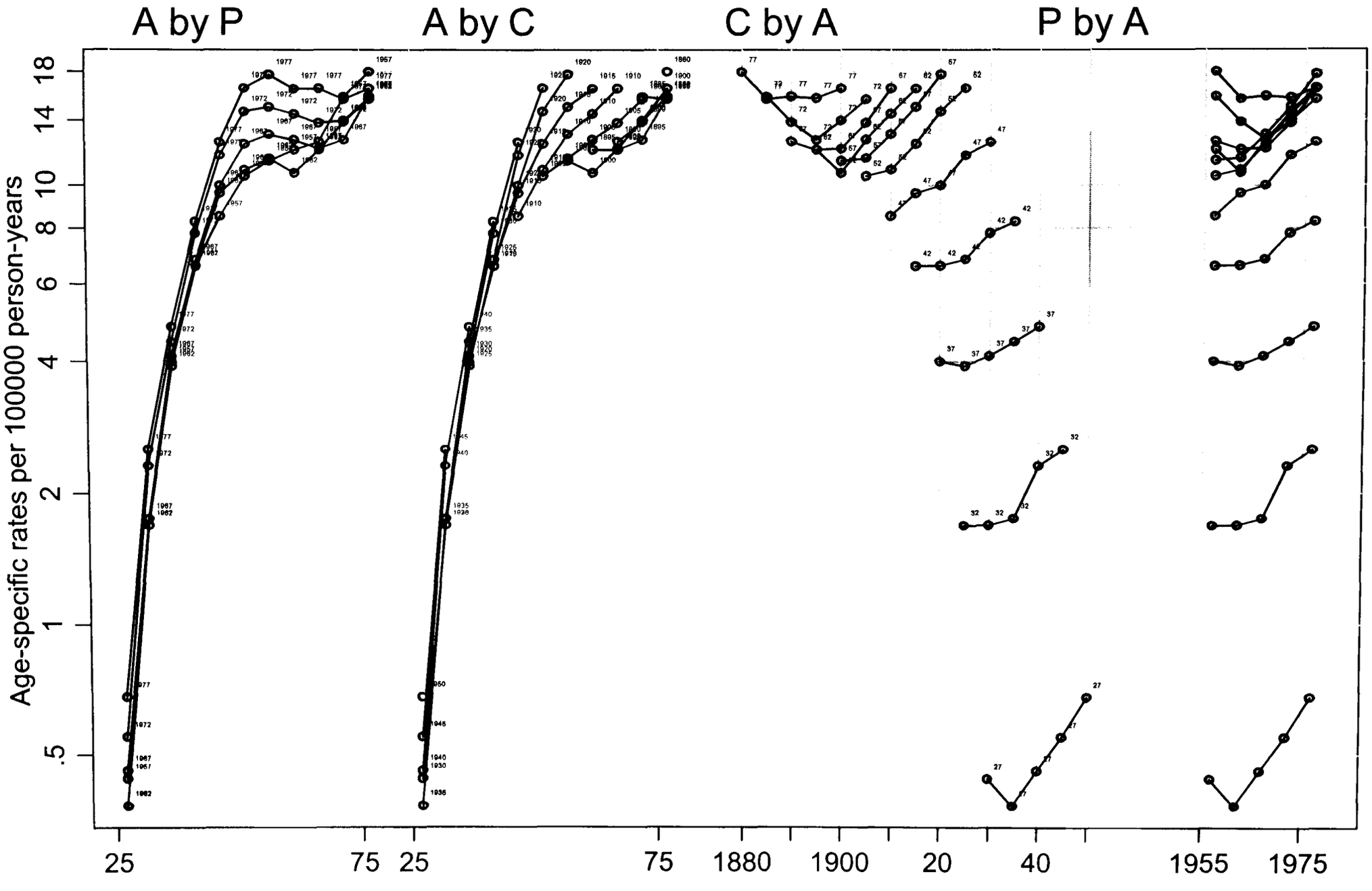
interest is directed primarily at how rates vary temporally, rather than how they may differ by age.

The centre-right and extreme-right graphs in Figure 3.3 show the Japanese female breast cancer mortality rates as C by A and P by A plots. Uniform changes in the rates in specific periods or birth cohorts can be more readily identified when the period and cohort lines are connected by their respective age group.

Period effects are evident if there is a sudden change in the slopes in each of the studied age groups at a given period of time, for example, following the introduction of screening or a new diagnostic tool that leads to a similar change in the rates among all affected age groups. Period effects often indicate possible artefacts that may affect all age groups similarly, such as would result following a change in classification.

Cohort effects are established if a sudden change affects a particular generation (irrespective of their age at diagnosis). Often, such changes in rates among a particular generation are followed by the continuation of the trend in successive generations, symptomatic of the introduction or removal of a highly carcinogenic agent (changes in tobacco consumption or in sexual behaviour are well-known examples). The C by A plots in Figure 3.3 illustrate its value – uniform increases in rates of breast cancer are seen in successive generations of Japanese women born since the turn of the twentieth century. The use of equivalent time scales for period and cohort forces the length and basic shape of the lines to be the same for both period and cohort, and in doing so, provides a first indication of the nature of the identifiability problem in applying APC models; while the regular trend corresponds to both period and cohort, changes in the rates at specific points on either time axis (the non-linear components) are identifiable (see 3.3).

Figure 3.3: Representations of rates by time. Left to right: rates vs. age by period (A by P); rates vs. age by cohort (A by C); rates vs. cohort by age (C by A); rates vs. period by age (P by A). Breast cancer, Japan 1953-77 (Source: [68])



3.1.4.4 Other graphical methods

The graphical depictions conveyed thus far project the three-dimensional response surface onto a two-dimensional plane via the use of line charts. A difficulty in interpretation in the isolation of one of the time factors has led to the advocacy of more complex multi-dimensional methods. One display attempts to simultaneously depict the effects of age, period and cohort using a 'contour' plot, and such displays may have certain applications when the temporal patterns are complex. Ultimately however, the need to concurrently control for all three factors in a graphical analysis leads aptly to the use of a modelling framework, set out below.

The disentangling of the age-specific rates for many neoplasms is not as straightforward as the classic lung cancer example above. Boyle and Robertson use the latter example to show the benefits of a 'surface' or 'perspective' plot, where age, time (period or cohort), and the rate are the X, Y and Z-axes, respectively [109]. In certain instances the surface plot conveys information that could not be gleaned from the traditional line plot; although as Holford points out, such a representation is often complex to interpret [110]. The magnitude of a specific effect is difficult to assess, and given that only two of the three axes are displayed in any one graph, it remains unclear as to how the rates in one axis change at a predetermined point of the other time axis.

Other methods have attempted to simultaneously graph the age, period and cohort attributes by creating a diagram consisting of equilateral triangles, the three sides of which represent the effects of age, period and cohort. Contour plots describe the response curve in terms of a set of projected lines that are constant on the two-dimensional plane (e.g. age vs. period or age vs. cohort). These graphs are considered particularly useful for more complex situations where multiple disease aetiologies are considered likely. Following the parallel lines on either axis enables one to gauge how fast rates are changing according to how rapidly contours are crossed. Regions where contours are parallel on the period axis indicate no temporal trend in the rate by calendar time. Conversely, if they cross, there is evidence of a period effect. The diagonal lines indicate constant changes in cohort and, in the same way, generational effects can thus be simultaneously evaluated according to whether the contours are parallel or cross on the diagonal axis. Such representations have largely been attributed to Weinkam and Sterling [176], although, as Keiding point outs [177,178], activity in this area stem back at least to the 19th century demography in Germany, including such an equilateral representation by Lexis in the context of marriage-death models [70].

Graphical displays may also exploit multivariate techniques including biplots and correspondence analysis. Robertson and Boyle comprehensively review various graphical approaches to APC analysis [109]. In general, the usage of more elaborate graphical methods than the standard line charts described in 3.1.4, has been rather minimal.

3.2 Descriptive measures of temporal change

3.2.1 The role of statistical modelling

Conclusions based on graphical means are often not straightforward and may not by themselves provide satisfactory levels of inference. It is in these situations that our understanding of the evolution of cancer risk can be greatly enhanced by the use of more formal statistical procedures. Models offer quantitative and comparable estimates of trend based on objective criteria for choosing the best description of the data, and statistical tests to decide whether the trends may be real or due simply to chance [57]. The consequences of subjective judgments based exclusively on graphical descriptions are thus avoided. The interpretation of cancer trends is however often complex and statistical models will not provide definitive answers. When used skilfully they may however aid interpretation of the observed temporal patterns.

Time trend data should be analysed according to the problem under investigation, and the structural characteristics of the data. In cancer monitoring, the goal might be to quantify recent trends in cancer, making statements as to the needs for future health priorities on the basis of anticipated future trends. The EAPC provides a summary of the magnitude and direction of the trend, and is obtained from log-linear modelling (see 3.2.2). This procedure has an arbitrary element however, in that the trend estimate will depend on the extent of log-linearity in the selected period. Alternatively, one may wish to determine the EAPC for periods of time between statistically significant abrupt changes in the linear trend, as discussed in 3.2.3.

3.2.2 Estimated Annual Percentage Change

Assuming the background age-specific rates over time are proportional on an arithmetic scale, and constant on a log scale, the EAPC of the age-standardised rate can be estimated from the slope parameter on fitting a log-linear model to the summary rate and including the time axis as a covariate:

$$E[\log r_j] = \mu + \delta \cdot j \qquad \{3.1\}$$

The log-transformed age-adjusted rate r_j in period j is assumed to be normally distributed with mean λ_j, δ is the slope over j, μ is the intercept. The EAPC is the value $e^{\delta}-1 \approx \delta$ if δ is small. If however there is a degree of curvature in the trend on a log-scale, the model is likely to be inadequate and the EAPC not interpretable. Alternative models that allow polynomial terms for time may be explored. Models with quadratic and cubic terms (or if necessary higher order terms could be added to {3.1} to determine the extent of curvature over and above the fitted linear slope:

$$E[\log r_j] = \mu + \delta_1 \cdot j + \delta_2 \cdot j^2 \qquad \{3.2\}$$

$$E[\log r_j] = \mu + \delta_1 \cdot j + \delta_2 \cdot j^2 + \delta_3 \cdot j^3 \qquad \{3.3\}$$

The models are hierarchically nested so comparisons of model {3.2} with {3.1} and model {3.3} with {3.2} may be tested for second and third-order curvature respectively.

Alternatively (and as a test of the proportionality assumption required above), the mean rate of change in the age-specific rates can be estimated on assuming the number of cancer cases d_{ij} is distributed as a Poisson random variable with rate $r_{ij} = d_{ij}/Y_{ij}$ where Y_{ij} is the number of person-years in age group i and period j, assumed fixed and known, and a_i is the effect of age group i, δ the linear slope when period is fitted as a continuous covariate over calendar time j.

The model is then:

$$E[\log r_{ij}] = \mu + a_i + \delta \cdot j \qquad \{3.4\}$$

In statistical packages, the model is implemented by specifying d_{ij} as the response variable and the $\log(Y_{ij})$ as an offset. Estimation of the parameters using Poisson regression is preferable to methods which assume the cases are normally distributed, as the precision of the estimates is optimal (as measured by the standard error) using the Poisson distribution [179].

The log-linear model of {3.4} is unlikely to be a sensible model if, as is common, there are different proportional changes in different age groups [180]. One might consider testing for this by fitting an age-period interaction of the form:

$$E[\log r_{ij}] = \mu + a_i + \delta_j \cdot j \qquad \{3.5\}$$

Thus, in estimating the EAPC based on the overall trend in the age-adjusted or age-specific rates, one should strictly first test the assumption of proportionality in the age-specific rates. Certainly, the EAPC as an overall descriptive measure is useful and commonly applied in practice (see 3.5). The calculation of a 95% confidence interval (95% CI) for the slope is an indication of whether the trend is real or random. Simple models such as {3.5} have also been used for making short-term predictions of cancer rates [180].

Cohort effects can be considered as a special form of an age-period interaction with a single observation in each cell [181]. A lack of proportionality in age-specific trends by period may suggest important (non-linear) cohort effects, and one might bypass the above modelling procedure in favour of a more sophisticated APC analysis. The concept of a regular trend being ascribed to calendar period is an assumption that cannot be tested, and for a sufficient span of data, the APC framework that reports the regular time trend or *net drift* (δ in {3.4}), may be a more practical and sensible approach (see 3.4.1.1.3).

Estimation of the mean annual *absolute* change can be easily accommodated in the framework of models {3.4} and {3.5} by specifying an *identity* rather than a log link, and fitting the rate directly with no offset. In an attempt to balance the overall age-adjusted estimate according to the underlying structure of the population, it is common to weight by the person-years at risk rather than give equal weighting to all age groups. Alternatively, weighting by the number of cases effectively minimises the influence of age curves with substantial random errors while providing more weight to age groups considered more influential (and important) in view of having more cases associated with them.

3.2.3 Automated procedures

In estimating the rate of change, there is an assumption of log-linearity in the cancer rates over time, but if there are elements of curvature in the trend, the EAPC will give incorrect and imprecise estimates of the average unit change. Moreover, if one wishes to describe only recent short-term trends, the particular time base for which to estimate the slope is often arbitrary and, in the absence of highly stable rates over time, the EAPC will differ appreciably according to the period of time nominated. One proposal involves modelling that identifies sudden changes in the trend, and on that basis, estimates the direction and magnitude of the slope for each epoch of time where rates are relatively stable.

Interrelated methods have been devised by Chu *et al* [182] and by Kim *et al* [183], and the latter implemented in a specially written (and freely available) statistical software package entitled *Joinpoint* [184]. While both techniques involve fitting of a piecewise model to the time trend, the techniques used to determine the unknown joinpoints differ somewhat.

3.2.3.1 The stepwise method

According to the method of Chu *et al* [182], the predictor variables δ_S represent each of the possible linear slopes from year j to J, where $j \geq 1$ and J is the most recent year in the analysis. The baseline model includes an intercept term and a slope δ_1 over the whole period. Weighting by the total annual number of cancer events, the selection procedure then identifies which of the δ_S causes the most significant change in the overall trend. A Bonferroni correction for multiple comparisons is applied to the p-value so that $p < 0.05/J$ is considered a significant contribution. If none of the δ_S are significant, then the procedure ends and the two-factor model denoting a simple linear trend across the whole period is accepted. Otherwise, the most significant δ_S is added to the model. The stepwise procedure continues in this fashion, testing for significant changes in the slope defined by δ_S. At each stage, the terms already included in the model are re-tested and eliminated if they are no longer statistically significant. A final model is reached when no further significant changes in the trend are observed.

3.2.3.2 The joinpoint method

As with the above method, the idea behind the joinpoint regression model is that linear trends should be derived over a few continuous linear phases. The procedure is motivated by the problem of determining joinpoints, the points in time for which significant changes in the trend are detected, and in doing so, estimate the linear trend between each set of joinpoints (or *segments*, as they have been described). The maximum number of joinpoints is user-specified rather than obtained via the stepwise procedure above. To determine up to two joinpoints, for example, a model indicating no change is compared against the model containing two joinpoints. If the null hypothesis of no joinpoints is rejected, then the procedure is applied to test the null hypothesis of one joinpoint against the alternative of two joinpoints. Otherwise, the test for the null hypothesis of no change is considered against the alternative of one joinpoint. Another consideration on identifying the final joinpoint model is to estimate confidence regions for the parameters. The test statistic is obtained by the grid search method suggested by Lerman [185] and its p-value is computed using the permutation procedure.

The Joinpoint program fits the simplest piecewise model according to the user-specified minimum and maximum number of joinpoints [184]. The program starts with the minimum number of joinpoints (e.g. 0 joinpoints, a straight line) and tests whether more joinpoints are statistically significant and must be added to the model (up to that maximum number). This

enables the user to test whether an apparent change in trend is statistically significant. The tests of significance utilise a Monte Carlo Permutation method described by Kim *et al* [183]. The models may incorporate an estimate of the variation for each time point (e.g. when the responses are age-adjusted rates) or use the standard Poisson model for counts or rates.

Given the automated nature of the search for linear trends, particular focus on recent temporal patterns, and the fact that cancer data from vital sources in different populations are often available for variable spans of time, the program has obvious applications to descriptive analyses of multiple regions or countries. One concern refers however to the plausibility of a procedure that exclusively identifies only abrupt changes in trends that act linearly. The merits of the technique are further discussed in Chapter 5, where it is systematically applied to endometrial cancer incidence and mortality trends across Europe.

3.3 The age-period-cohort model 1: components of the dataset and notation

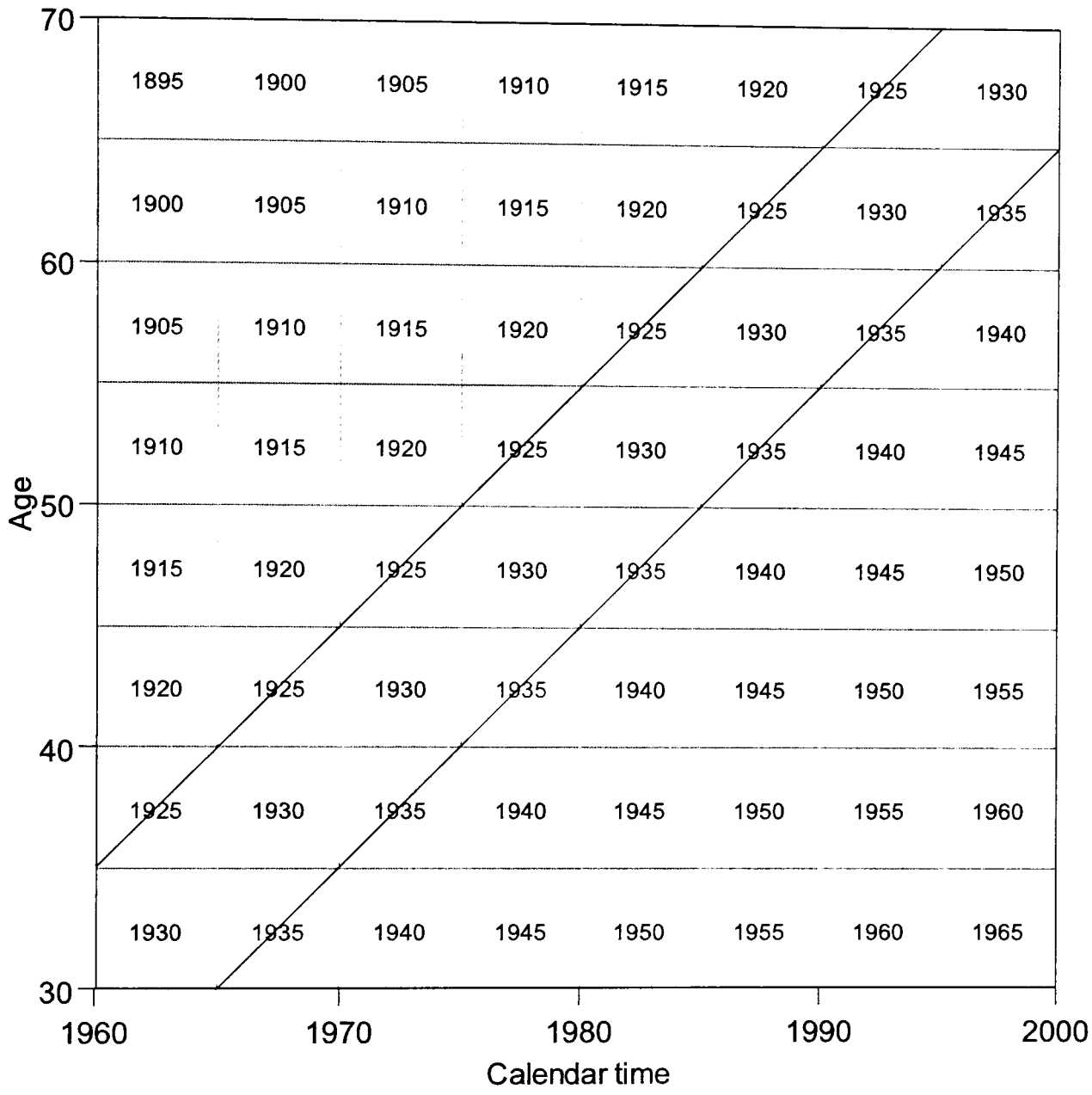
To provide the epidemiologist with clues to the aetiology of disease, time trends are often jointly considered using age, time of event and date of birth. The approach, outlined in detail below, involves the fitting of age, period and cohort as explanatory variables in a log-linear Poisson regression model of the number of disease events, offset by the corresponding person-years. APC modelling [63,66-68,87] has become a standard technique for the temporal analysis of disease rates, and applications to cancer trends regularly appear in the peer-reviewed medical and epidemiological literature.

3.3.1 The age-period tabulation of rates

Data from vital statistics systems are often made available at an aggregated level, usually by five-year age group and single calendar period. While APC methods that deal with unequally spaced intervals are available [66,106], they introduce further complexities, and typically, APC analyses proceed using equally-spaced five-year age and five-year period groupings (the so-called quinary-quinquennial estimates), as initially described by Case [71]. The Lexis diagram in Figure 3.4a gives the midpoints of the birth cohorts for each of the cells in an age-period classification for which the age groups are 30-34, 35-39,...,65-69 and periods 1960-64, 1965-69,...,1995-99.

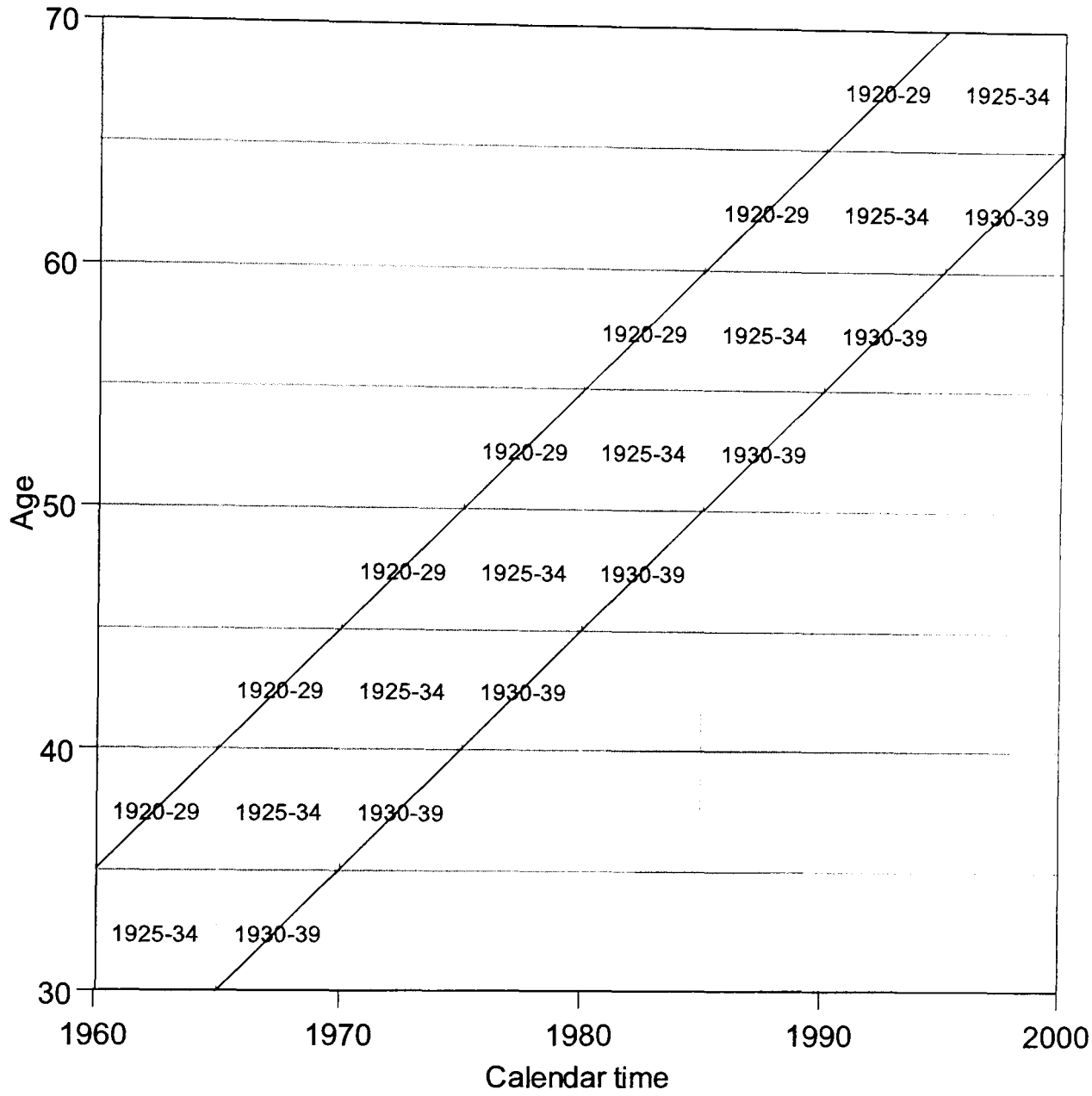
The central value of birth cohort is easily derived on subtracting the midpoint of each age category from the midpoint of the corresponding period. Moving diagonally in the Lexis diagram from bottom left to top right identifies cells and the cohort midpoints, with the earliest cohort in the oldest age group (top left cell) and the most recent cohort in the youngest age group (bottom right cell). The number of rates associated with each cohort varies from one to eight as one moves from the extreme cells towards the middle diagonal.

Figure 3.4a: Lexis diagram depicting midpoints of birth cohorts for each of the cells in an age-period classification for five-year age classes 30-69 and five-year periods 1960-99



Complete sets of age groups and periods are available, but earlier and later birth cohorts are underrepresented however, with only the midyear cohort (1930) complete. Given the crude tabulation of age and period, the cohorts are synthetic; each cohort represents a 10-year span that overlaps with every other cohort by exactly five years. The cohort identified as 1930 in Figure 3.4a within the two diagonal lines travelling from bottom left to bottom right of the table represents the experience of a generation born between 1 January 1925 and 31 December 1934. Adjacent 10-year cohorts to the left and right overlap and they therefore also partially represent the cohorts born 1925-29 and 1930-34 respectively (Figure 3.4b).

Figure 3.4b: Lexis diagram for five-year age classes 30-69 and five-year periods 1960-99. The 10-year cohort with midpoint 1930 is identified as well as adjacent and overlapping cohorts



Often the main focus of interest is the evaluation of trends occurring among more recently-born cohorts, as the impact of recent carcinogens may show up more clearly in this group [113]. Trends in younger generations also naturally lend themselves to a future prediction; these birth cohorts will, in time, enter the age groups associated with the greater part of the cancer burden. Unfortunately, as has been clarified already, young cohorts are represented by rather few age-period cells that contain relatively few cases. Approaches to cancer predictions involving the APC model are briefly discussed in 3.4.6. Before turning in detail to the statistical aspects of APC analysis, some general comments are provided on selecting a suitable age, and usage of finer resolutions than that afforded by a quinary-quinquennial grouping.

3.3.1.1 Selection of age range for APC analysis

Some restriction on the age range considered is usually necessary. The oldest age groups are often excluded on the grounds that the quality of mortality statistics in the elderly is particularly affected by a lack of precision and coding of the death certificate, as well as by erroneous decisions regarding the underlying cause of death [23,136]. For incidence data, case ascertainment is less effective in the very old, in part due to inaccuracy in the abstraction and coding of diagnostic information, and in part due to competing causes of death, with a result that a neoplasm is either not recorded as the underlying cause of death, or is not recorded at all. In addition, trends in the elderly are more likely to be affected by the extent to which diagnostic investigations have been sought [23]; the intensity of examinations has likely increased over time, as technology develops.

Most epithelial tumours are rare below the age of 30, and it is common practice to exclude this age group from an analysis of adult cancers; the numerators of the age-specific rates, associated as they are with few events, will provide little extra information. Prostate cancer, primarily a disease of the elderly, is uncommon in men aged under 50, so a temporal analysis that restricts attention to an older age range, more representative of the burden, may be appropriate.

For testicular germ cell cancer, most incident cases occur in the 15-54 age range, and an analysis that focuses the investigation on such a restricted age group has been proposed [186]. A bimodal age curve of HL incidence has been observed in some populations, stratified analyses reflecting the possibility of a multiple aetiology might be considered. Menopausal changes notably affect the risk of women developing certain cancers associated with hormonal control (e.g. breast, endometrial and ovarian cancer) and further stratification by age may be necessary, e.g. according to menopausal status.

3.3.1.2 Five-year groups versus finer classifications of age and/or period

The use of narrower intervals for age and period may permit a more detailed analysis of temporal patterns. For example, an analysis at the individual level enables the description of temporal curvature with greater precision and resolution via the use of spline regression [187-189] (see 3.4.5.5). A focus on methods based on a five-year age-period classification is in part a convention laid down by the availability of incidence and mortality data from vital sources, and corresponding population data from official statistics in five-year age intervals.

Some registries have both one-year incidence & population data, and it is constructive to contrast the relative utility of trend analyses using data at higher and lower levels of resolution (see 3.4.5.5).

Interpolation techniques are however often required to estimate the populations estimates that correspond to the resolution of age and period, such as Beer's method that preserves five-year totals [190]. Tarone and Chu [102,103] have consistently used APC models based on two-year age and period spans in analysing cancer trends in the U.S.(see 3.4.3.2 and 3.4.5.4).

3.3.2 The role of statistical modelling

Given the limited number of variables that require our attention in conventional APC analyses, graphical analyses of time trends have often been considered adequate descriptions of temporal data. As Kupper *et al* conclude [67], such a display avoids the potential for errors associated with "researcher bias" in presenting one solution from the many available from APC modelling (see 3.4 below). Yet the interpretation of time trends of many neoplasms is often unclear, and deciding whether trends can be attributed to period or cohort on the basis of graphical descriptions is itself somewhat arbitrary. Modelling has shown its value over and above purely graphical methods, particularly on consideration of biological or epidemiological information that lends itself to a particular presentation and interpretation of the model effects.

3.3.3 Notation

The APC log-linear model involves additive contributions of the three time effects on the logarithm of the rate, and is given by:

$$E[\log r_{ij}] = \mu + \alpha_i + \beta_j + \gamma_k \qquad \{3.6\}$$

where, as above, $r_{ij} = d_{ij}/Y_{ij}$ is the rate of cancer occurrence with Y_{ij} the number of person-years in age group i and period j, assumed fixed and known, α_i is the effect in age group

indexed i for $i=1,2,..,I$, β_j the effect of period indexed j $(j=1,2,..,J)$, and γ_k the effect of birth cohort with index $k=1,2,..,K$ linearly dependent on period and age as $k=I-i+j$. The number of cancer events, y_{ij} are assumed to be distributed as a Poisson random variable with mean λ_{ij}. In its multiplicative form the model is:

$$\lambda_{ij} = MA_iP_jC_k \qquad \{3.7\}$$

where λ_{ij} is the untransformed rate, M the baseline rate, and A_i, P_j, and C_k are the antilogs of the age, period and cohort effects. The model can be estimated readily in statistical packages using maximum likelihood techniques, with the numbers of events fitted as a generalised linear model assuming Poisson errors and a log link function relating the mean to the linear component of the model [191]. Given $\log(r_{ij}) = \log(y_{ij}) - \log(n_{ij})$, the logarithm of the corresponding person-years can be declared as an *offset*, an added constant set to unity for which estimation is not required.

The goodness-of-fit is determined by the deviance, D, the ratio of likelihoods from the currently fitted model L_F and the saturated model L_G respectively, with:

$$D = -2\log(L_F / L_G) \qquad \{3.8\}$$

The fit of the model can be tested by comparing D with the χ^2 distribution on the residual degrees of freedom (d.f.). The goodness-of-fit of submodels (see 3.4.1.1) can be tested in the same way, with the contribution of the individual effects assessed by comparing differences in the deviance of two nested models with the χ^2 distribution on the corresponding difference in the degrees of freedom.

3.3.4 What is the identifiability problem?

Intrinsic to recognising the inherent limitations of the APC model is the fact that knowledge of any two factors implies knowledge of the third, making one of the factors redundant [69,87,106]. As mentioned above, the index of cohort is defined by the corresponding indexes of age and period, and hence the three factors are exactly linearly dependant on each other.

Although submodels are not free from potential biases, they at least are identifiable. Subjecting {3.6} to a common set of constraints, such as fixing the first level of each of the effects to zero so that $\alpha_1 = \beta_1 = \gamma_1 = 0$, or applying the so-called usual constraints whereby

the sum of the effects of each is zero i.e. $\sum_i \alpha_i = \sum_j \beta_j = \sum_k \gamma_k = 0$, does not realise a unique set of parameters; rather, there are an infinite number of them [68]. It is an inescapable fact that identification of any two of age, period and cohort identifies the third; in modelling terms, this signifies that the linear components of each factor cannot therefore be identified. One further linear constraint must be imposed to ensure a unique solution, but the crux of the problem is that the choice of model constraint and the resulting parameter estimates are completely arbitrary in the absence of compelling external information that one can bring to bear in making the selection. The following text critically explores the many choices open to the researcher wishing to derive and interpret results from the APC model in the unavoidable presence of non-identifiability.

3.4 The age-period-cohort model 2: advocated approaches

The main techniques are classified into four groups that, though not mutually exclusive, serve to highlight the relative capacity of each method to provide an honest representation of the trends as well as an informative solution, given concerns regarding their degree of conservativeness, arbitrariness, and complexity.

- **Simple (potentially arbitrary) approaches** – specifying an additional constraint on the parameters in an APC model, or dropping one of the factors altogether;
- **Conservative (potentially arbitrary) approaches** – using an estimable function (curvature) but adding a specified slope of one factor (based on external information or otherwise) to provide a unique solution;
- **Conservative (never arbitrary) approaches** – restricting summary to a reformulation of the APC model parameters that identifies an estimable function e.g. invariant to the constraint imposed;
- **Complex (entirely arbitrary) approaches** – mathematical solutions proposed by observing particular mathematical relationships between the time components.

A fifth miscellaneous group includes (often more complex) approaches that do not easily fit into one of the above categories.

It is appropriate to start with simple, commonly applied strategies for dealing with identifiability, for which the potential for arbitrariness is often overlooked (see 3.4.1). Clayton and Schifflers' logical ordering of nested models and their introduction of the net drift is fundamental to understanding the difficulties, and is introduced here.

Holford's approach forms the next section, and provides further insight into the nature of identifiability, as well as a sensible (and potentially informative) method. The main strategy

involves explicit quantification of the magnitude of the slope for one of the factors, which once specified, immediately quantifies the remaining slopes. Addition of the linear component to the corresponding curvature provides the solution – its implementation and function is discussed in 3.4.2.

Estimable functions are parameterisations that offer summaries that are identical for a given arbitrary set of APC parameters. More conservative approaches based solely on such functions steer clear of any imposition of arbitrary statements and are discussed in 3.4.3. A number of quantifies can be derived that are estimable and may fulfil the investigative objectives of a temporal study [110].

Other more technical approaches are discussed in the remaining two sections. Methods that ensure identifiability through particular mathematical formulations are examined in 3.4.4. Section 3.4.5 describes miscellaneous techniques that include extensions to the three-factor model, non-linear models for which parameters are identifiable and non-parametric methods. A final section (3.4.6) relates the utility of results from the APC model to the prediction of future cancer burden.

3.4.1 Simple constraints on the model parameters

3.4.1.1 Dropping one factor

Perhaps the easiest way to circumvent identifiability is to ignore the three-factor model. In the study of time trends of cancer, certain conditions lend themselves to a logical choice of the age-period (AP) or age-cohort (AC) model. Indeed, this practice is incorporated in the definition of the "age-period-cohort model" in Everitt's *Cambridge Dictionary of Statistics in the Medical Sciences*: "various methods have been suggested for disentangling the dependence of the factors, although most commonly one of the factors is simply not included in the modelling process" [192].

Other than avoiding the necessity to deal with the identifiability problem explicitly, adoption of two-factor models is often made on the basis of goodness-of-fit. Often this involves securing the observation that one of these models yields a reasonably good fit, or at least fits better than the other two-factor model; the AP and AC models are not directly comparable, as they are not nested within each other.

The root of the problem with the two-factor approach stems from the fact that there will be an inherent bias in the resulting estimates should one of the three effects be wholly linear [67]. The inability to quantify or test the linear part of the effects of age, period and cohort is encapsulated in Clayton and Schifflers adoption of a net drift term to quantify a function of slopes that is both estimable and interpretable (as the regular time trend). The logical

ordering of models, with the nested age-drift (AD) model examined prior to the two-factor models, forces acceptance that tests for period or cohort effects only involve tests of their respective non-linear components (see 3.4.1.1.3).

Given its apparent simplicity relative to methods dealing with the full APC model however, two-factors models are commonly applied in the cancer epidemiology literature. Before bringing AD models into the discussion, some characteristics of the AP and AC models are examined.

3.4.1.1.1 Age-period models

An AP model may reasonably describe quasi-parallelism of age-specific curves by calendar period on a semi-log display. Clayton and Schifflers specify two features that may yield such an observation: 1) when there are immediate (or delayed but predetermined) effects on the log-transformed rates; 2) when there are constant increases or decreases of the same quantity over calendar time across all age groups [63]. Using the same notation as above, it can be written:

$$E[\log r_{ij}] = \mu + \alpha_i + \beta_j \qquad \{3.9\}$$

The model may provide an acceptable description should the period effects over and above age explain a significant amount of variation and {3.9} does not suffer from a significant lack-of-fit. In the absence of cohort influences, one might consider adopting the AP model, although if cohort also provides a significant improvement to the age-only model, the adoption of {3.9} as the sole representation of the observed data is unjustified.

Certainly there are many examples where strong period effects are present in disease trends. The introduction of an intervention affecting trends irrespective of age at a fixed point in calendar time will produce period effects. Rapid changes in the prevalence and distribution of one or more risk factors in the population at a single point in time may also give rise to period effects, with the abrupt decline in the risk of cardiovascular disease in the U.S. [65], a commonly cited example.

Period effects may be observed in cancer trends where effective screening programmes have been implemented, and a reduction in rates is seen across all age groups invited to participate. Where such a test detects pre-invasive malignancies, both incidence and mortality rates will decrease; tests that detect cancer at an early stage will, in theory, only reduce mortality trends. The introduction of national cervical screening programmes in several of the Nordic countries led to rapid period-specific declines in cervical cancer incidence and mortality in all screened age groups, notably in Finland, where an 82%

decline in mortality was observed from its peak in the late 1960s to its nadir in the early-1990s [193]. The importance of examining period effects in assessing the effectiveness of cytological screening is revisited in Chapter 4.

More often, period effects point to artefactual changes (e.g. changes in coding, in diagnostic practices, and in ascertainment) that act on rates in a likewise fashion across all affected age groups. MacMahon and Trichopoulos, in discussing the complexities of interpreting temporal variation, state that "most difficult to deal with are those components of trends relating to the effect of changes in clinical concepts, diagnosis and terminology, because such changes evolve gradually" [194]. Gradual changes in cancer rates over calendar time across all age groups would strongly imply a linear effect of period, although linear trends cannot and never will be detected by AP models, or indeed any other class of APC model (see 3.4.1.1.3). This link between non-identifiability and artefactual changes in cancer trends is perhaps overlooked in APC studies; steady and ongoing improvements in diagnostic ability, for instance, will go undetected in APC models, and the interpretation of cohort parameters, for instance, may be substantially altered on identifying a true linear increase with calendar time. The difficulties in quantifying these artefactual changes can at least be explored by modelling the impact of a plausible range of period slopes on the resultant cohort trends. This strategy is discussed in 3.4.2.1.3.

3.4.1.1.2 Age-cohort models

AC models may be represented by quasi-parallelism of age-specific curves according to birth cohort on a semi-log display, indicating constant increases or decreases in rates seen within a particular generation irrespective of their age at diagnosis, that is, within a specific birth cohort equally throughout life [63]. The model is of the form:

$$E[\log r_{ij}] = \mu + \alpha_i + \gamma_j \qquad \{3.10\}$$

The model can be established as providing a reasonable fit using tables of deviances, as above. The lack of ability to detect linear slopes of any of the time components of course remains, yet one of the most frequent means of summary of APC data seen in the literature involves the presentation of results from the AC model. Why? Other than on statistical grounds (e.g. if the model yields a reasonable fit), or an obvious route to avoid the non-identifiability issue, it is well founded that exposures to strong risk factors often follow generational patterns. The root causes of many cancers are related to lifestyle factors, and the protracted exposure required before the development of a neoplasm implies that cancers will occur two or more decades later, and rather than affecting all groups simultaneously, will show up in certain cohorts whom have had greater exposure than

others. The changing distribution and prevalence of smoking, sexual behaviour, and diet, for instance, may be heavily related to societal or peer-related influences which put men and women at higher (or lower) risk in successive generations [195]. Further, exposures that occur within a relatively narrow age range, such as those that occur early in life, should also manifest themselves as cohort effects [195].

3.4.1.1.3 The problem with two-factor models: Clayton and Schifflers net drift

In 1987, Roush and colleagues (with Holford as second author), considered the following models to systematically describe incidence data in Connecticut for 20 cancer sites [196]:

i. Models with age, period and cohort (as {3.6});

ii. Models with age and period (as {3.9});

iii. Models with age and cohort (as {3.10});

iv. Models for which choice between AP and AC was ambiguous.

Notably absent was the AD model incorporating regular trend which Clayton and Schifflers [63] introduced in the same year. The net drift parameter represents the average annual change in the rates over time, the passage of time that is common to calendar period *and* birth cohort, a quantity that cannot be disentangled between them, given the algebraic relationship that identifies cohort as the difference of period and age. The AD model can describe a situation whereby the two-factor models {3.9} and {3.10} fit the data equally well, and for which models in iv. of Roush and colleagues' above categorisation [63] might better be described by:

$$E[\log r_{ij}] = \mu + a_i + \delta \cdot j \qquad \{3.11\}$$

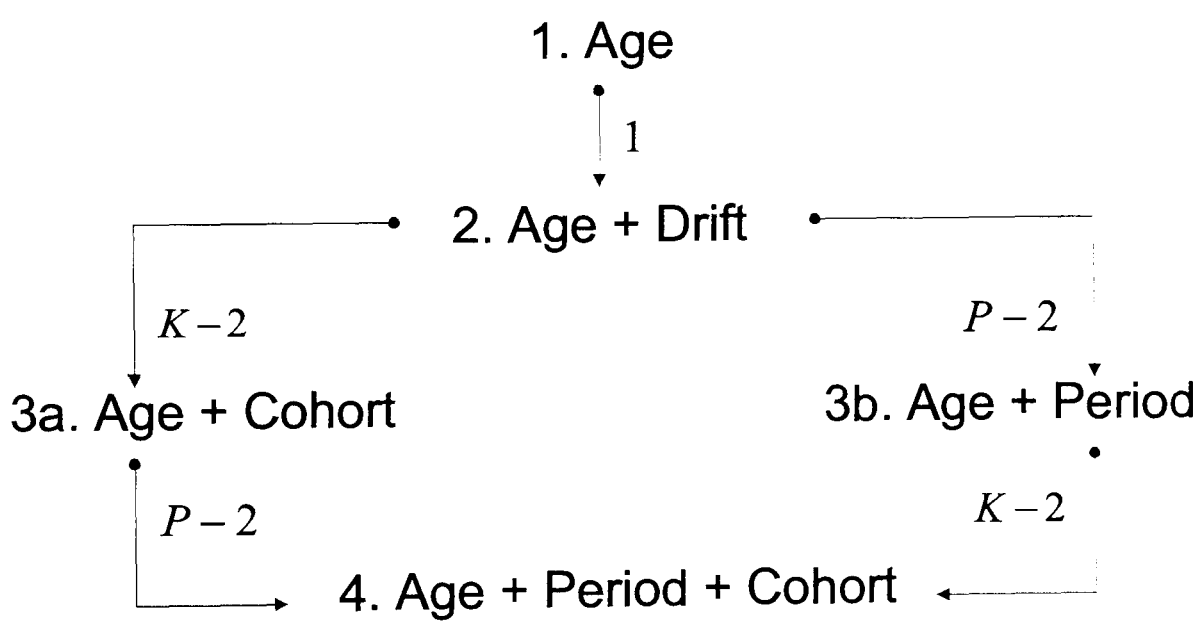
Model {3.11}, already stated as {3.4}, implies the same linear change in the logarithm of the rates over time in each age group. Given the linear component over time is identifiable but cannot be allocated in any way to period or cohort, δ can be estimated by either specifying period or cohort as a continuous covariate, with the EAPC estimated as $(e^{\delta} - 1) \times 100$, expressed in terms of the unit of origin.

Holford [66] and others had already shown that several functions of the three slopes were estimable (see 3.4.2.1), however it was Clayton and Schifflers who suggested that the net drift, as the sum of the period and cohort slopes, should become an integral part of the APC modelling strategy, as an estimate of the rate of change of the regular trend [63], and as a means to partition first order and curvature effects [68]. The net drift obtained from a data series spanning decades includes observations in the distant past, and may not provide a

good indication of recent trends. One sensible modification would be to estimate the trend for the whole study period and for the 15 years (say) of most recent data, enabling a comparison of the relative magnitude and direction of long-term vs. contemporary trends.

The Clayton and Schifflers papers [63,68] established a formal modelling strategy that forced age in all models and prioritised a test of the significance of the regular trend, and in doing so brought the concept of (non-identifiable) linear and (identifiable) non-linear effects down to the level of the two factor models. Specifically, the authors recommend fitting a hierarchy of models (Figure 3.5), starting, given its importance on carcinogenic processes, with a baseline model including age but no temporal trend.

Figure 3.5: Clayton and Schifflers' logical order of APC model fitting [68]

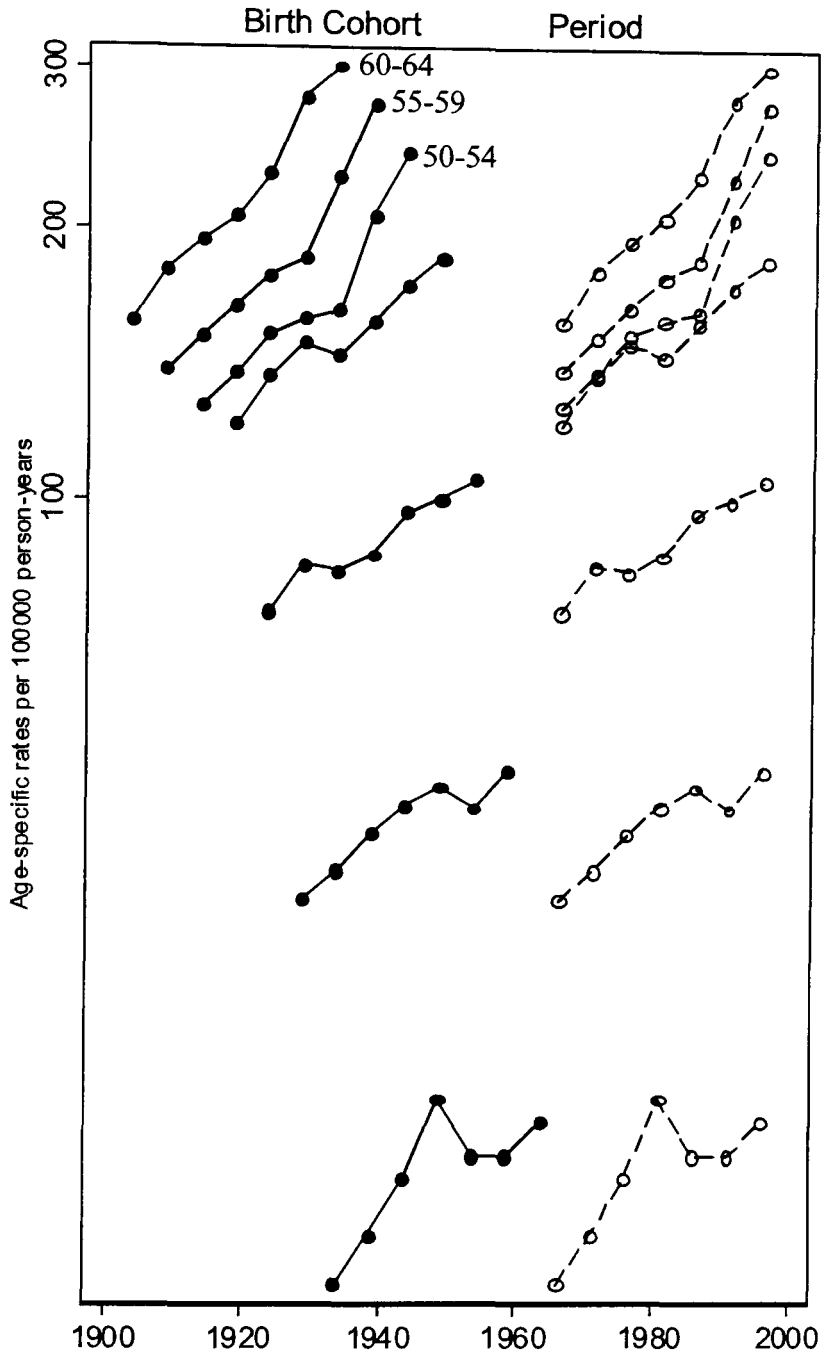


The relative contribution of each effect in the hierarchy is determined by comparing the change in the deviance and degrees of freedom in two sequentially-fitted models with the appropriate χ^2 statistic. A comparison of an age-only model with {3.11} is a one d.f. test for the net drift; a comparison of models {3.9} versus {3.11}, and model {3.10} versus {3.11} provides $P-2$ and $K-2$ tests for the effects of non-linear period and non-linear cohort, respectively. Comparing model {3.6} versus {3.10} tests for the effects of non-linear cohort effects, with a further loss of $K-2$ degrees of freedom adjusting for net drift and non-linear period. Finally, the comparison of model {3.6} versus {3.9} tests the $P-2$ effects of non-linear period, adjusting for net drift and non-linear cohort.

Such a modelling framework asks the researcher to acknowledge the inherent problem in both two-factor models as well as the APC model; that the linear component of each of the effects are neither identifiable nor statistically testable, being hopelessly entangled due to the algebraic relationship that identifies birth cohorts. The model-fitting procedure has become standard in APC studies, but a number of related difficulties in APC modelling, as discussed by its authors [63,68] are perhaps less well appreciated (see 3.5).

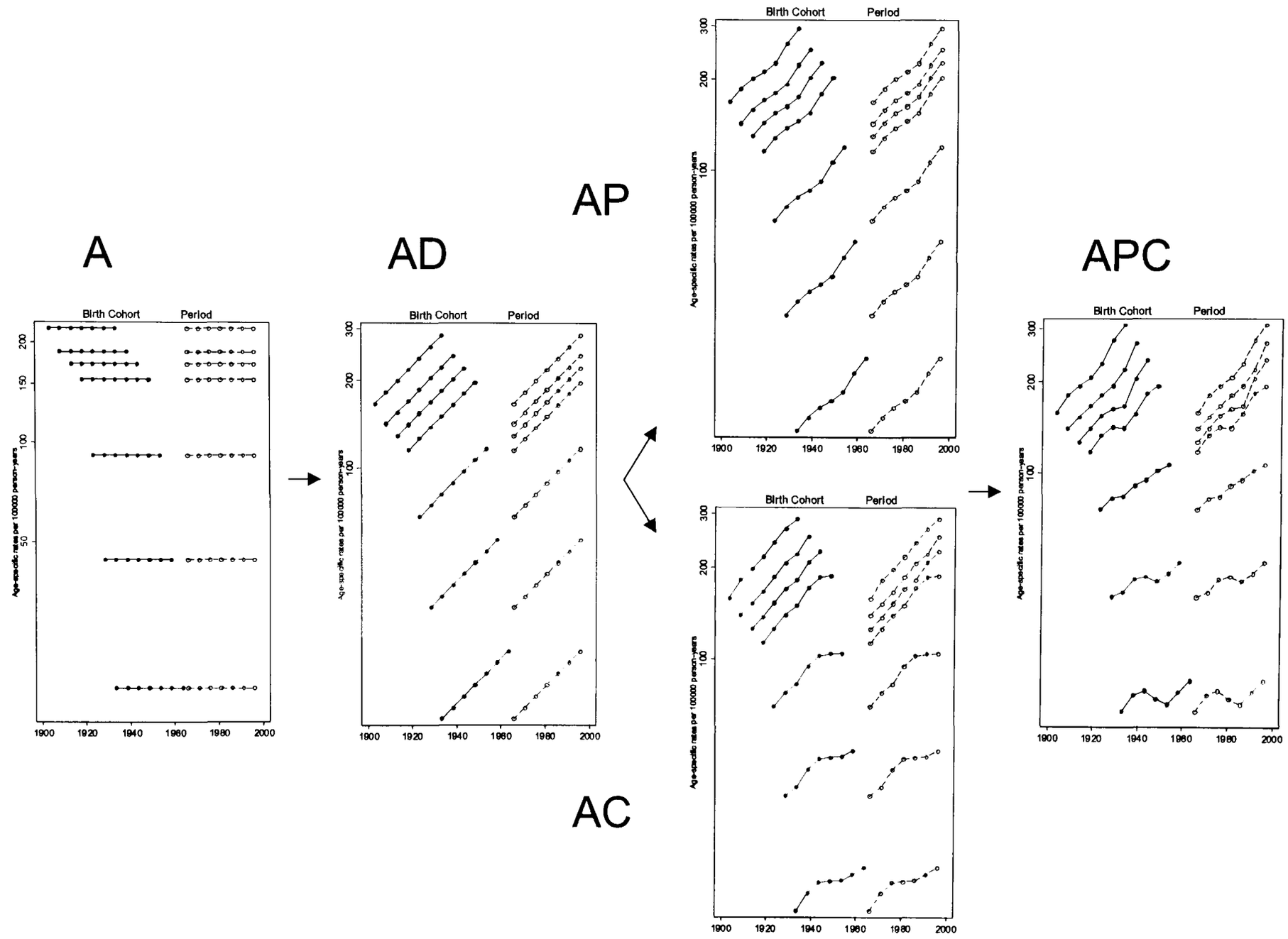
A graphical display of the fitted rates from the APC model and submodels provides a simple but effective demonstration of both the identifiability problem and the characteristics of each. Figure 3.6a shows the observed rates (aged 30-64) of breast cancer incidence data from Sweden, 1964-98, and the estimated rates from each of the models (Figure 3.6b) in the same logical ordering as Clayton and Schifflers recommended [68]. The fitted rates from the age model (A) depict horizontal lines (no time trend) and represent the mean rates for each age group. Rates from the AD model represent linear trends for period and cohort that necessarily are of the same order of magnitude, given that the cohort lines differ from the period lines only in terms of a simple subtraction of the age group represented. Rates from the AP model impose period curvature over and above the net drift to all age groups; the sharp increases in diagnosis are the result of a prevalence round of screening in Sweden – primarily affecting women aged 50-64. Fitted rates from the AC model reflect the possible attenuation of rates in breast cancer incidence in younger generations, noted by Persson *et al* [197], although mammography may have also had a recent impact among peri-menopausal women. Finally, the fitted rates of the APC model impose both non-linear period and cohort curvature over and above the net drift.

Figure 3.6a: Observed rates of breast cancer incidence vs. cohort and period by age, Sweden, 1964-98



Perhaps unsurprisingly given the complexity of the trends, none of the models fit in the above example; the APC model is a rather blunt instrument for summarising such temporal patterns. More generally, maximum likelihood estimates for parameters assuming Poisson errors often leads to a situation where none of the candidate models adequately fit the data, due primarily to the large number of events than any systematic departure from the model [66]. Several established methods for dealing with the effects of overdispersion are available [191,198].

Figure 3.6b: Graphical depiction of fitted rates by birth cohort obtained on fitting the APC model and its submodels according to Clayton and Schifflers' procedure [68]



Day and Charnay have suggested a consideration of the factors across several registries (see 3.4.5.3) to improve the possibility of detecting period or cohort effects [65]. As Holford comments however, such an approach may still miss important trends if the effects of period or cohort are relatively linear [107].

3.4.1.1.4 Two-factor models in practice

Given the direct interpretation afforded by their use, few researchers have dwelled on potential biases with two-factor models. Their use is more justified when selected on the grounds of goodness-of-fit and where there is some rationale for the adoption of a specific model. In practice, this is not always the case, and there may be difficulties gleaning insight without succumbing to over-interpretation.

Hermon and Beral describe long-term trends (1950-92) in breast cancer mortality rates by calendar period and birth cohort in 20 countries using AP and AC models respectively, linking these to trends in several reproductive variables [199]. The authors graphically depicted the trends in period and cohort effects as rate ratios in each country (obtained from the respective two-factor models), suggesting these "are comparable to a relative risk estimate and can be interpreted in a similar manner" [199].

The problem of interpretation comes down to the placement of drift. A focus on period effects will place the drift with period, likewise with cohort, and an honest interpretation would confine discussion to *changes* in the slopes. Given the magnitude of the slopes are necessarily arbitrary, a particular choice will affect the values of the rate ratios.

In the study, the results were not generally over-interpreted, but in the discussion the difficulty obtaining insight with this approach emerged: "in [several countries] mortality rates are either constant or have recently levelled off or have began to decline. The decline appears in part due to birth cohort effects and in part due to period effects although it is sometimes difficult to separate these effects using mathematical models" [199]. No observed data were presented, nor was the goodness-of-fit of either model established; it therefore remains unclear as to whether period and cohort effects (or both) impacted on the reported trends. This is important as much of the discussion centred on concomitant generational changes in nulliparity, age at first birth and completed family size.

Baron *et al* also attempted to avoid the identifiability problem by presenting both AP and AC models of trends in non-epithelial cancer incidence in Denmark, Finland and Sweden 1961-90, by sex [200]. Although the analysis of deviances of the APC model and submodels was displayed, they also presented relative risk estimates derived from both two-factor models. The authors state: "we could not justify *a priori* assumptions regarding the rates to allow

unique estimation in the full APC models, and chose not to present multiple estimates, based on different allocations of the non-unique linear drift effect. Therefore we present results from the basic AP and AC models, although in certain cases, none of the partial models adequately represent the data" [200].

Indeed, of the six populations, only for Finnish males did the two-factor (AC) model fit the data. For four of the populations, the APC model best described the data. Quite why estimates of the trends were derived from the AP and AC models rather than the APC model is not clear as no justification of the approach is given. Further, the authors (from the abstract) note that modelling "suggested that the dominant factor in the underlying increases were birth cohort effects" [200], although both non-linear period and cohort effects significantly improved the fit in all six populations. Only rate ratios from the AC model were presented, and the "increasing" cohort effects described as "relatively strong", with a comparison between countries, indicating "trends were most pronounced for Finland, and somewhat less marked in Sweden" [200].

One problem illustrated in this example is the assertion of cohort influences without particular justification. Non-epithelial cancers (the majority of which are haematological cancers) are particularly susceptible to artefactual increases as a result of improving diagnostic ability that should show up as period effects (linear if gradual, non-linear if sudden). Adjusting the cohort effects to simultaneously allow for the possibility of uniform increases in successive periods (e.g. that gradual improvements in diagnostic ability may be largely responsible for the increasing trends) would radically alter the interpretation of the generational influences.

Kupper and colleagues state that "adoption of a two-factor model based on standard goodness-of-fit criteria is invalid when the population effects for one of the factors (age, period or cohort) follow a non-horizontal linear pattern" [67]. Some studies in the literature have also bypassed the use of deviances in adopting a particular model on the basis of its non-linear effects, instead preferring *a priori* beliefs to inform the selection process (see 3.5).

Interestingly, the use of AC models has been advocated by Clayton and Schifflers for systematic studies across many populations [68], although the authors do not offer guidelines or a justification of this statement. Perhaps the authors would have cited the 1985 study by Roush *et al* as a good example of their use. In the study AP, AC and APC models were systematically fitted to incidence for 25 adult cancers, with cohort a significant factor in 34 of 44 datasets [201]. Certainly, comparisons of birth cohort trends in different populations may help establish or confirm hypotheses regarding differences in the underlying distribution

and prevalence of risk factors, and such an approach is taken in the analysis of trends of cancers of the cervix, endometrium and testis using the APC model in Chapters 4 through 6, respectively.

3.4.1.2 Equating two or more parameters

Given the problems with two-factor models, it is logical to consider the full APC model as the primary option. Moreover it also often provides the best fit: Roush *et al*, in their systematic study of incidence data in Connecticut by cancer site and sex, found APC analyses led to a choice of APC model in 20 of the 44 datasets: there were 14 AC models, seven AP models and three for which there was "no clear choice of model" [201].

An alternative to limiting inference to the two-factor model is to equate two, rather than all of the parameters of one of the effects. A unique set of parameters for age, period and cohort can be obtained by assuming, for instance, that the first and last, or two neighbouring effects, are equal. The main problem relates to the difficulty in securing a sensible preference as to which two effects to equate. There is rarely an example of a trend for which one can assume the effect of two age groups, period or cohorts are equal; the solution is thus arbitrary in the absence of compelling information regarding the underlying nature of the trends.

Two approaches may ensure some level of plausibility and are discussed below. The first involves the presentation of one or more solutions on equating two effects of one factor that reflect the researcher's *a priori* beliefs regarding a feature or features of the temporal trend (see 3.4.1.2.1). A more general proposal, as advocated by Clayton and Schifflers is to equate the first and last effects of one factor (either period or cohort) in an attempt to force attribution of the drift to the other factor (see 3.4.1.2.2). As will be seen, neither method is without problems however, lending support for an explicit quantification of one of the slopes (see 3.4.2).

3.4.1.2.1 Selecting constraints from plausible scenarios

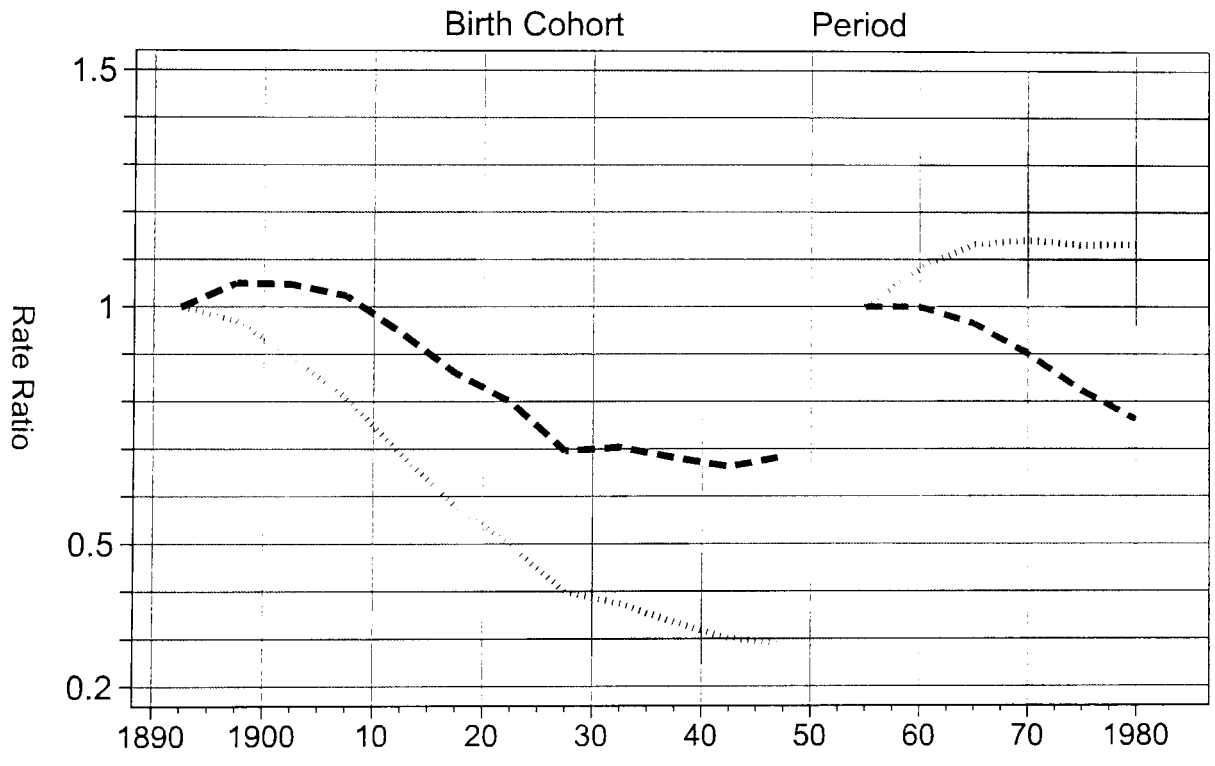
Achieving a credible interpretation of time trends on assuming that two levels of one factor are equal requires knowledge of the epidemiology of the disease in the study population. Plausible scenarios may be explored using several alternative sets of estimates, as in Hamajima and Lee's 1987 study [202] described below.

Several constraints were used to represent age, period and cohort trends in gastric cancer mortality in Japan 1955-80 [202]. On acknowledging different constraints led to widely varying trends in age, period and cohort, the authors introduced several constraints on the

period parameters such that a) $\beta_1 = \beta_2$ produced long-term declines in mortality risk; b) $\beta_2 = \beta_3$ introduced a peak period-wise around 1960 and c) $\beta_3 = \beta_6$ (in men) or $\beta_4 = \beta_6$ (in women) allowed risk to level off in more recent periods.

Figure 3.7 presents cohort and period effects for stomach cancer trends in men for scenarios a) and c), as described in tabular form in the original paper [202]. Clearly, the period effects are very different. Scenario a) involves early period-related increases in the 1960s and a constant trend in the 1970s. Corresponding cohort declines are largely constant in successive generations born since 1900. Scenario c) indicates constant period-specific declines from the 1960s, but successive cohort declines only in generations born between 1900 and the late-1920s, cohort trends being relatively flat elsewhere. The authors suggest that the true period effect might be found somewhere between a) and c), interesting, as Figure 3.7 would suggest an underlying slope for period of approximately zero, a general method proposed implicitly by Clayton and Schifflers [68] in the same year and explicitly by Holford [66] some years earlier.

Figure 3.7: Stomach cancer mortality trends by birth cohort and period in Japan on equating two period effects based on plausible assumptions; dotted line represents $\beta_1 = \beta_2$; dashed line, $\beta_3 = \beta_6$ (Source: [202])



This way of circumventing non-identifiability was used earlier by Barrett in 1972 in the study of cervical cancer mortality rates [87]. Two solutions, one based on equating the last two cohorts, the other the last two periods, were selected more on *a posteriori* grounds in that they provided sensible parameter estimates rather than an *a priori* preference for a particular constraint. His later mortality studies of bladder [69] and prostate cancer trends [88] were based on a single set of parameters on equating the first and last period effects (see 3.4.1.2.2). Each of Barrett's studies emphasised the importance of interpreting the deviations from linearity of each factor, rather than their unidentifiable linear slopes.

Insight is therefore possible with such a technique, provided a range of constraints is used to present the trends, and the particular choices of constraints justified. It is difficult however to escape the arbitrary nature of such a parameterisation; often there is an insufficient level of understanding of the cancer trends to set two effects to equality, and differences in opinion between observers will certainly exist.

3.4.1.2.2 Clayton and Schifflers' suggestion: mean first differences

Clayton and Schifflers proposed a solution involving the de-trending of the adjacent effects of one factor so that the corresponding overall slope is equal to the mean of the successive first differences [68]. For the period effects these are:

$$(\beta_2 - \beta_1),(\beta_3 - \beta_2),...,(\beta_J - \beta_{J-1}) \qquad \{3.12\}$$

By imposing $\beta_1 = \beta_J$, the period line is forced to return to the baseline value (assuming the default reference category is $\beta_1 = 0$), effectively achieving an underlying slope that approximate a horizontal slope of gradient zero. In this parameterisation, the cohort effects contain all of the net drift and can be examined and interpreted under the hypothesis that the linear trend is entirely attributable to generational influences.

Likewise, setting $\gamma_1 = \gamma_K$ attempts to eliminate the linear component of cohort, thereby sending the net drift to the period effects. On constraining the extreme cohort effects to zero however, a problem emerges. Clayton and Schifflers advocated the method due to its relative simplicity – most statistical software programs will automatically alias the first and last effects of the last-entered variable – but refrained to discuss the possible errors such an approach may introduce.

The random error associated with small numbers in the single cell occupied by the youngest cohort in the age-period table, as discussed in 3.3.1, can often lead to wide fluctuations in the corresponding model parameter. It may be of a large enough positive or negative magnitude to have the effect of tilting the drift upwards or downwards, respectively. In such

cases, the constraint $\gamma_1 = \gamma_K$ will poorly serve its function as a means to allocate the entire drift to period, potentially leading to erroneous interpretation.

Tarone *et al* examined breast cancer mortality trends by period and cohort in the U.S. and Canada [203]. The authors acknowledge that the cohort effects from the APC model that appeared in their paper (their Fig.1), and reproduced here as Figure 3.8a, cannot be interpreted as relative risk estimates, while the main emphasis of their paper is quantification in the *changes* in the slopes (see 3.4.3.2). Nevertheless, such a parameterisation is not uncommon in the recent literature (see 3.5), and several papers have included a citation to their paper (and others) as a justification for its use e.g. [204].

Further, it is worth considering the particular interpretation that is served by their choice of constraints (the zero cohort slope in Figure 3.8a joins those parameter estimates that are set to equality for U.S. whites, the first and last effects). The negative linear trends indicates that the U.S. cohort slope would have taken on a very different trend and direction if the second and second-last effects had been constrained to be equal. Had the latter parameterisation been adopted, the U.S. cohort effects would have undergone a counter-clockwise rotation similar to the crude display in Figure 3.8b.

The chosen constraints are particularly important in interpreting the period trend, which would have experienced an equal but opposite (clockwise) rotation, that is, equating first and last effects would have had the effect (in the above example) of attenuating the period trends relative to those obtained on equating the second and second-last parameters. Both choices of constraints for cohort purport however to be approaches that approximately yield a cohort slope of zero.

Alternatives to Clayton and Schifflers' suggestion have been described by Møller [205] and include a refitting of the model on removing the youngest cohort, or computation of the mean first differences following exclusion of the first and last cohorts. More generally, Kupper *et al* have shown that when one of the age, period and cohort effects follows a straight line pattern, equating any two effects in {3.6} will lead to that effect being deemed unimportant according to the usual goodness-of-fit measures, with the consequence that the particular constraint will rotate the estimated linear pattern to a horizontal position [67]. A better understanding of the linear relation between the factors may be obtained by thinking in terms of the individual rotations of the effects of each factor on changing the slope of one, a concept introduced in 3.4.2.

Insufficient information on which to base the equating of two effects effectively reduces the viability of the method in analysing most cancer trends. However, a presentation and

interpretation that examines the parameters on allocation of drift to cohort by equating the first and last periods can be seen as an honest approach, and where appropriately used, not without some interpretative value.

Assuming such a slope for period may be less appropriate if gradual artefactual changes have occurred. Adami *et al*, for instance, reported in an article published in *The Lancet*, uniform increases in total cancer risk in successive cohorts in Sweden and "suggest a worrying pattern of increasing population exposure to carcinogenic influences" [206]. The solution obtained, on setting the first and last periods to zero in an APC model, naturally placed the drift with cohorts. Interpretation of regular trends as purely birth cohort could have been interpreted – on suitably allocating the drift to cohort – as period effects, hence their strong conclusions were somewhat unjustified, as remarked upon by Bonneux *et al* in a subsequent correspondence to the journal [207]. The difficulty allocating the drift estimate precisely, coupled with more general difficulties with interpretation, brings us to a related but more flexible approach advocated by Holford [66].

Figure 3.8a: Trends in breast cancer mortality in Canada, U.S. blacks and whites (trends in the latter shown as open white circles). Underlying slope drawn on the basis of two sets of constraints on cohort parameters from APC model: horizontal line: assuming (for U.S. whites) first and last parameters are equal, negative line: assuming second and second-last effects are equal (scan of source document [203])

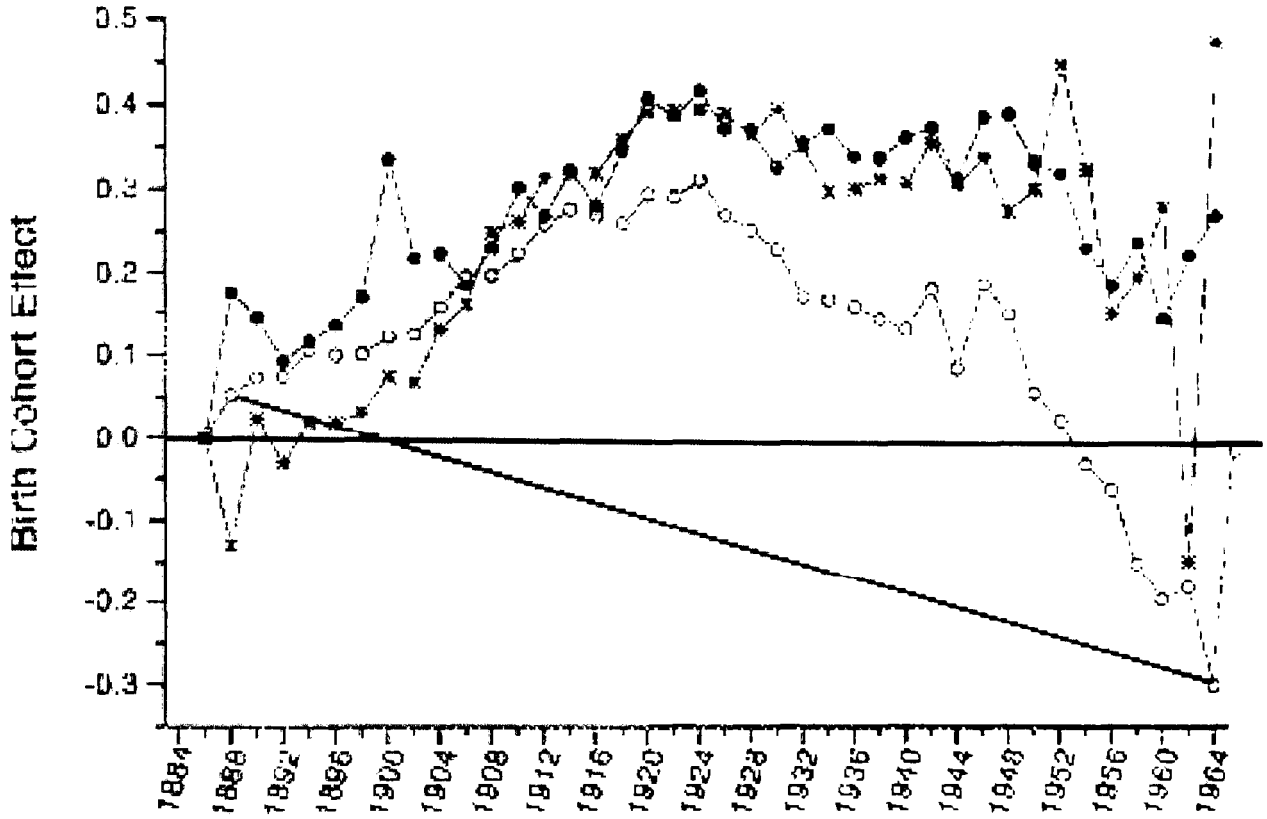
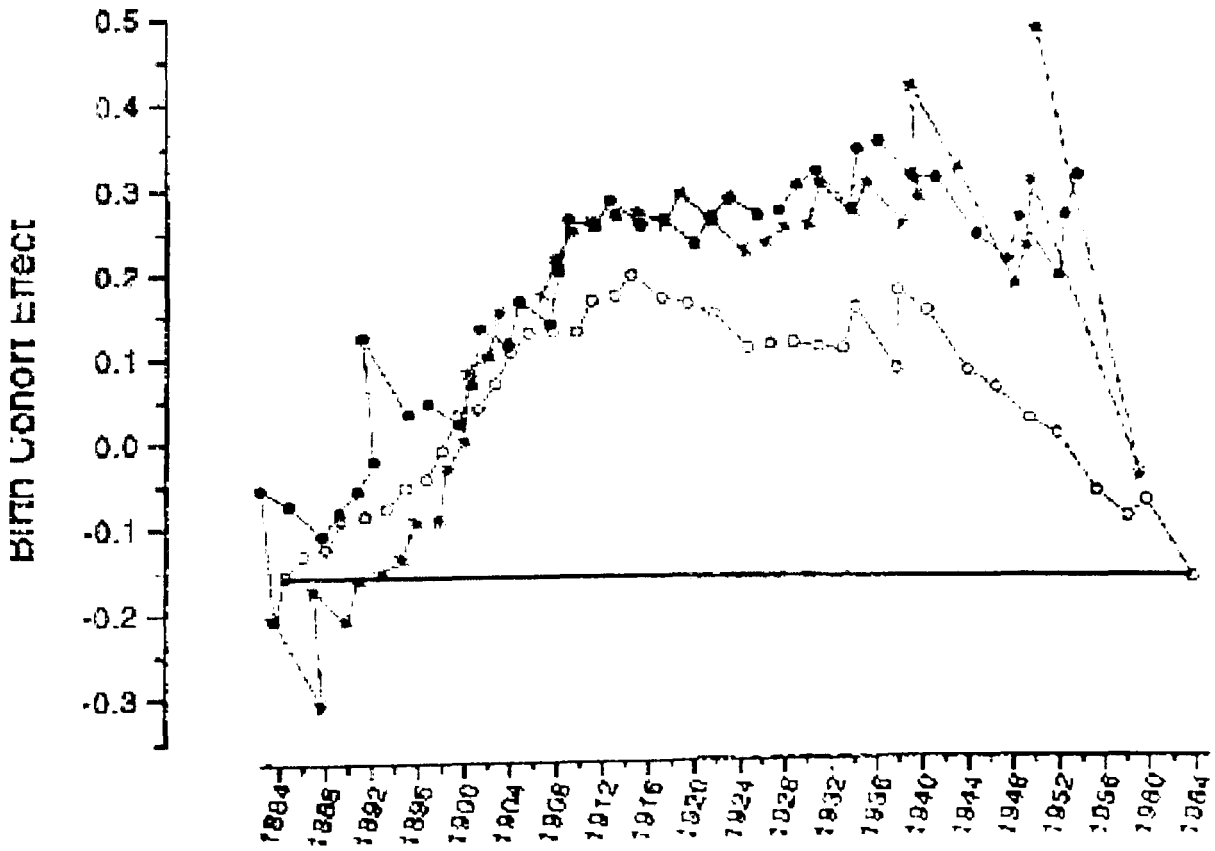


Figure 3.8b: Crude representation of counter-clockwise rotation of effects in Figure 3.8a (for U.S. whites, shown as open white circles) on assuming second and second-last effects of cohort are equal



3.4.2 Holford's approach to non-identifiability

Holford suggests that given the large number of parameters included in {3.6}, for simplicity it is sensible to highlight the non-identifiability in terms of two sets of parameters [66], one representing a linear function of the three slopes, and the other the identifiable curvature of each effect such that:

$$\alpha_i = \left(i - \frac{I+1}{2} \right) \times \alpha_L + \varphi_i \qquad \{3.13\}$$

$$\beta_j = \left(j - \frac{J+1}{2} \right) \times \beta_L + \varphi_j \qquad \{3.14\}$$

$$\gamma_k = \left(k - \frac{K+1}{2} \right) \times \gamma_L + \varphi_k \qquad \{3.15\}$$

where α_L, β_L and γ_L represent the linear terms for age, period and cohort, and φ_i, φ_j and φ_k the respective elements of curvature. The linear dependency $k = I - i + j$ generates slopes that are wholly arbitrary and inestimable, while the curvature terms are invariant to any set of constraints imposed [66-68,107,108].

There are a number of ways in which curvature can be represented in a model. Rogers noted that for any random pair of numbers (x, y) the linear function:

$$x\alpha_L + y\beta_L + (y - x)\gamma_L \qquad \{3.16\}$$

is invariant to any particular specific set of constraints enforced, in other words, it is an estimable function. Thus setting $x = y = 1$ implies $\alpha_L + \beta_L$ is estimable, while $x = 0, y = 1$ designates that, as has already been seen, the sum of the period and cohort $\beta_L + \gamma_L$ is also estimable (see 3.4.1.1.3). This term will be denoted *Holford's drift* as it is obtained from the full APC model. It is however usually a close approximation of the Clayton and Schifflers' net drift δ obtained from {3.11}.

Equation {3.16} implies that although the overall slopes are unrestricted, they do not vary independently. Holford [107,108,110] showed that fixing the value of any one slope leads to estimation of the other two:

$$\alpha_L' = \alpha_L + v \qquad \{3.17\}$$

$$\beta_L' = \beta_L - v \qquad \{3.18\}$$

$$\gamma_L' = \gamma_L + v \qquad \{3.19\}$$

Here $\alpha_L^{'}$, $\beta_L^{'}$, and $\gamma_L^{'}$ are biased representations of the respective slopes of age, period and cohort generated on fitting the APC model, with ν is an indeterminate constant that may result in increasing or decreasing trends of each slope. α_L, β_L, and γ_L then correspond to the true (non-identifiable) values of age, period and cohort. If one is prepared to make particular assumptions on one of the slopes, specifying the magnitude of the trend, or restricting the values that the slope can take, the values of the other two slopes, or the range of values, are immediately estimable, respectively. To ensure this, postulation as to the direction and magnitude of a slope should be ideally founded on biological or epidemiological evidence; otherwise, if erroneous, a bias in all of the effects is incurred. Holford and colleagues have mainly discussed plausible assumptions that restrict the values of the period slope (see 3.4.2.1).

The unique curvature terms for the three components can be determined by linear contrasts, based on the residuals from a simple linear regression [110]. Alternatively, one can partition the effects of the linear and curvature components in a design matrix with independent columns that yield a unique linear combination of parameter estimates. The partitioned design matrix X is:

$$\mathrm{X} = \left[1 \middle| \mathrm{A_L} \middle| \mathrm{A_C} \middle| \mathrm{P_L} \middle| \mathrm{P_C} \middle| \mathrm{C_L} \middle| \mathrm{C_C}\right] \qquad \{3.20\}$$

where $\mathrm{A_L}$, $\mathrm{P_L}$, $\mathrm{C_L}$ are the linear components and $\mathrm{A_C}$, $\mathrm{P_C}$, $\mathrm{C_C}$ and the curvature components of the age, period and cohort effects respectively. The regression parameters that correspond to X are denoted by the vector:

$$\pi = \left[\varphi_0 \middle| \alpha_L \middle| \varphi_i \middle| \beta_L \middle| \varphi_j \middle| \gamma_L \middle| \varphi_k\right]' \qquad \{3.21\}$$

To obtain the curvature terms of the design matrix, the curvature regression parameters are set to be orthogonal to the linear components, allowing a polynomial model of high order to be fitted in single variables for age, period and cohort. Holford's approach to generating such a matrix is given in an Appendix in his 1983 paper [66]. For I levels of age, the regressor variable defined in a matrix Z_{ij}^{*} has *i*th row and *j*th column are given by

$$Z_{ij} = \begin{cases} +1 & ,i = j \\ -1 & ,i = I \\ 0 & ,\text{otherwise} \end{cases} \qquad \{3.22\}$$

The linear trend can be found for age as before with the column vector L denoted by

$$L_i = i - \frac{1}{2}I - \frac{1}{2} \qquad \{3.23\}$$

The matrix orthogonal to L that provides the curvature elements is:

$$\mathrm{Z}^* = \mathrm{Z} - \mathrm{L}(\mathrm{L}'\mathrm{L})^{-1}\mathrm{L}'\mathrm{Z} \qquad \{3.24\}$$

Of interest are the overall curvature components of age (φ_i), period (φ_j) and cohort (φ_k) rather than particular orders of curvature, and these may be obtained by multiplying the matrix orthogonal to the linear component with the vector containing the regression parameters:

$$\varphi_i = A_C.\alpha_i \qquad \{3.25\}$$

$$\varphi_j = P_C.\beta_j \qquad \{3.26\}$$

$$\varphi_j = C_C.\gamma_k \qquad \{3.27\}$$

Individual categories of age, period and cohort are calculated by adding together the corresponding linear and overall curvature components as in formulae {3.13}, {3.14} and {3.15} respectively. The method of assuming a slope (or slopes) for one factor and its implications to the study of cancer trends will now be discussed.

3.4.2.1 Specifying an overall slope

Holford [98] demonstrates that hypothesising as to the true gradient of one of the slopes in {3.17} through to {3.19} leads to fixed estimates of the slopes of the other two components (in terms of the identified constant v). This has an important application in APC analysis; if it is reasonable to utilise existing biological or epidemiological arguments to allocate a particular value, or range of values to one slope, the infinite set of possible values of the parameters of all three components will be limited to a range that is consistent with possible explanations regarding the temporal nature of the observed trends.

If the particular specification of the slope is incorrect, the estimates of each slope are biased; selecting a range of slopes however leaves some margin for error, allowing the researcher to contrast the age, period and cohort effects, based on their particular preference(s) for the fixed slope, with other plausible specifications. The technique highlights the fundamental problem with APC modelling: while the departures from linearity for age, period and cohort are unique and local curvature identifiable, the slopes are not, so that the overall trend is entirely dependent on these unknown quantities that can take on an infinite range of values. As the three slopes are mathematically interrelated however, an

arbitrary specification of just one of them leads immediately to an identifiable but, necessarily, subjective solution.

The most commonly applied technique involves making assumptions regarding the slope of the period component of the trends. Holford describes the justification of a procedure that imposes a zero period slope [110], as used in the systematic study of incidence trends in Connecticut 1940-79 [208]. The choice of restriction on period was motivated by: (1) the necessity to leave age in the model unaffected given its clear biological importance, leaving a choice of either period or cohort to be inconsequential; (2) of the two remaining effects, empirical evidence pointed to cohort effects being more important for trends in incidence; (3) assumptions on period slope at least allowed estimation of period curvature, and therefore the procedure were less restrictive than a two-factor modelling approach. The methods described below have been used extensively by Holford and colleagues, mainly in a series of articles describing trends in the incidence of various cancers in Connecticut (see 3.4.2.1.2 and 3.4.2.1.4).

3.4.2.1.1 Zero period slope

The assumption of negligible (linear and non-linear) period effects in describing the AC model of {3.10}, and the equating of the first and last period effects of {3.6} in an attempt to obtain a negligible linear period effect, has been respectively discussed in 3.4.1.1 and 3.4.1.2. In the current context, the requirement of $\beta_L = 0$ places no restriction on φ_j, while the average linear trend should consistently provide a more accurate description of the underlying partition of a zero slope to period and a slope equalling Holford's drift to cohort.

From {3.18}, $v = \beta_L - \beta_L^{'}$ and on assuming a true period slope of zero, $v = -\beta_L^{'}$, the negative of the linear term for period, obtained from the vector described in {3.21}. Imposing the respective value for v in {3.17} and {3.19} therefore provides unique estimates for the slopes for age such that $\alpha_L = \alpha_L^{'} - v$ and for cohort, $\gamma_L = \gamma_L^{'} - v$, where $\gamma_L = \beta_L^{'} + \gamma_L^{'}$ is Holford's drift. A program written by the author of this thesis in **R** [209] demonstrates the technique in practice, in the study of bladder cancer incidence in Italy [68] (Appendix 3).

3.4.2.1.2 The zero period slope method in practice

Zheng *et al* assumed a period slope of zero in studying adenocarcinoma of the cervix incidence using SEER data according to race [210]. An explanation for the preference is not given, although it would presumably be related to the birth cohort phenomenon driven by changing sexual behaviour and the prevalence and distribution of oncogenic types of HPV, alongside a relative inability to detect cervical adenocarcinoma using cytological screening

(see Chapter 4). The authors concluded that the trends were cohort-driven, starting in generations born in the mid-1920s, an observation seen in blacks and whites, although the increase was considered stronger in white women.

Zheng *et al* applied the same constraint in studying bladder cancer incidence between 1935 and 1992 in Connecticut, justifying the assumption on the grounds of strong birth cohort effects in previous findings of incidence trends in bladder and other tobacco-related cancers [211]. The authors observed that cohort effects were increasing in generations born before the mid-1930s, but for generations born thereafter, a levelling or decline in rates was apparent in both men and women. Although an increasing period slope (e.g. via an increasing diagnosis of benign tumours) may have altered the interpretation, such an effect was dismissed, on the grounds that it could not explain the long-term increases in the regular trend.

3.4.2.1.3 Restricted ranges of period slopes

If a specific identification of one slope is considered of insufficient plausibility, an obvious extension imposes a constraint on the range of possible values for one of the slopes, with the range determined, where possible, by existing biological or epidemiological knowledge. As with the zero slope method, period effects are most often considered for restriction, as it is considered the least influential of the three effects. The method is however a less arbitrary solution given that it draws attention to the lack of identifiability – the overall cohort trends often adopt very different courses even with relatively minor adjustments to the magnitude of the linear period slope.

3.4.2.1.4 The range of slopes method in practice

Effects obtained on specifying a choice of possible slopes are derived in the same way as the zero slope procedure. In proceeding, possibilities regarding the choice of slopes are dependent on the availability and degree of persuasiveness of background knowledge that one can bring to bear to provide explanations for the characteristics of the trend. The more precise the specification of the range, the stronger the assumptions regarding one or more of the slopes must be.

Holford *et al* in studying incidence trends of Non Hodgkin lymphoma (NHL) in Connecticut 1935-89 anticipated that the increases were partly related to diagnostic practices, and thus trends in age, period and cohort were examined according to various period slopes that took account of the extent of the artefact: slopes of 0, +0.1, +0.2, and +0.3 were considered [212]. The magnitude of a given slope relates to the unit of time of the period effect, five years in this study, and hence a slope of +0.1 represents a 2% increase in gradient per

annum. The level of inference of the subsequent effects is dependent on the degree of belief that the increases in the drift are due to gradual period increases. The method generates hypotheses depending on a particular choice of slope and may reveal interesting cohort-specific observations irrespective of extent of attribution of drift to period.

For some cancers, one may wish to assume that an overall negative trend by period or cohort is not feasible and bound the range of the slopes accordingly. Wickramaratne *et al* in a temporal study of the trends in major depression in the U.S. showed that the joint assumptions of period-specific increases $\beta_L \geq 0$ and cohort-specific increases $\gamma_L \geq 0$ can be addressed [213]. Adding γ_L to both sides of the first inequality gives $\beta_L + \gamma_L \geq \gamma_L \geq 0$ where $\beta_L + \gamma_L$, as already shown, is Holford's version of drift and therefore estimable. Similarly, $\beta_L + \gamma_L \geq \beta_L \geq 0$ and $\alpha_L + \beta_L \geq \alpha_L \geq \alpha_L - \gamma_L$ specify the age and period slopes respectively, with $\alpha_L + \beta_L$ and $\alpha_L - \gamma_L$ also estimable functions. The authors suggested that the method could be considered for investigating trends in cancer, where it is known *a priori* that time trends are biased upwards due to improving medical care and diagnosis. Trends in thyroid cancer, melanoma and NHL are obvious candidates for such statistical treatment, yet the method has been rarely put into practice.

Otherwise, less certainty as to particular attributes of the linear trend for period, leads to a safer tactic whereby one adopts a family of curves that encompasses the possibility of negative, zero and positive slopes for one of the factors (usually period). In a number of studies examining histological trends of cancer incidence in Connecticut by Zheng *et al* [214-216], the authors obtained identifiable solutions by fixing the period slopes through the range –0.2 (+0.1) +0.2 for investigating the age, period and cohort effects for oesophageal cancer [216], and the range –0.2, 0.0, +0.2 for similar enquiries regarding the trends of stomach and lung cancer [214,215].

3.4.2.1.5 Other possible restrictions

One option not addressed by Holford's group involves utilising a slope for age that satisfies what is known regarding the age structure of some cancers. From the 1950s, characteristic curves for different forms of cancer have been established [61,166,217-222]. Prior to screening, the age-specific incidence rates of invasive cervical cancer for instance, have been shown to be similar in shape irrespective of the international population examined [221]. In Chapter 4, estimates of age, period and cohort effects of cervical squamous cell carcinoma incidence are obtained on assuming a slope for age that mimics this unique age structure. Fixing age "frees" period and cohort – slopes of these effects are not dependant

on *a priori* assumptions – an independent assessment of the impact of cytological screening against a background of changing generation-specific risk can be made.

For hormone-dependant cancers in women, Pike has related the rate of change in the age-specific incidence rates to *effective tissue age* [220,222,223], and has shown the correspondence in age curves of breast, endometrium and ovarian cancers on setting the rate of *tissue ageing* to a different constant level according to the period of a woman's reproductive life [220]. Consequently, there is potential for seeking solutions that assume a particular slope in keeping with what is known regarding the underlying age structure in terms of the disease processes. This approach is partially applied in Chapter 5, whereby the age curves of endometrial cancer incidence are fixed within a postmenopausal age range in order to assess the period and cohort trends in European countries.

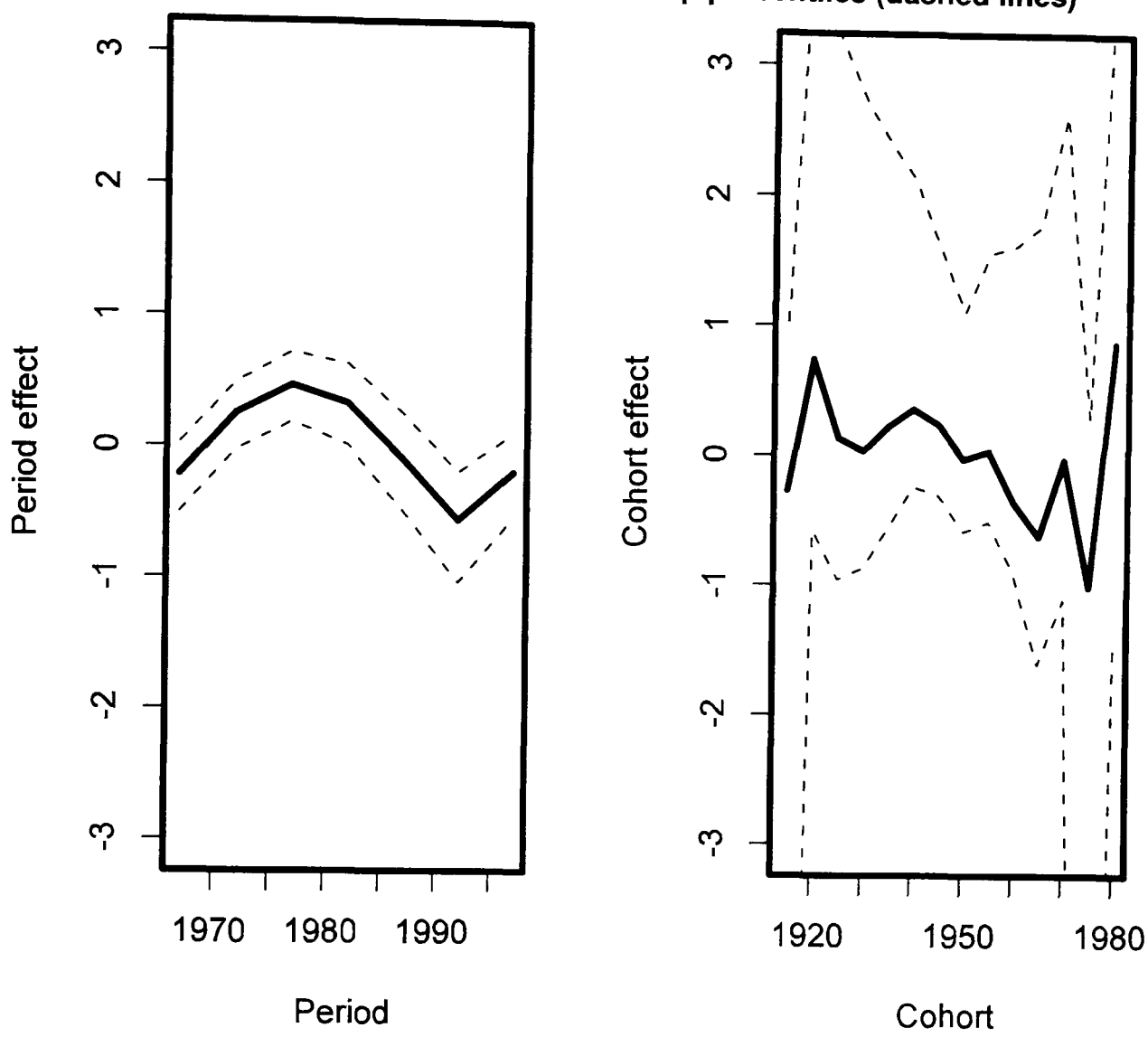
3.4.2.2 Attaching confidence limits to Holford's estimates

There is no easy way of obtaining standard errors using the above modelling approach. The regressions on age, period and cohort are complex functions of the underlying dataset and the resulting parameters therefore have virtually intractable standard errors. One might follow the suggestion of Carstensen and Keiding who advocate a method that fits period to the residuals of an age-cohort model [224]. Their method therefore prioritises time scales, ranking period lowest, but does allow the standard errors to be readily obtained.

A relatively simple way to gauge the variability in Holford's estimates is to obtain confidence intervals based on *bootstrapping* percentiles [225]. The bootstrap is now a common procedure for estimating the sampling distribution of an estimator by resampling with replacement from the original sample [226]. To illustrate how the approach works in practice, a 95% confidence interval for the period and cohort effects obtained from Holford's method is shown in Figure 3.9 using testicular cancer mortality data from Norway 1965-99. The success of treatment from the early-1970s on certain forms of testicular cancer would suggest that period effects should dominate the mortality trends and a cohort slope of zero is assumed in this example (see Chapter 6 for further exploration).

The bootstrap interval was constructed in **R** [209] assuming that each cell followed a binomial distribution for which the rate and the number of person-years at risk represented the probability of success and number of trials, respectively. The original mortality data were resampled 1000 times and the 2.5 and 97.5 percentiles of each of the curvature components of the 1000 sets of estimates of φ_j and φ_k were selected to obtain the percentile interval depicted in the Figure.

Figure 3.9: Period and cohort effects, based on Holford's approach (solid line) and 95% confidence limits, based on bootstrap percentiles (dashed lines)



3.4.3 Restriction to estimable functions

Several authors, notably Holford [66,98,107,108,110] and Clayton and Schifflers [68] have stressed the importance of solutions that reveal the mathematical dichotomy of overall slopes that cannot be uniquely determined, and their deviations, estimates of the curvature that can. Each factor is characterised by a slope that may take on a wide range of values, while maintaining a set of identical deviations. Clayton and Schifflers, after discussing briefly two sensible parameterisations (Holford's zero period slope method (discussed in 3.4.2.1.1) and their own simpler (but potentially imprecise) mean first differences approach (3.4.1.2.2), propose a final preference, a reparameterisation that provides unique estimates of each effect, regardless of the particular set of constraints imposed. This ensures identifiability by focusing solely on a summary of estimable curvature and in doing so, avoids the need to make arbitrary statements regarding the linear trend. The approach leans to the conservative side with regards interpretation – trends are not informed by possible values of

the slopes. Certainly the proposal remains however one of the more statistically valid solutions to the problem [227].

3.4.3.1 Second differences

A unique set of age, period and cohort parameters can be obtained by utilising the fact that on an antilogarithmic scale, non-linear effects can be expressed as relative risks between adjacent age, period or cohort levels [68]. Using cohort parameters from an APC model as an example, second-order effects identify *changes in the magnitude* of trends by comparing the position of a particular cohort relative to the preceding and subsequent cohort. Second differences have the useful property that the estimated cohort values are affected only by neighbouring data [68]. On an additive scale, for $k = 2,3,...,K-1$ the c_k^* are the second differences:

$$C_2^* = (C_3 - C_2) - (C_2 - C_1) = C_1 - 2C_2 + C_3 \qquad \{3.28\}$$

$$C_3^* = (C_4 - C_3) - (C_3 - C_2) = C_2 - 2C_3 + C_4 \qquad \{3.29\}$$

$$\vdots$$

$$\vdots$$

$$C_{K-1}^* = (C_K - C_{K-1}) - (C_{K-1} - C_{K-2}) = C_{K-2} - 2C_{K-1} + C_K \qquad \{3.30\}$$

On a multiplicative scale the γ_k^* thus represent adjacent relative risks:

$$\frac{\gamma_3/\gamma_2}{\gamma_2/\gamma_1}, \frac{\gamma_4/\gamma_3}{\gamma_3/\gamma_2}, ..., \frac{\gamma_K/\gamma_{K-1}}{\gamma_{K-1}/\gamma_{K-2}} \qquad \{3.30\}$$

Decelerations in the trend ($\gamma_k^* < 1$, concave curvature) provide evidence that increasing rates are slowing down with time, or declining rates are decreasing more rapidly with time. Conversely, accelerations ($\gamma_k^* > 1$, convex curvature) indicate either a reduction in the pace of the decreasing rates, or the speeding-up of increasing rates. γ_k^* approximating unity indicate that local trends are unchanging, or relatively linear. Abrupt increases or decreases should be considered most important, with values close to unity indicative of regular linear increases or decreases.

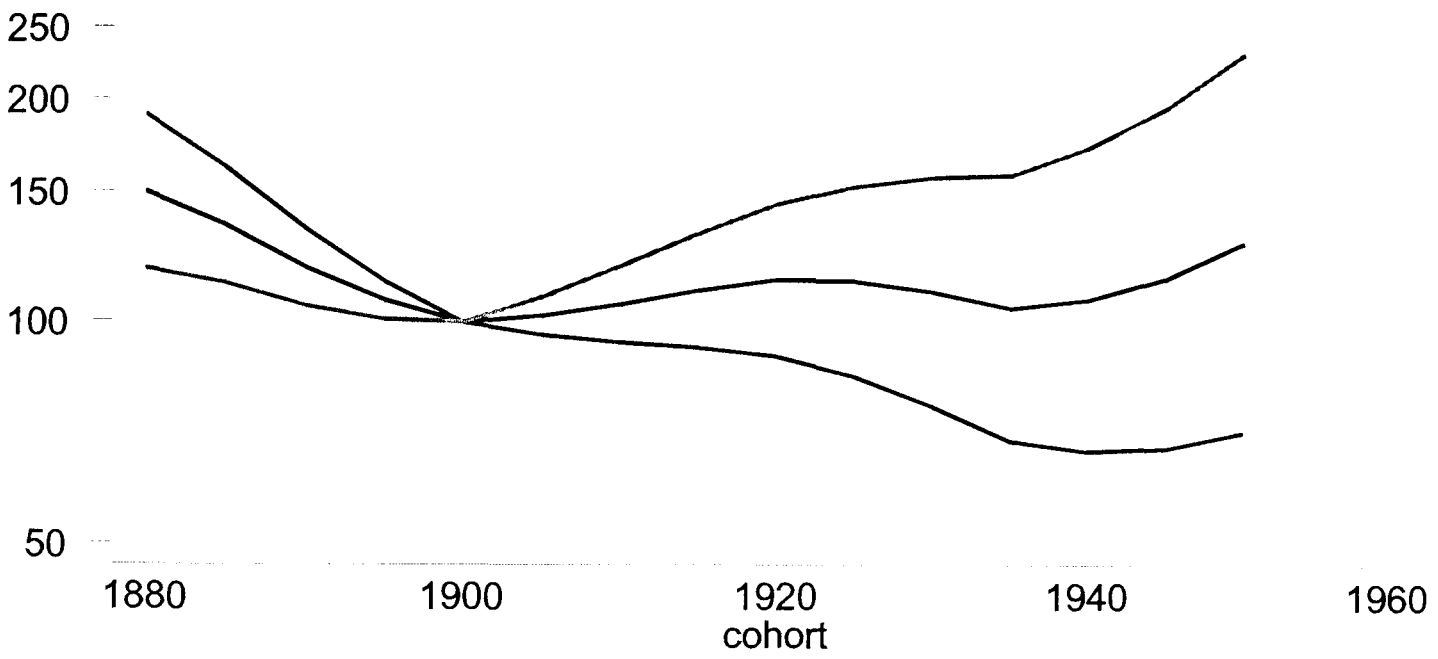
Second differences may be interpreted more readily when graphically presented alongside the observed and fitted rates – indications of local departures from linearity, acceleration or decelerations in the cohort trend can be substantiated on inspection of a cohort graph depicting trends in cohorts as they reach the same age. 95% CI based on the calculation of

the standard errors serve to indicate the precision of the model parameters, and in particular, the considerable caution required in interpreting estimates of trend curvature representing the youngest cohorts.

Despite their advocacy by Clayton and Schifflers, few examples of their application occupy the cancer trends literature (e.g. [228,229]). Certainly the concept of second differences is somewhat difficult to grasp, given that they constitute the relative risk of first-order relative risks based on two adjacent cohorts. Perhaps the main problem is the low level of insight that can be gleaned from such a conservative approach, particularly if interpreted without prior knowledge of the observed rates or possible sets of model effects. Figure 3.10 shows the second differences and sets of model estimates for cohorts using the breast cancer data example in Japan from the second of the APC articles by Clayton and Schifflers [68]. The accelerations in risk in successive cohorts born since the turn of the century are detected by the second differences (abrupt increase around 1900, $\gamma_k^* > 1$), although a display of possible model estimates aids interpretation. The observed trends in the C by A plot shown in Figure 3.3 suggest the possibility of cohort-specific increases from 1900. A deceleration around 1920, and a further acceleration in 1935 is implicated in the model effects in Figure 3.10. This observation, if real, may be related to a time window between the wars for which risk was not increasing in pre-menopausal women.

More generally, a presentation that is restricted to curvature effects without knowledge of the linear trends is considered by some to be of limited use, given the obvious lack of basic information regarding even the direction of the trend [67]. Tango and Kurashina however demonstrated that by focusing on estimable curvature, some insights into trends in mortality from major diseases in Japanese men were possible [101], particularly the accelerations in risk of diabetes, liver cirrhosis and ischaemic heart disease in cohorts born 1925-40, the same cohorts for which an acceleration in breast cancer mortality was noted by Clayton and Schifflers using the same approach [68]. Tango and Kurashina also suggested examining the mean of the adjacent second differences so as to detect changes that may have occurred within the five years that overlap between two successive cohorts [101].

Figure 3.10: Second differences and three sets of APC model estimates dependent on choice of constraint, as presented by Clayton and Schifflers' in their second APC paper, 1987. Breast cancer, Japan 1953-77 (Source: [68])



3.4.3.2 User-defined identifiable contrasts

Tarone and Chu extend the use of contrasts offered by Clayton and Schifflers [68], developing a method that allows a priori hypotheses to be tested [103]. The authors define γ_{L1} and γ_{L2} to be the slopes of the linear trend in two epochs such that for cohort indices $c_1 < c_2$, such that:

$$\gamma_c = \theta_1 + \gamma_{L1} c \quad \text{for } c \leq c_1 \qquad \{3.31\}$$

$$\gamma_c = \theta_2 + \gamma_{L2} c \quad \text{for } c \geq c_2 \qquad \{3.32\}$$

where θ_1 and θ_2 are the intercepts of the two cohort lines. They show that while the slopes for the transformed parameters may not be identifiable, the *difference* in the slopes $\rho_1 - \rho_2$ is an invariant function. Any comparison of the slopes between two groups of cohort is estimable, but relies on a sound basis of specific epidemiological enquiries to construct hypotheses *a priori*, that avoid merely data dredging and multiple testing.

Tarone and Chu [103] examine the slopes of the linear trends in breast cancer mortality in the U.S. in terms of evaluating pre-defined contrasts. In particular the contrast:

$$C_1 = \gamma_{k+7} - \gamma_k - (\gamma_{h+7} - \gamma_h),\ h+7 \le k \qquad \{3.33\}$$

is analogous to the local curvature obtained using the second differences [68]. Similarly, in an approach analogous to an earlier study involving nonparametric methods [102] (see 3.4.5.4), all relevant cohorts make a contribution to the linear contrast comparing the slopes in two blocks of eight cohorts:

$$\begin{aligned} C_2 = {} & 7\gamma_{k+7} + 5\gamma_{k+6} + 3\gamma_{k+5} + \gamma_{k+4} - \gamma_{k+3} - 3\gamma_{k+2} - 5\gamma_{k+1} - 7\gamma_k \\ & - (7\gamma_{h+7} + 5\gamma_{h+6} + 3\gamma_{h+5} + \gamma_{h+4} - \gamma_{h+3} - 3\gamma_{h+2} - 5\gamma_{h+1} - 7\gamma_h) \end{aligned} \qquad \{3.34\}$$

Similar contrasts can be constructed for determining the change in age and period slopes. Robertson and Boyle applied the method (and the same cohort contrast C_2) to compare breast cancer incidence and mortality trends in Scotland [230]. They showed that cohort effects post-1900 were similar for both incidence and mortality, and that increases in birth cohort mortality after 1925 match those seen in the previous study of the U.S. and Japan. Robertson and Ecob recently used the method to compare overall cancer mortality in men and women in later versus earlier periods of death, and in cohorts defined by their dates of birth, before or after World War II, stratified by U.K. region. They demonstrated that there were no substantial differences across regions in terms of the curvature of the three effects, with evidence of decelerating mortality rates in both period and cohort-specific terms in women, but not in men [231].

3.4.4 Mathematical solutions

The approaches to circumventing identifiability considered in the last two sections have involved either the bringing to bear of external information to provide a solution or range of solutions (3.4.2), or a reparameterisation that is strictly invariant to any proposed solution (3.4.3). Both methods have their merits: the former at least removes some of the arbitrariness in selecting solution(s), should the method have groundings in biological or epidemiological plausibility, the latter focuses attention and interpretation only on what is

identifiable. Two methods are outlined below that employ mathematical approaches to obtain unique estimates of the linear slopes of age, period and cohort, thus solving, or appearing to solve, the identifiability problem.

3.4.4.1 Penalty function approach

The approach proposed by Osmond and Gardner uses an identifiability constraint obtained by finding the best agreement between two-factor models and the full model [96]. The authors find values for the age, period and cohort slopes α_L^*, β_L^*, and γ_L^*, by estimating $\tilde{\nu}$, the unknown constant introduced in equations {3.17}–{3.19} estimated in this method on minimising the penalty function, the sum of the squares of the differences between the parameters of each of the three two-factor models and the full three-factor model weighted by a goodness-of-fit measure, such as the deviance [112]. Clayton and Schifflers describe the Osmond-Gardner method as a partition of the drift between period and cohort in a ratio that depends on the relative magnitude of the non-linear effects [68]. The value of $\tilde{\nu}$ obtained is used to "correct" an arbitrary three-factor model, much in the same way as the imposition of an assumed slope identifies all effects (see 3.4.2.1).

The solution obtained depends on the number of levels of each factor, the parameters in the two-factor models and their relative goodness-of-fit [107], and both Clayton and Schifflers [68] and Holford [107] have argued that the solution obtained remains an entirely arbitrary one, given the failure to allow for biological plausibility. Clayton and Schifflers also note that in situations where both the AP and AC models fit the data (and for which the AD model may be a better realisation), much of the drift will be sent to the cohort effects, simply because it has more parameters.

Decarli and La Vecchia proposed a similar procedure to the penalty function approach – they minimised a weighted sum of the squared distances – and also provided a routine for implementation in GLIM [120]. Perhaps as a result of the availability of a ready-made program, the method has found numerous applications in cancer studies in the last 20 years [232-234]. The ability to find a single solution appears inviting, although justification of the method is not always apparent. Authors of a study of trends in six European countries indicate the approach was chosen because of "its applicability to large numbers of routinely produced datasets and due to ease of interpretation" [234]. One might however argue that the arbitrary partition of drift is disadvantageous in making meaningful comparisons of trends between populations.

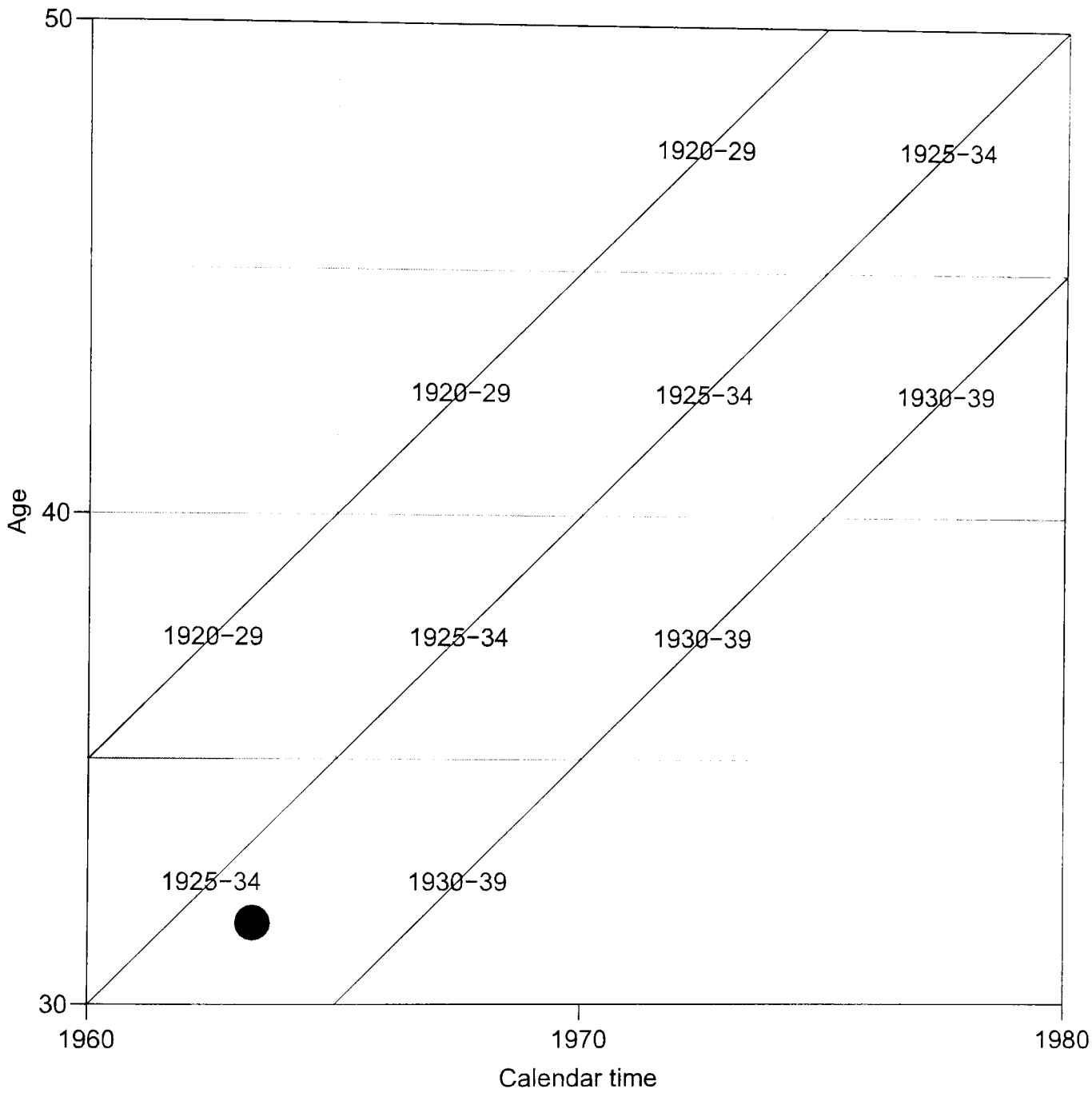
3.4.4.2 Individual records approach

Robertson and Boyle describe a method that exploits the additional information available from individual records (lacking in grouped data) to solve the identifiability problem [100]. By forming a two-way table of age and period based on individual data rather than aggregates, the cohorts minimally overlap, as one may assign each case to their year of birth. Each cell of a five-year age by period classification can be split into two birth cohorts spanning five years. The 10-year overlapping cohort identified with midpoint 1930 in Figure 3.4 can be diagonally partitioned into unique cohorts with all cases in the lower triangle of Figure 3.11, born between 1925 and 1929, and all cases in the upper triangle born between 1930 and 1934. Cases on the diagonal are still overlapping, but divided equally between the two triangles [100].

Using the same notation for age and period above, the indices for cohort, k^*, are now almost free of overlap, being represented in age group i and period j by $j-i+I$ in the lower triangles and $j-i+I+1$ in the upper triangles. The method provides a unique set of parameters when fitted in any statistical package, as the identifiability problem has been solved given i, j and k^* break the linear dependency between the three factors [107].

The errors in the approach were rapidly forthcoming after its publication, taken up by numerous authors including Clayton and Schifflers [68], Osmond and Gardner [235], Tango [236] and others [107,108,110,224,237], and acknowledged by the original authors themselves [111,112,238]. The problem lies in the indices being unrepresentative of their respective times [107]; assuming age and period are uniformly distributed across a single cell, the 10-year cohort will in upper triangles disproportionately represent older ages diagnosed towards the start of the period, and in lower triangles, younger ages diagnosed later in the period. For a uniform age distribution across the age-period cell represented by mean age index i, Holford [107] has shown that the mean ages for the two triangles (as depicted in Figure 3.11) are $i-\frac{1}{6}$ (lower) and $i+\frac{1}{6}$ (upper); for period $j+\frac{1}{6}$ (lower) and $j-\frac{1}{6}$ (upper); and cohort $k+\frac{1}{3}$ (lower) and $k-\frac{1}{3}$(upper). In APC modelling, the mean values of age, period and cohort therefore must be used, since in any part of the Lexis diagram, k must equal $j-i+I$. On refitting the model with unbiased indices for all three factors, the identifiability problem re-emerges. In Figure 3.11, the correct mean values for the three factors in the lower triangle of the lower left age-period cell are given.

Figure 3.11. Lexis diagrams depicting near non-overlapping birth cohorts for upper and lower triangles of each age-period cell; the central values in the lower triangle of the bottom cell are $31\frac{2}{3}$, $1963\frac{1}{3}$ and $1931\frac{2}{3}$, for age, period and cohort, respectively.



3.4.5 Other statistical approaches

There a number of other methods that do not correspond to the four categories listed in the beginning of section 3.4. These are briefly described below.

3.4.5.1 Non-linear models

The APC model of {3.6} does not take account of the possibility of interactions between the factors, for example, where period effects are dependant in some way on level of age, unrelated to the special form of interaction that constitutes a cohort effect.

A prime example relates to time trends in mortality from multiple myeloma, a cancer for which diagnosis is largely dependant on the availability of medical facilities and the intensity of laboratory testing [239,240]. Velez *et al* observed that in England and Wales, 1953-1977 [240] (updated and extended to international populations by Cuzick [241-243]), increases in death rates were steepest in the 1950s, the period in which diagnostic advances were greatest. Further, the most rapid increases were observed in men and women aged over 70; rates were less rapidly increasing in younger age groups in England and Wales, and rather stable in other Western countries [240-243]. Cuzick considered this observation an example of an age-dependant period effect masquerading as a cohort effect [243]; artefactual forces acting near the time of death (such as diagnostic improvements and greater access to medical care among the elderly) were a more plausible explanation than a generational effect whereby some exposure or exposures exclusively affected older persons [242].

Studies in the late-1970s and early-1980s by Moolgavkar *et al* [93] established that various interactions over and above the AC model were estimable and in some instances could be given a biological interpretation. In particular, the model introduced by Moolgavkar *et al* and used by James and Segal in the study of prostate cancer mortality [95] extended the APC model to the form:

$$E[\log r_{ij}] = \mu + \alpha_i.\delta_j + \beta_j + \gamma_k \qquad \{3.35\}$$

The effect of age α_i is included as multiplicative factor with period denoted as δ_j, with the period and cohort effects as in {3.6}. This is a non-linear model that does not suffer from non-identifiability; the interaction enables the age curves across periods to vary by a fixed multiplicative factor [68].

The drawbacks are the obvious difficulty in interpretation, the possibility of introducing unrealistic assumptions, and the computational difficulties in obtaining convergence that are sometimes associated with such models. Further, if {3.6} provides a reasonable fit i.e. $\delta_j \approx 1$, {3.35} reduces to {3.6} and the identifiability problem re-materialises [68,108]. Tango and Kurashina [101] and Lee and Lin [244] have used similar approaches to the above, although the former authors focused on curvature effects, and the latter introduced a more complex interaction in the APC model such that $E[\log r_{ij}] = \mu + (\alpha_i + \gamma_k.\delta_i).\beta_j$.

Fienberg and Mason have studied possible extensions to the full model with polynomials and outlined those interactions that do not suffer from the identifiability problem [106]. As Holford states however, interpreting interactions from higher-order models in light of the identifiability problem usually leads to quite a complex interpretation [108].

3.4.5.2 Using external data

Holford has reviewed approaches that introduce external information to achieve an identifiable solution without the need for arbitrary constraints [108]. One tactic is to specify the functional form of age using the multistage models introduced by Armitage and Doll [166]. In its multiplicative form, the effect of age has the same distributional form as the Weibull hazard such that $A_i \propto i^{\eta}$, where η represent the number of stages minus one. In log-linear terms $\alpha_j = \eta \log(i)$, and η is unknown, requiring estimation from the data. The factors are no longer linearly dependant, but the usefulness of the model will be dictated by its ability to correctly specify the functional form of age [108].

Although many cancer types were observed to conform to the simple patterns described by the Armitage-Doll model, systematic departures soon emerged for certain cancers, and a number of modifications reflected this, such as the two-mutation model, have been proposed [245,246]. Holford applied the model and some of the proposed extensions to lung cancer trends in Connecticut 1935-88 [247]. Models that included polynomials for age and allowed the age effects to differ according to susceptibility fitted well.

More recently, Luebeck and Moolgavkar fitted multistage models to colorectal cancer in the U.S. by fitting the age-specific incidence as a two- to five-stage clonal expansion model [245] that mathematically incorporated the sequence of genetic events that define the main pathway to colorectal cancer occurrence. Adjusting for period and cohort effects, the authors suggested trends in colon cancer could be attributed mainly to the effect of calendar period [248]. The models were also informative regarding the prospects for prevention – the administration of nonsteroidal anti-inflammatory drugs was reported to be very efficient at lowering colon cancer risk substantially – even when the intervention began later in life.

Trends in risk factors have been used as a more direct measure of time than the surrogate measures of period and cohort. Brown and Kessler predicted lung cancer mortality in the U.S. to 2025 by incorporating changes in the composition of cigarettes – average tar exposure over each calendar period allowing for a sufficient time lag – adjusting for age and cohort [55]. Holford points out that the successful use of external data in this model relied on the non-linear nature of the period effects; had levels of tar changed with calendar time in a linear fashion, a dependency with age and cohort would have once again arisen [108]. Stevens and Moolgavkar derived estimates of the relative risk of lung and bladder cancer due to smoking in England and Wales, by incorporating a function of the proportion of smokers and the cumulative number of cigarettes smoked, as a cohort effect, adjusted for period and age [249]. Such approaches have the potential to produce a unique set of

parameters that are plausible, although the effects of the two 'free' factors will be determined by the underlying accuracy of the data used to fix the third.

3.4.5.3 Fixing age curves across populations

Day and Charnay proposed an analysis involving several registries and fixing the age-specific curves in order to separate the effects of period and cohort [65]. Should common age curves give a good representation – the adequacy of the assumption can be tested – the authors recommend inclusion of registries considered to have either minimal period or cohort effects. By doing so, period and cohort factors can be uniquely identified in other registry areas where both effects are deemed important, and for which a plausible solution is reached on assuming a fixed biological age curve.

In studying trends in lung cancer in Slovenia and Finland, Day and Charnay assumed that period effects were negligible in Slovenia and fitted a common age curve to the data from the two countries, thereby enabling period and cohort effects to be examined in Finland [65]. Clayton and Schifflers were critical of an approach that fixed the age structure across registries however, citing the likelihood that populations in different localities may have experienced differing exposure profiles and subsequently, a heterogeneity in their respective age patterns [68].

Boyle *et al* extended Day and Charnays' approach, exploring incidence trends in malignant melanoma in a national registry area (Norway) but allowing for sex and subsite as well as age, period and cohort factors [94]. Of particular interest was the lack of statistical associations in the interactions between age and the other factors, enabling the fixing of age curves across such strata, thus ensuring identifiability. The authors suggested two possible interpretations: one that involved a common age curve but different cohort trends for each subsite for both sexes, and another for which there was a common cohort curve that varied by age, sex and subsite.

3.4.5.4 Non-parametric methods

Tarone and Chu described a method that allowed them to examine mortality trends of breast cancer mortality in the U.S., without the need for a formal model specification [102]. The nonparametric approach compares age-specific rates between adjacent effects of cohort (or the other factors), on the basis of the sum of the negative decreases, constructing a permutation test of the null hypothesis that there is no cohort trend. The exact mean and variance for n comparisons in the same age group is $n/2$ and $(n+2)/12$, respectively. The expected number must take into account the range of possible comparisons in any

particular diagonal, given the number of rates associated with each cohort varies from the extreme cohorts to their maximum number along the middle diagonals (see 3.3.1).

3.4.5.5 Splines and curvature

Most analytic strategies, from Case's article in 1956 [71] onwards, have focused on an age-period table with equally-spaced five-year age and five-year period groupings, at least in part reflecting the availability of the data from vital sources. The categorical approach has a certain amount of flexibility; but where there are small numbers involved, it may be desirable to smooth the curvature either by the use of polynomials or splines [110]. Heuer cited the loss of information at the aggregated level and the lack of possibilities in examining interactions as motivation to analyse the data at a more detailed level, for example in one-year intervals, using regression splines [250]. The possibilities to implement such an approach is dependant on the resolution of data available. Unequally-spaced analyses of trends, for example using single calendar periods and five-year age group are feasible approaches to data pertaining from vital sources, so long as the indices of age, period and cohort are corrected to represent their respective times [66].

Spline functions are functions that represent polynomials that are joined together at knots (pre-defined points), with continuous derivatives at the knots. Carstensen and Keiding have reviewed the various forms of splines available [224]. They often take the form of cubic splines, but modifications of cubic splines such as restricted cubic splines and natural splines, force the trends to be linear outside the outer knots. The authors noted the need to specify the knots *a priori* and recommended the use of natural splines, as they are considered most stable.

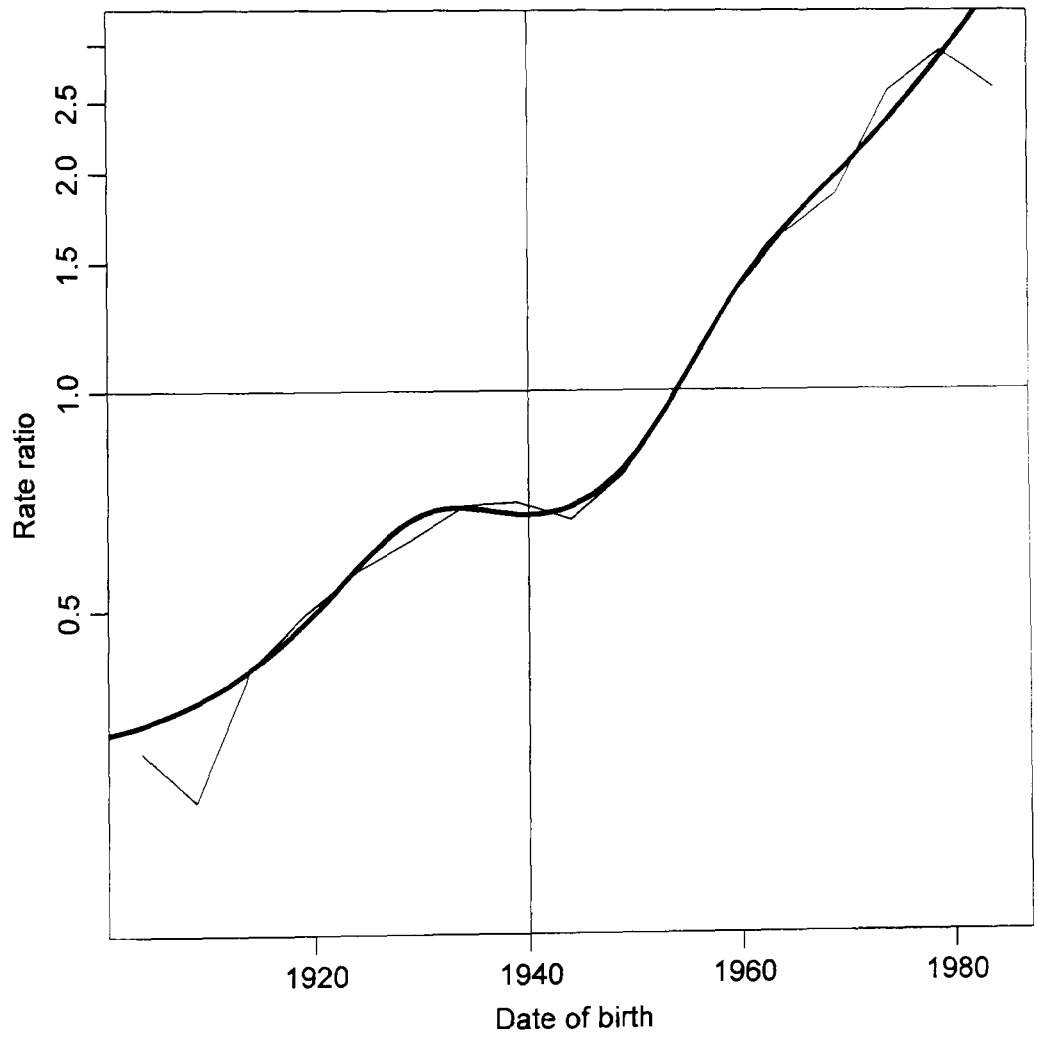
To compare an APC analysis involving a 5-year quantisation of age and period with one based on single year data, an application to testicular cancer incidence in Norway 1954-2003 is provided in Figure 3.12. In the figure, the smoothed cohort effects based on the 1-year data are obtained via an implementation of natural splines in **R** [209]. The allocation of knots at cohort values of 1920, 1930,..., 1970, as well as the boundary knots, were specified *a priori*. The APC analyses of the higher and lower resolutions of the data was based on identical procedure, whereby the period effects were conditional on the estimated age and cohort effects, and the drift term was explicitly allocated to cohort (see 4.5.2.2.2). The reference cohort is 1954-55 and 1950-59 for the 1- and 5-year analyses respectively.

Given the 5-year tabulation of age and period generates synthetic cohorts over 10-year spans compared to 2-year cohorts in the single year analysis, the former is less able to accurately identify important short-term effects and may tend to wash out weaker ones. In

Figure 3.12, a short-term wartime effect in Norway, involving an attenuation of increasing risk of testicular cancer in men born 1940-5 is evident in both curves, as has been demonstrated previously [251]. The additional information conveyed by the single year analysis is the more precise identification of a minimum risk in the generation born around 1940.

There are a number of prior examples of the use of splines in APC modelling of cancer rates. Sasieni and Adams examined trends in cervical cancer incidence and mortality using natural cubic splines, citing justification on the grounds that the method enabled flexibility in the modelling of the fluctuating cohort trends [189]. Zheng *et al* examined rates of cervical adenocarcinoma rates in the U.S. using cubic splines to smooth the trends given the relative rarity of the histology [210]. An example of the application of natural cubic splines to incidence trends of cervical adenocarcinoma is given in Chapter 4.

Figure 3.12. Comparison of cohort effects from an APC model based on a 5-year versus 1-year quantisation of age and period. The vertical line denotes the risk ratios for the cohort born in 1940



3.4.5.6 APC models and cumulative risk

Cumulative risk has certain advantages over age standardisation as a form of direct standardisation; the weights of the standard population equal the width of each age group,

and are therefore no longer entirely arbitrary. Further, the cumulative risk is directly interpretable as a measurement of lifetime risk, assuming no other causes of death are in operation.

Coleman *et al* in a comprehensive analysis of incidence and mortality trends of 23 cancers worldwide used an approach that systematically presented trends in each population according to lifetime risk defined by their birth cohort [8,57]. As the youngest and oldest cohorts were not entirely represented in the age-period table, the method had a prediction component; the authors extrapolated the smoothed cohort effects from an APC model backwards and forwards in time. To obtain efficient smoothing, polynomials of each factor were continually added until polynomials of order two levels above the present best-fitting model failed to significantly improve the fit. Several studies have applied this approach, including papers examining international trends in cervical squamous cell [252] and cervical adenocarcinoma incidence, respectively [253].

3.4.6 Predicting future cancer burden

Making provision for health services for cancer requires not only knowledge of the current pattern of occurrence, but also an estimate of the likely evolution in the future. MacMahon states, in an introductory text to temporal studies of cancer incidence, that "[predictions] if accurate, are clearly of great value for planning purposes. But it is a tricky business and it is a courageous epidemiologist who enters it – particularly if he or she is of an age to see the prediction evaluated by the passage of time" [254]. Predicting cancer occurrence is rightly considered a hazardous exercise: for some cancers in some populations, we can be reasonably confident that trends observed in the past will not hold in future.

Much of the contemporary work on making predictions of cancer incidence, from both a theoretical and practical perspective, stems from scientists working at the Finnish Cancer Registry. Their first report, which involved predictions of the 12 most common forms of cancer in Finland for 1980, was published in 1974, based on the linear extrapolation of trends from 1957–68 [255]. Key to further developments of methods over the next three decades has been a continued validation of prior attempts at prediction. A recent study provided an empirical comparison of 15 different prediction methods in predicting the incidence of 20 cancer sites in the five Nordic countries [256].

Predictions, according to Hakulinen, can be divided into those made for administrative and scientific purposes [13]. Accurate predictions can aid health planners attempting to optimise resources (e.g. for prevention, early detection, treatment, rehabilitation and palliative care), and explanations for deviations between the observed rates and those predicted are often

useful to establish in order to understand why predictions fail (e.g. a failure of the method vs. shift in trends following prediction). In a more scientific setting, cancer predictions may give advanced warning (and impetus) for the need for action, particularly where unfavourable trends are potentially modifiable by intervention.

It is important to note that predicted numbers are a composite of population growth and ageing, as well as changing risk. Demographic changes substantially alter the expected number of future cases, and ageing will continue to have major consequences on the burden of disability and chronic diseases projected over the next 50 years, particularly in the developing world.

The extrapolation of trends of cancer rates into the future is a necessary proxy for the changing prevalence and distribution of risk determinants, given that risk factors for most cancers, where established, are neither singularly powerful enough to model directly, nor available at the prerequisite level of detail required.

Changes in the size and particularly in the ageing of the population often constitute a larger component of predicted increases in burden than corresponding changes in risk [257]. Indeed, predicted increases in the absolute numbers might arise from demographic changes even when existing trends are stable or declining. It is therefore important that the potential for misinterpretation is minimised by focusing on the impact of risk and the reduction of risk through prevention [257].

3.4.6.1 Predictions using the APC model

The potential of the cohort method in predicting future disease burden dates back to Andvord and his study of tuberculosis mortality published in 1930 [80]. He discusses the extrapolation of (the favourable) trends in younger generations into later ages as a way of estimating future mortality. Frost's riposte to this echoes both the utility and inherent difficulties in making predictions, citing the idea as "both tempting and encouraging but perhaps dangerous" [73].

Osmond was one of the first to advocate the APC model for predictions and details the methodology that projects the underlying age-, period-, and cohort-specific trends into future time periods [258]. The APC model can be written as $R_{ij} = \exp(\alpha_i + \delta.j + \beta_j + \gamma_k)$, where R_{ij} is the incidence rate in age group i in calendar period j with δ the net drift parameter. As the three components are mutually dependent, it is possible to estimate only the regular trend and its deviations, not whether period or cohort-specific factors are responsible for the slope. Holford showed that the change in time between a projected rate and the rate within

the study period was an estimable function, and therefore predictions did not suffer from a lack of identifiability. In closing their APC paper, Clayton and Schifflers however state "in recent years there has been several attempts to use an APC model fitted to past data to forecast rates... Unfortunately [Holford's assertion [98]]... is a strong assumption that will rarely be justified in practice" [68].

That drift will remain constant in future periods is a major assumption. Several studies of prediction in the Nordic countries have aimed to address the issue by "damping" the projected trend on the aforementioned belief that rates will not continue to increase forever. The most recent study systematically predicted the number of cases up to 2020 of 20 types of cancer for each sex in the Nordic countries [257]. The prediction involved the APC model but one that allowed for an increasing reduction in the projection of drift with future time. Variations in the method (50% reduction in drift after 10 years, gradual reduction in drift every five years) have been shown empirically to perform favourably [256].

The other difficulty stems from the use of the exponential function in predicting from log-linear models, giving rise to predictions that grow exponentially over time, and for some cancer types, unrealistically high predictions [180]. A power model such as $R_{ij} = (\alpha_i + \delta.j + \beta_j + \gamma_k)^5$ has been proposed to reduce the growth in the predicted rates. Møller and colleagues found that the model improved predictions, as did methods that emphasised trends in the last decade [256]. Some or all of these conditions (power model, dampening of drift, emphasis on recent trends) have been incorporated in a number of recent prediction studies [257,259,260].

Berzuini and Clayton have developed a Bayesian approach to smooth the effects of age, period and cohort groups, taking a second differences approach (see 3.4.3.1) that prevents the rate estimates for adjacent groups from differing too much from each other [261]. The model originates from the APC model, using the exponential function between the rate and the effect variables, and thus for some cancers has given rather extreme predictions.

Where a lesser data span is available, simpler models that contain only the age and the drift component of the APC model have been developed in Finland [179,180,262]. Such models have been applied to annual data 1990-2000 rather than over consecutive five-year periods. To avoid the exponential growth over time, models that were linear with time were applied to cancers with increasing trends [262]. The disadvantage of the approach is that it does not incorporate cohort-specific patterns. Nevertheless, it has been shown to perform well compared with other prediction methods [256].

Past experience of exposure to causative or preventive factors, or the availability of preventive and therapeutic procedures, is not a sure guide to the future. For this reason, or simply on the grounds of insufficient data, future scenarios are sometimes confined to consideration of the effects of probable demographic changes, assuming that future rates remain constant at the present level. It is often considered that such simple methods would not produce any less accurate predictions than those assuming a projection of this drift into the future. However, an empirical study of cancer incidence in the Nordic countries showed that projecting current trends resulted in predictions closer to the rates observed 10 years later than the constant rate approach [256], although the latter performed reasonably well. In GLOBOCAN 2002 [263], future numbers of cancer cases and deaths can be calculated by this means for 2005 to 2050, and can incorporate specifications of the likely future EAPC in five age groups.

The innovative *Cancer Scenarios* project in Scotland has gone beyond the simple provision of predicted numbers and rates, soliciting the expertise of specialists to discuss future preventative and treatment-based interventions in terms of their capacity to modify incidence and mortality trends, projected up to and including the period 2010-2014 [264]. Predictions of cancer are also now commonplace in peer-reviewed medical and epidemiological articles; calculating the future course of epidemics of lung cancer in relation to smoking [54,55,265-267], and mesothelioma in men exposed to asbestos [268-271] have been particularly intensively researched.

3.5 The age-period-cohort model 3: review of APC studies 2000-2004.

To ascertain the extent to which the strategies considered above were applied by researchers in recent practice, this section of the thesis involves a review of peer-reviewed statistical, medical and epidemiological journals publishing relevant articles over the five-year period 2000 to 2004. The final list of articles for review was assembled over several stages.

A list of candidate papers was established on the basis of a merge from three independent sources. Papers published 2000-04 that cited one of 16 key references on APC analyses were identified using the citation search facility in *Web of Science's Science Citation Index Expanded* database. After a further restriction to articles in English, 188 articles were found, and upon review, 112 were relevant to the study of cancer.

A parallel step involved an individual search of papers in PubMed that contained any of the fields (*age**, *period**, *cohort**, *trend**) in combination with *(cancer* OR neoplasms* OR tumor* OR tumour*)* and a publication date 2000-04, for which 220 articles were retrieved

and, of which, 93 considered relevant. The third component was a search of relevant articles in a bibliographical database over the same period held by the author on a time trends database of 22 cancers. The three sets of articles were then merged in *Reference Manager* to obtain a final list of 256 papers.

The final stage involved a necessity to moderate the number of papers to those that were directly relevant and appeared in journals that regularly publish such studies, so as to allow a broad examination of editorial policies regarding their inclusion. A restriction to journals that published five or more articles on the topic during the five years was imposed, which reduced the number of studies to 100 (Table 3.1), about two-fifths of the previous total. The top seven of the nine Journals (*Int J Cancer, Eur J Cancer Prev, Cancer, Cancer Causes Control, Br J Cancer, Eur J Cancer, and JNCI*) were specific to cancer research.

Of these, 40 were studies investigating cancer data that presented an analysis involving age, period and cohort effects using the APC model. Two papers that focussed exclusively on future predictions and one that assessed the impact of screening were excluded, and the final list therefore included 37 papers [204,252,272-307]. Table 3.2 presents details of the papers. All journals were represented by at least three articles, with the largest number published in *The International Journal of Cancer* (10 studies). The exception was *The Lancet* where none of the articles were of relevance (being either letters, commentaries, or not directly involving APC approaches).

Table 3.1: Journals publishing one or more time trends studies per year on average, 2000-04, according to the criteria set out in 3.5

Journal	Number of articles 2000-04
Int J Cancer	24
Eur J of Cancer Prev	14
Cancer	12
Cancer Causes Control	11
Brit J Cancer	10
Eur J Cancer	9
J Natl Cancer Inst	8
Int J Epidemiol	7
Lancet	5
Other journals	156
Total number of articles	256

100 articles = 39.1% of total number found

Table 3.2: Finalised list of studies utilising APC modelling approaches to describe cancer trends in one or more populations

Journal	Number of articles 2000-04
Int J Cancer	10
Eur J Cancer	5
Brit J Cancer	4
Cancer	4
Eur J Cancer Prev	4
Int J Epidemiol	4
Cancer Causes Control	3
J Natl Cancer Inst	3
Total number of articles	37

The following methodological elements were examined:

- Presentation of observed trends;
- APC methodology adopted;
- Specific technique used to circumvent identifiability where applicable;
- Tabular presentation of the model fit and parameters;
- Graphical presentation of the model fit and parameters.

It was anticipated that the results of the review would inform the guidelines developed in this chapter, potentially shedding some light on the rationale for a particular approach to time trends analysis and APC modelling. Table 3.3 provides some brief notes on the main features of the methods employed in each of the 37 papers reviewed. The following text attempts to encapsulate the main points arising from these findings.

3.5.1 Aims of the studies

The objectives of the studies were diverse. Typically, the papers described the time trends of a specific cancer in a single population, but specific aims over and above a broad synthesis of the trends were sometimes given, e.g. an examination of lung cancer related to observed trends in the tar yield of cigarettes [274] or adolescent smoking [301] in Australia and Norway respectively, or mesothelioma trends in the U.S. in relation to SV40 contamination at birth [302].

Most commonly studied were trends in lung cancer (8 articles), malignant melanoma and breast cancer (6 articles each). 22 papers focussed on incidence-based trends, 11 on mortality, and the remaining four analysed both. Only two papers dealt with more than one distinct cancer site (one examining trends in four common cancers [297], the other within diagnostic groups of childhood solid tumours [293]). The majority of incidence studies did

however include sub-analyses of trends in defined histological groups or anatomical subsites. Only five studies analysed trends of a particular cancer across populations from more than one country, either at the international [252,253,299] or European level [284,307].

3.5.2 Tabular presentation of observed trends

Some basic form of tabulation of trends data was provided in most studies, the commonest approach being an age-period tabularisation with cells representing either cases or rates. The grouping of age and period was commonly five- or 10-year, but other ranges were also applied, particularly for age. Person-years at risk or percentages, the latter as a proportion of the marginal totals, were also provided in some studies, as was a tabular presentation of trends in age-standardised rates. A further breakdown by histology, subsite, stage etc was commonly presented in more detailed studies. A handful of studies did not include a tabulation of the basic information, but only in one study was there no provision of observed data in either tabular or graphical form.

3.5.3 Graphical presentation of observed trends

Study approaches to the visual display of observed trends were quite heterogeneous, an indicator of the multiple options available in producing them (see 3.1). Over half of the reviewed articles did not provide graphical depictions of the observed trends, opting for a tabulation as the sole means of providing basic information. Where a visual approach was provided, one of the most frequent displays involved a plot of the age-standardised rates (either for all ages or truncated over one or more age ranges) versus calendar period. A number of standard populations were utilised in their production; by far the most commonly-used were the World and European standard – although standards local to the study population were also applied to the study of trends in Hong Kong, Sweden and the U.S. In plotting the trends, the abscissa was usually represented by period either annually or as five-year aggregates, but other groupings (two-year aggregates, three-year moving averages) were also employed among the 37 papers reviewed. There were no clear preferences of scale for the ordinate, although there was perhaps a tendency for studies to use an arithmetic scale where age-adjusted rates were plotted.

The other main approach was a more detailed breakdown of rates according to age, period and cohort (see 3.1.4.3). Most commonly applied were C by A plots (in 11 studies) while P by A and A by P plots were also depicted (in five and four studies respectively). Again, there was no clear convention to providing either a semi-logarithmic or arithmetic scaling, with some authors (possibly *a priori*) having preferences for arithmetic or logarithmic scales, irrespective of the trend measure being plotted. Few studies explicitly considered the

principles regarding either the size of the graph in terms of the ratio the of Y:X axis (dependant on the range of values presented on each axis) or the labelling of the axes (see 3.1). Exceptions were several U.S. studies [285,291,302] (one of the co-authors in all three studies was the first author of the paper providing guidelines for presentation for rates [165], as was described in detail in 3.1.3).

3.5.4 APC methodology used to present model estimates

The numerous approaches adopted in these articles in presenting the effects from APC modelling reflect the wide range of choices of solution presently available, as reviewed in 3.4. The papers by Clayton and Schifflers were among those cited as standard references to APC modelling in the majority of the 37 articles. Nevertheless, the rather few methods advocated by Clayton and Schifflers in their 1987 paper [68] is at odds with the heterogeneity of methods used to reach a solution (or solutions) in the reviewed articles 2000-04: eight studies used a two-factor approach (six papers adopted the AC model only); five studies presented the effects by taking the first and last effect of cohort and/or period effects; a further three used a constraint that equated two levels of one factors; drift was attributed to period or cohort (or both) in five papers; linear contrasts were used to compare birth cohort slopes in four; cumulative risk based on polynomial expansions of the AC or APC model were estimated in three studies, and miscellaneous other methods were also practiced (penalty function approach; fitted rates; SCMR). Seven studies did not explicitly present effects from the APC model, while in six articles where modelled trends were presented, it was not clear as to the method used to reach the solution.

3.5.5 Tabular presentation of the model fit / parameters

Close to half (16) of the 37 studies explicitly provided some form of tabulation of the deviance of the APC model and/or submodels in order to examine (with the corresponding degrees of freedom) the goodness-of-fit of the APC model and/or submodels, and the variation explained by each factor. The Clayton and Schifflers modelling approach illustrated in Figure 3.5 was utilised in many of these articles, although the age-drift model was not fitted in several. In studies where numerous subgroup analyses were undertaken, it was more common to present the deviance for the best-fitting model only. In the remaining studies without tabulation of the goodness-of-fit, several provided details of the deviance of the models presented in the text; others provided no information on model fits.

The EAPC was explicitly presented in 15 of the studies reviewed, in 11 as a separate table, but in those remaining, as part of a tabulation of the observed data. In the majority of studies, the EAPC was derived not from the net drift, but from a log-linear model of the form

outlined in 3.2.2. 95% CI were almost always provided. Joinpoint regression was used in only one study and the results were not shown. Tables of parameter estimates were incorporated rarely, with the presentation usually carried out via graphical means (see 3.5.6 below).

3.5.6 Graphical presentation of the model fit / parameters

Only eight of the studies failed to provide some form of visual presentation of the model effects. Of the 29 studies including graphics, all but one included a cohort representation of the effects. Five studies showed effects for all three factors, and 11 studies showed effects for period and cohort. Only one study exclusively presented modelled trends versus calendar period.

14 of the 29 studies provided antilog estimates as rate ratios, whereas eight produced trends effects based on the untransformed maximum likelihood estimates. Calculation of the effects as rates and as cumulative risk were other forms of presentation of the model results, as was the description of trends using the fitted rates from the APC model. 95% CI were included in some studies, but not in the majority.

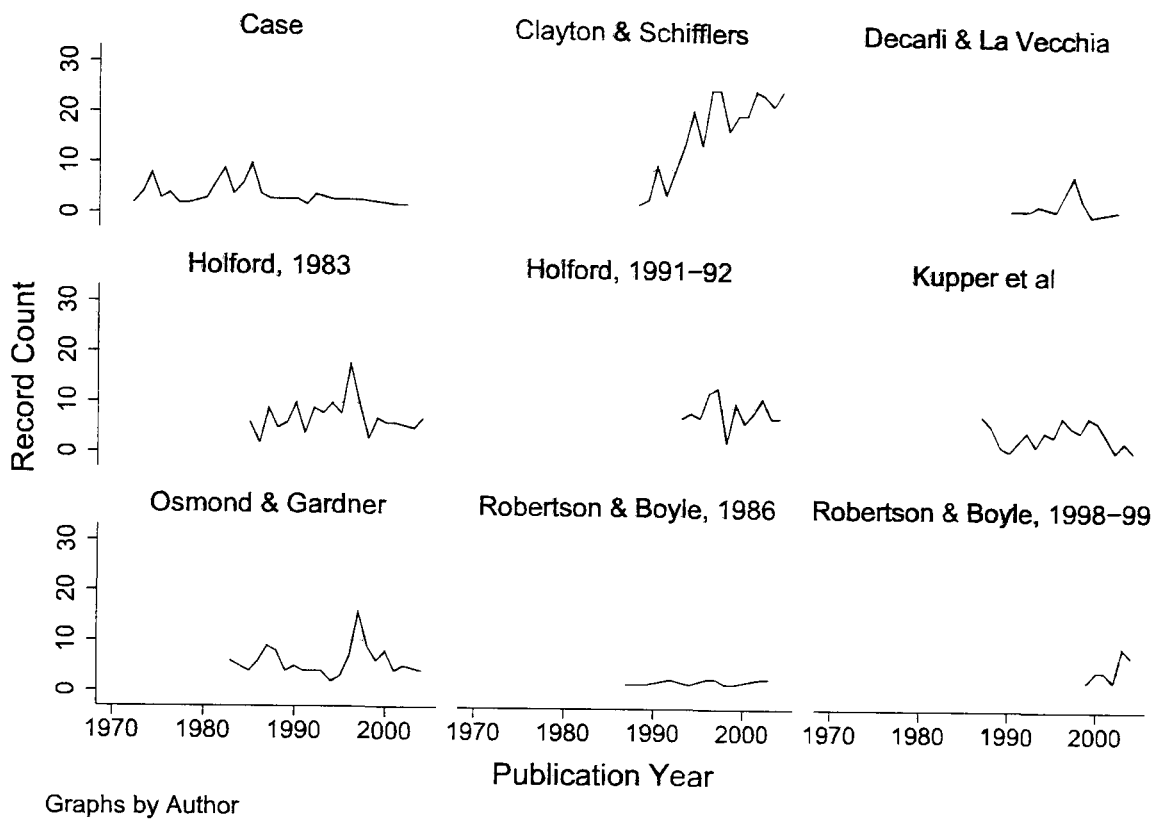
3.5.7 Other relevant methodological considerations

In a few of the reviewed studies, trends in risk factors directly related to the cancer being investigated were included in the analysis and/or interpretation. Thus in three temporal studies of lung cancer, trends in smoking patterns in the study population were also presented [274,301,307]. Similarly, two temporal studies of mesothelioma [302,304] provided risk factor patterns relevant to the study aims (import of raw asbestos in Norway, SV40-contaminated poliovirus vaccine in the U.S.). Two studies of female cancer (breast and cervix) included data on local trends in reproductive factors and historical patterns of rates of tested positive serum syphilis, respectively [290,298].

3.5.8 Trends in citation numbers of major APC articles

To get an indication of the consensus with regards the key APC papers, Figure 3.13 provides a graphical description of the numbers of citations in scientific journals for each of nine selected papers since their year of publication.

Figure 3.13: Trends in number of citations vs. year of publication for nine original or review articles on APC models in the scientific literature (Source: *Web of Science's Science Citation Index Expanded*)



Graphs by Author

Clearly, the Clayton and Schifflers' papers have been increasingly cited from their publication date in 1987, with more than 20 citations per year 2000-04. Most of the other studies varied from 1-10 citations annually with no real trends discernible (possibly some peaks in popularity of, or output using, a particular method are observed). Holford's original 1983 paper combined with his later reviews 1991 and 1992 would be the only serious challenger to the papers by Clayton and Schifflers, representing an approximate total of 15 citations annual in recent years.

3.5.9 Concluding remarks

Some interesting findings were obtained following the mini-review of methods that presently comprise an APC analysis of cancer trends. It was clear that there was some adoption of Clayton and Schifflers' (and to some extent Holford's) principles of APC analysis beyond merely being an appropriate citation, as might have been implied in the results in 3.5.8; in general terms, a majority of the papers reviewed could be considered technically competent in terms of the analytic strategies employed, with some demonstrating both an understanding of the identifiability problem in practice and due caution in interpretation of the APC effects.

However, there remained tremendous inconsistency with regards the method selected to present formal estimates via APC modelling. Among the 37 papers, nine methods were employed in presenting the model effects. Further, there was rather little exposition surrounding the basis of this choice. In some, but not all studies, the choice of model was dictated by the goodness-of-fit of model according to Clayton and Schifflers' framework [68], but justification for a particular choice of APC model effects (or exclusive representation using a two-factor model) was less apparent. One common rationalisation was reference to the use of the chosen method in previous studies; few articles, however, discussed their particular solution in terms of biological or epidemiological plausibility.

Presentation of observed data leading to the more formal APC analyses was considerably heterogeneous among the 37 studies, both in terms of tabular and graphical representations. The importance of tabulated data at this level has not received much emphasis in this chapter, yet an important aspect of temporal studies is the provision of basic information such as number of cases and person-years at risk. These provide some indication of the impact of the trends (in public health terms), and the degree of variability represented in the underlying data.

The graphical methods used to examine the time trends were as diverse as the wide array of choices to consider in their composition. For the purposes of comparability across studies, some level of standardisation of output would however seem appropriate. In producing the age-standardised rates for instance, at least three standards were used other than the World and European standards (conventionally used for international and European comparisons respectively). Despite sensible guidelines regarding the use of arithmetic or logarithmic scales for the rates axis, and recommendations regarding the dimension of plots [165], such features of the graphs appear to largely reflect the preferences of the researcher(s).

A number of methods were applied in practice in presenting the APC effects. That almost one-quarter utilised a two-factor approach (six papers adopted the AC model only) is in spirit with Everitt's definition of the APC technique [192] (see 3.4.1.1). Goodness-of-fit tests were not uniformly applied among the papers, though in some they informed the choice of presentation. Few studies provided a rationale for a particular solution, either in terms of biological or epidemiological evidence, or otherwise.

Cohort (rather than period) effects predominated in the graphical presentation of the APC analysis, to be expected given that the analysis (as opposed to simpler age-calendar period approaches to trends) implies particular attention to generational influences. This observation, and the common tendency towards adoption of the AC model in some studies,

may point to *a priori* beliefs in the importance of cohort effects among researchers, and in some instances explain the bypassing of goodness-of-fit tests and the detailed consideration of period effects.

The statistical measure used to convey the trends may have depended on the method utilised. For example, graphics depicting rate ratios were more often obtained from two-factor model analyses on an antilog transformation of the effects; papers utilising Holford's method and the APC model were often presented as the logarithm of the effects, and for which the sum of the effects presented all add to zero, a presentation style used invariably by Holford himself in the numerous collaborative studies of cancer trends in Connecticut (see 3.4.2). The EAPC was used in almost half of the studies, yet only in the minority was this calculated within the APC framework, based on estimation of the drift. More commonly, a separate log-linear modelling exercise was performed to obtain the measure.

Interestingly, from the perspective of assessing systematic approaches, very few studies examined more than one cancer by topography. Many of the reviewed studies of incidence trends did however provide further APC analyses by histology or topography.

Table 3.3: Summary description of methodological characteristics of 37 retrieved papers examining cancer trends using the APC model in eight peer-reviewed journals 2000-04

#	Journal	Reference	Cancer site (data type), population (period studied), aim of study	Presentation of observed data	APC methodology (as a means to present model effects)	Tabular presentation of model results	Graphical presentation of model results	Comments
1	BJC	Blizzard and Dwyer	Lung (mortality), Australia (1965-98). Aim was to determine whether lung cancer mortality trends were related to reductions in the 'tar' yields.	Graphics: A by P (both 10-yr) by sex. A by C by sex (both log scale).	AC model only	None	Cohort effects as rate ratios (AC model with effects relative to cohorts with highest rates)	Prevalence of smoking and age at starting smoking, both presented by birth cohort nationally and regionally. Strange cohort constraint to use for presentation.
2	BJC	Leung et al	Breast (incidence), Hong Kong (1973-99). Aim was to describe long-term trends, distinguishing between time period and birth cohort.	Table of 5-yr rates (+ population) for 5-yr ages and periods 1975-99. Graphics: A by P (5-yr) + ASR (World) (log scale). C by A (5-yr) (arithmetic scale) .	APC model, assumed first and last P/C effects equal to zero.	EAPC by 5-yr age 1973-99 + sign of 2nd-order term. Total deviance, adjusted R^2 for 5 APC models. Period and cohort effects from APC model	Cohort effects as rate ratios (APC model with constraint that first and last periods = 0).	
3	BJC	Liu et al	Thyroid (incidence), Canada (1970-96). Aim was examine incidence trends by age, period and cohort.	Graphics: aggregated Incidence ASR (World) by three-year period by sex 1970-96 (arithmetic scale).	APC model, assumed first and last cohort effects equal to zero.	EAPC for 4 age groups+ all ages 1970-96.	Age, period and cohort effects as logarithmic effects (APC model with cohort constraints).	Cite Tarone and Chu (1996) regarding use of particular constraint to achieve identifiability.
4	BJC	Severi et al	Melanoma (mortality), 9 countries/regions (1960-94), Aim was to investigate whether decreases has been recently observed in long-term mortality data.	Graphics: TASR (World standard) by period 1973-99 for each sex and country (arithmetic scale).	APC model, assume: (1) the entire drift is period effect. (2) drift is cohort effect.(3) drift is shared between period and cohort.	None	Cohort effects as rates (APC model with 3 different constraints) for each sex and country.	
5	Cancer	Chu et al	Prostate (mortality), U.S. SEER by race (1969-99). Aim was to investigate the recent decrease in mortality in white by examining incidence, survival, and mortality rates by race.	Graphics: ASR (U.S. Standard 2000) by single year 1969-99 (arithmetic scale) for each race.	Linear contrasts characterising slope of period effects 1991-97, and 1985-91. APC model, assumed first and last cohort effects equal to zero.	None	Period and cohort effects presented as logarithmic effects for each histology (APC model with cohort constraints such that first and last effects = 0).	

#	Journal	Reference	**Cancer site (data type), population (period studied), aim of study**	**Presentation of observed data**	**APC methodology (as a means to present model effects)**	**Tabular presentation of model results**	**Graphical presentation of model results**	**Comments**
6	Cancer	Cohn-Cedermark et al	Melanoma (mortality), Sweden (1970-96). Aim was to describe trends and investigate potential impact of primary prevention.	Graphics: ASR (Sweden 1970) by period 1970-96 (arithmetic scale). TASR (four age groups) by period 1972-96 and sex and cancer type, nationally and within selected regions (arithmetic scale).	AP model only, on basis of goodness-of-fit.	EAPC by period and sex and cancer type, nationally and within selected regions 1972-96, 1977-86 and 1987-96. Total deviance for 5 APC models.	Period effects as rate ratios for each sex (possibly AP model but not clear).	Not clear which model used to present period effects. presumably AP – cohort effects NS when added to AP model.
7	Cancer	McGlynn et al	Testicular germ cell (incidence), U.S. SEER by race (1973-98). Aim was to examine whether rates among white men have recently stabilised and whether rates among black men remain remained low.	Graphics: aggregated ASR (World) by five-year periods 1973-98 by age and histology (log scale). A by P (5-yr) for each histology. P by A (5-yr) for each histology (all logarithmic scale).	APC model, assumed first and last P or C effects were equal to zero in presenting the other (not clear).	Change in rates in each successive five-year period 1973–78 to 1994–98 by race and histology.	Period and cohort effects as logarithmic effects for each histology (APC model with cohort and period constraints respectively).	Not clear what parameterisation yields period and cohort effects.
8	Cancer	McNally et al	Solid childhood tumours (incidence), NW England (1954-98). Aim was to determine whether diagnostic improvements or reporting changes explained increasing trends.	Table of incidence and rates for ages <1, 1.4, 5-9, 10-14 and 0-14 by diagnostic group and sex for CNS and non-CNS tumours for period 1954-98. TASR (World standard) of CNS Tumours by Diagnosis and five-year periods 1954–1998.	APC models were fitted with aim to detect significant period and cohort curvature adjusted for other factor. Significant non-linear period effects reported for certain groups in text. Not explicitly presented.	Relative risk of diagnosis with CNS and non-CNS and in the latest period vs. in previous periods.	None	Relative risk based on a model involving sex and age only.
9	CCC	Myrdal et al	Lung (incidence), Sweden (1958-94). Aim was to estimate age, period and cohort effects with an emphasis on sex-specific trends by histological subtype.	Tables of number of cases by 10-yr age group and 5-yr period 1958-94. Graphics: ASR (Sweden 1970) and TASR (Sweden 1970 10-yr.) by period, histology and sex 1958-94 (all logarithmic scale).	AC model used to display cohort effects.	Total deviance for 5 APC models. Period effects from AP model.	Cohort effects as rate ratios for each sex	

#	Journal	Reference	Cancer site (data type), population (period studied), aim of study	Presentation of observed data	APC methodology (as a means to present model effects)	Tabular presentation of model results	Graphical presentation of model results	Comments
10	CCC	Pompe-Kim et al	Breast, cervix, lung, mouth and pharynx (incidence), Slovenia (1965-94). Aim was to evaluate age, period and cohort trends and predict cancer-specific incidence up to 2009.	None	AP or APC or "modified" models that incorporated effects of different smoking and drinking habits in different age groups. Age, period and cohort effects obtained assuming zero period slope?	Total deviance for 3 APC models (APC vs. AP vs. Modified APC) by cancer and sex.	Age, period and cohort effects as rate ratios.	Not clear if zero period slope methods was used to present the effects. Study focussed on predictions up to 2009. Smoking/drinking effects appear to be added as an interaction with the additive effects of age, period and cohort. Not clear where external data derive from, nor what assumptions of the "calculated age effect typical for Slovenia" meant when effects from APC model presented.
11	CCC	Strand et al	Lung (incidence), Norway (1954-98). Aim was to describe the national trends in lung cancer incidence among young adults and the relationship to adolescent smoking.	Table of incident cases by sex, age, and period 1954-98. 5-yr age-spec. rates by sex and period. Graphics: P by A (5-yr for 3 age groups) 1954-98 stratified by sex (arithmetic scale).	Fit of APC models inspected. effects not reported or displayed.	None	None	Smoking prevalence on the right Y-axis of observed trends. Age-adjusted (world) incidence rates of lung cancer by period + smoothed lines by a locally weighted least-squares curve-fitting method (loess).
12	EJC	Bray et al	Lung (mortality), 15 EU countries (1967-99). Aim was to estimate current stage of lung cancer epidemic in 15 EU countries by sex and relate period and cohort effects to smoking prevalence.	Table of ASR (European standard) + ranking by sex and country 1975, 1985 and 1995. SMR by country and sex. Graphics: TASR vs. period by age group (30–64 and 65+) (European standard) (logarithmic scale).	Observed and fitted rates of best-fitting model shown. second differences used to identify local departures from period and cohort regular trends.	Direction and magnitude of most recent change in trends from year where recent changes was observed.	Fitted rates shown vs. observed rates by country and sex.	Trends in % prevalence of smokers by country and sex also given.
13	EJC	Colonna et al	Thyroid (incidence), French registries (1978-97). Aim was to study time trends using data from 5 registries with complete data and geographical variation in 8 registries for a shorter period.	Table of ASR (World standard) and distribution of cases for each histological type by period, sex and age. Regional SIR by sex and histological type.	AC model with a smoothing spline.	Assessment of the recent rate of increase and geographical homogeneity tested according to deviance tables by time x registry interaction. EAPC 1982-96 by region and histological type	Cohort effects presented as rate ratios (in women).	

#	Journal	Reference	Cancer site (data type), population (period studied), aim of study	Presentation of observed data	APC methodology (as a means to present model effects)	Tabular presentation of model results	Graphical presentation of model results	Comments
14	EJC	de Vries et al	Melanoma (incidence and mortality), Netherlands (1989-98 and 1950-99). Aim was to determine incidence and mortality trends and test for birth cohort effects on mortality.	Table of age-specific incidence rates 1989–97 by histological subtype and anatomical site two age groups (35.64, 65+). ASR (European standard) by histological subtype and anatomical site and sex. Stage distribution by sex. Graphics: Incidence and mortality ASR (European standard) vs. period (3-year moving average) by sex (EAPC for each trend given in legend). Incidence and mortality rates vs. period (3-year moving average) in three age groups for each sex (EAPC for each trend given in legend). Trends in incidence ASR (European standard) vs. three-year periods by region for each sex. (all arithmetic scale)	APC models fitted according to Clayton and Schifflers method. Not explicitly presented.	Coefficients from Poisson model inc. region and period only.	None	Best-fitting APC described in text only.
15	EJC	Gonzalez-Diego	Ovary (mortality), 15 EU countries (1955-93). Aim was to provide an in-depth analysis of mortality trends, characterise any differences between countries, and outline possible causes.	Table of ASR (European Standard) by country for each five-year period 1955-93, rate ratios and EAPC by country for 1955-93 and 1979-93 separately for all ages and for 35-64. Graphics: mortality ASR (European standard) vs. five-year period by country within region (arithmetic scale).	Effects from APC model estimated in 3 ways: 1) Osmond-Gardner method 2) and allocation of drift to period and 3) to cohort.	Total deviance for 5 APC models for each country.	Age, period and cohort effects presented as rate ratios by country assuming 1) Osmond-Gardner method 2) and allocation of drift to period and 3) to cohort.	
16	EJC	Stang et al	Melanoma (incidence), German Democratic Republic (1961-89). Aim was to study differences in the magnitude of age, period and cohort effects between sexes and subsites.	Tables of number of cases by sex and anatomical site 1961–89. Graphics: A by P (10-yr) according to sex and subsite. C by A (5-yr) stratified by sex (both logarithmic scale).	APC models fitted according to Clayton and Schifflers method. Method used in presenting effects not indicated.	EAPC by sex and anatomical site 1961–89.	Age, period and cohort effects presented as rate ratios by sex.	Best-fitting APC described in text. Not clear how P and C effects are obtained – possibly by adding drift to each effect before its presentation.

#	Journal	Reference	**Cancer site (data type), population (period studied), aim of study**	**Presentation of observed data**	**APC methodology (as a means to present model effects)**	**Tabular presentation of model results**	**Graphical presentation of model results**	**Comments**
17	EJCP	Alvarez-Riesgo	Breast cancer (mortality), Asturias, Spain (1975-94). Aim was to describe trends and in relation to screening.	Table of incidence rates and number of cases by five-year age group and periods 1959-97 + ASR (European standard) and cumulative rate by period. M/I ratio vs. 1-yr period. ASR 1994 by EU country (possibly World standard but not stated).	Submodels up to and including two-factor models fitted.	Total and change in deviance for 3 APC models (A, AP, AC). Period and cohort effects presented as rate ratios obtained from AP and AC models respectively.	Period and cohort effects presented as rate ratios obtained from AP and AC models respectively. Age effects based on one of two-factor models?	Exposition of method used to present APC estimates not entirely clear. appears to be use of two-factor models. not clear whether age effects presented are cross-sectional or longitudinal.
18	EJCP	Bouvier et al	Gastric (incidence), Cote d'Or, France (1976-95) Aim. was to examine role of age, period and cohort on incidence trends by subsite and histology.	ASR (World standard) by 5-yr period and age stratified by sex 1976-95. ASR (World standard) by subsite and age stratified by sex 1976-95. Graphics: C by A (10-year) (arithmetic scale) stratified by location and sex. C by A (10-year) (logarithmic scale) stratified by histological type and sex.	Cumulative risk obtained from best-fitting AC model with polynomials (as in Coleman et al, 1993).	Cumulative risk (30-74) by histological type and birth cohort stratified by sex for best-fitting AC model with polynomials.	None	
19	EJCP	Mitry et al	Colorectal (incidence), Cote d'Or, France (1976-95). Aim was to present incidence trends by subsite.	Table of ASR (World standard) by 5-yr period and subsite stratified by sex 1976-95. Tables of number of cases and % by 5-yr period and subsite stratified by sex 1976-95.	APC models allowing for polynomials for each effect (as in Coleman et al, 1993). Cumulative risk obtained from best-fitting AC model with polynomials.	Table of total deviance for best-fitting APC model with polynomials by subsite stratified by sex.	Cumulative risk (30-74) vs. birth cohort by subsite stratified by sex for best-fitting AC model with polynomials.	
20	EJCP	Svensson et al	Colorectal (incidence), Norway 1958-97. Aim was to examine colorectal trends by sex and subsite via APC modelling.	Graphics: cases and % by sex, age and subsite 1953-97. ASR vs. 5-yr period 1953-97 (?World standard) by Nordic country (arithmetic scale) for each sex. ASR vs. 5-yr period 1953-97 by subsite (arithmetic scale) for each sex.	APC models fitted. Method used in presenting effects not indicated (either from the AC model or assuming drift with cohorts – not clear).	Total deviance for 5 APC models.	Cohort effects as rate ratios.	Not clear how C effects are obtained – possibly on adding drift or via AC model.
21	IJC	Arbyn and Geys	Cervix (mortality), Belgium (1954-94). Aim was to study age, period and cohort trends.	Proportion of Uterine cancers by age and reference population (table and graphic). Graphics: number of deaths and ASR (European standard) in five-years periods by site, Belgium, 1954–1994. C by A, for corrected and uncorrected cervical cancer (arithmetic scale).	Standardised cohort mortality ratios (relative risk of cervical cancer death for a given cohort relative to the average mortality of all cohorts).	EAPC by 5-yr age 1954-94. Standardised cohort mortality ratio (SCMR), with relative risk of cervical cancer death for a given cohort relative to average mortality of all cohorts.	SCMR in successive cohorts by correction status.	Authors explicitly mention in the Introduction that study of trends based on APC models is part of ongoing work.

#	Journal	Reference	Cancer site (data type), population (period studied), aim of study	Presentation of observed data	APC methodology (as a means to present model effects)	Tabular presentation of model results	Graphical presentation of model results	Comments
22	IJC	Blizzard and Dwyer	Lung (mortality), Australia (1982-95). Aim was to examine trends by histological subtype and impact of switch to filter-tip cigarettes in a setting where their tar yields remained unchanged for a decade.	Table of number of cases by sex, histology and 10-year birth cohort.	AC model presented for histological subsites for which the AC model fitted and period effects did not significantly contribute.	Linear contrasts of parameter estimates to changes in trends in particular cohorts.	Cohort effects as rate ratios for each sex.	Study objective was to examine impact of filtered cigarettes on Australian population.
23	IJC	Chirpaz et al	Prostate (incidence and mortality), French registries (1982-96). Aim was to examine incidence and mortality trends with special emphasis on population screening by PSA.	Graphics: Incidence and mortality ASR (European standard) vs. period by French area. Incidence and mortality rate vs. P by A (various age groups). C by A (all logarithmic scale).	AP model for mortality. APC model for incidence, first and last cohort effects assumed equal to zero. Linear contrasts to compare specified cohort slopes.	Total deviance for 5 APC models. EAPC by five-year period 1982-7,87-93,93-5. Period effects in mortality from the AP model.	Period and cohort effects presented as logarithmic effects of incidence (from APC model with period constraints).	
24	IJC	Chiu et al	Lung (incidence, females), Hong Kong (1976-2000). Aim was to estimate age, period and cohort effects and explore underlying reasons.	Table of rates in five-year age groups and periods 1976-2000 with crude and ASR (Hong Kong 1990 standard). Graphics: ASR by single period 1976-2000 (arithmetic scale). C by A (logarithmic scale).	AP model used to display period effects, AC model to display cohort effects.	EAPC by 5-yr age group 1976-2000 and 1991-2000. Total deviance for 4 APC models (did not include AD model).	Period and cohort effects as rate ratios from AP and AC models respectively.	All models (including the APC) indicated a significant lack-of-fit. Graphic showing prevalence of daily smokers by age group in Hong Kong females, 1982–98 also given.
25	IJC	Lambert et al	Stomach (incidence and mortality), Japan, Slovenia, U.S. SEER (1975-95). Aim was to compare incidence and mortality trends by period and cohort to assess relative contribution of "unplanned prevention" vs. mass screening policy.	% with localised stomach cancer by country and period. Graphics: ASR Incidence and Mortality by single calendar year 1975-95 (World standard) by sex and stage for each country (arithmetic scale).	AC model used to display cohort effects.	EAPC 1975-95 by country and sex, incidence vs. mortality. EAPC by country and sex for each stage. Absolute change in overall and localised stomach cancer by age. Total deviance of best-fitting APC model by country and sex and for incidence, mortality and localised cancers.	Cohort effects as rate ratios from AC model.	
26	IJC	Minami et al	Breast (incidence), Miyagi Prefecture, Japan 1959-97. Aim was to examine period and cohort effects, with a focus on the importance of cohort.	Table of incidence rates by five-year ages and periods 1959-97. Graphics: ASR incidence vs. five-year periods for main female cancers 1959-97 (logarithmic scale).	APC model with cohort effects estimated assuming a linear period effect of 0.	Total deviance and change in deviance for 5 APC models.	Period and cohort effects as logarithmic effects from APC model assuming zero period slope.	Overdispersion dealt with using a quasi-likelihood approach. Table of risk factors (and local evidence for their effect) and national trends in prevalence of risk factors also given.

#	Journal	Reference	Cancer site (data type), population (period studied), aim of study	Presentation of observed data	APC methodology (as a means to present model effects)	Tabular presentation of model results	Graphical presentation of model results	Comments
27	IJC	Ulvestad et al	Mesothelioma (Incidence), Norway (1965-99). Aim was to analyse incidence trends and study consequences of asbestos and the effectiveness of the ban on its use.	Table of mesothelioma of the pleura incidence rates by 10-year ages and periods 1965-99 by sex. Graphics: ASR (World standard) vs. five-year periods by sex 1965-99. rates vs. five-year periods for three age groups 1965-99 (both logarithmic scale).	AC model used to display cohort effects.	Total deviance and change in deviance for 5 APC models.	Cohort effects as rate ratios from AC model.	Graph of import of raw asbestos to Norway after World War II and numbers/rates of mesothelioma of the peritoneum also given.
28	IJC	Verkooijen et al	Invasive lobular breast (incidence), Geneva, Switzerland (1976-99). Aim was to describe the trends in breast cancer incidence by histological subtype.	Graphics: ASR (European standard) vs. five-year period by histological subtype 1976–1999 (EAPC also displayed). TASR vs. five-year period, 5 age groups for ductal, lobular, and other histologies. ASR vs. five-year histology/stage (all arithmetic scale).	APC model used to test importance of cohort effects. Possibly fitted rates from APC model, but not clear.	None	? Fitted rates from APC model shown as C by A.	Not clear from paper how APC model was used and how the observation of significant cohort effects in lobular cancer was established. Not clear whether Fig 4 displays fitted (from APC) or observed rates.
29	IJC	Vizcainio et al	Cervical squamous cell carcinoma (incidence), 32 international populations (1973-91). Aim was to present a detailed analysis of the time trends in diverse settings.	Table of total number of cases and ASR (World standard) by subtype and country.	Cumulative rates obtained from best-fitting APC model with polynomials (as in Coleman et al, 1993) for age groups 25-49 and 50-74.	Total deviance for best-fitting APC model with polynomials. EAPC 25-49, 50-74 and 25-74 from net drift.	Cumulative rates vs. birth cohort (25-49, 50-74) by country and region for best-fitting APC model with polynomials.	
30	IJC	Vizcainio et al	Oesophagus (incidence by histology), 34 international populations (1973-95). Aim was to identify the relative importance of components of birth cohort, period in determining trends by histological type, and assess contribution of changes in the proportion of cases with specified histology.	Data quality indices by country and CI5 volume (5-yr periods). Table of cases and ASR (World standard) for each histology by country. Graphics: ASR (World standard) vs. CI5 volume by histological type stratified by country (all logarithmic scale).	Used only to indicate the best-fitting APC model. Not explicitly presented.	EAPC from net drift and best-fitting APC model for country and histology by sex.	None	

#	Journal	Reference	Cancer site (data type), population (period studied), aim of study	Presentation of observed data	APC methodology (as a means to present model effects)	Tabular presentation of model results	Graphical presentation of model results	Comments
31	IJE	Bulliard and Cox	Melanoma (incidence and mortality), New Zealand (1969-93). Aim was to assess long-term incidence and mortality trends in a high-risk country in relation to sun exposure and behaviour.	Table of observed birth cohort trends summarised by arrows denoting systematic increases or decreases in age-specific rates compared to previous generation for males and females. Graphics: ASR incidence and mortality (World standard) vs. one-year period by sex 1969--1993. ASR incidence (World standard) vs. one-year period (3-year moving average) by sex and anatomical site 1969–1993. C by A (logarithmic scale) for males and females.	Test of drift and non-linear effects reported in the text but no graphical or tabular presentations from APC model or submodels. EAPC reported using net drift.	EAPC 1969–1993 (based on drift) by sex and anatomical site.	None	Significance of linear trends versus non-linear effects of A, P and C mentioned in the text.
32	IJE	Li et al	Cervix (mortality), Shandong Province, China (1970-92). Aim was to describe time trends of cervical cancer and elucidate reasons for the findings.	Table of ASR (World standard) by survey area and five-year period. rates by 5-yr age group and period in Province. Graphics: P by C (arithmetic scale). number of cases and rates by 5-yr age group and period in one county.	APC model with age effects estimated assuming first two effects = 0, period effects estimated assuming first two effects = 0, cohort effect age assuming sixth and seventh effects = 0.	Table of age, period and cohort effects as (log) rate ratios and (antilog) rate ratios.	None	Rates of tested positive serum syphilis 1954-60 in Shandong also given. Putative risk factors in two age groups and rural/urban status also given.
33	IJE	Liu et al	Testicular germ cell (incidence), Canadian registries (1970-95). Aim was to examine differences in incidence patterns of seminoma and non-seminoma.	Table of number of cases and % 1970-95, rates 1970-1 and 1994-5, EAPC 1970-95 by histological type. Graphics: ASR incidence (World standard) vs. two-year period overall and by histological type 1970–1995. C by A (arithmetic scale for each histological type 1971-95.	APC model with cohort effects estimated assuming a linear period effect of 0.	Test of deviance of non-linear period and cohort effects for each histological subtype. Test of deviances of histology-curvature interactions for age, period and cohort.	Age, period and cohort effects of each histological subtype as logarithmic effects from APC model assuming zero period slope.	
34	IJE	Robertson et al	Breast cancer (incidence), Slovenia (1971-93). Aim was to investigate cancer trends in relation to trends in risk factors in a population with relatively little screening.	Graphics: P by A and C by A (both logarithmic scale).	APC model assuming first and last cohort effects equal to zero. addition of available demographic data on reproductive factors by birth cohort added to AP models. Linear contrasts characterising eight cohorts born 1900-14 with those born after 1924.	Total deviance for AP, and APC model + 7 extensions of the AP model incorporating reproductive data at the population level.	None	Demographic information on reproductive factors by birth cohort from official statistics and case-control studies also presented and used to replace cohort effects.

#	Journal	Reference	Cancer site (data type), population (period studied), aim of study	Presentation of observed data	APC methodology (as a means to present model effects)	Tabular presentation of model results	Graphical presentation of model results	Comments
35	JNCI	Jemal et al	Lung (mortality), U.S. SEER (1970-97). Aim was to evaluate recent trends.	Graphics: C by A (2-year bands) for males and females (logarithmic scale).	Cohort effects estimated on assuming last and second last cohort = 0. Linear contrasts used to compare specified cohort slopes.	None	Cohort effects as logarithmic effects assuming last two cohort effects are equal (last effect not presented).	In presenting cohort effects from APC model, authors acknowledge "different estimates will be obtained under different constraints", focus is on changes in slopes.
36	JNCI	Jemal et al	Melanoma (incidence), U.S. SEER (1973-97). Aim was to examine incidence patterns stratified by sex, age, tumour stage, and tumour thickness to determine whether increasing incidence is real or whether reflected improved diagnosis.	Graphics: ASR incidence (U.S. Standard) vs. one-year period 1973-97 by sex (logarithmic scale). C by A and P by A for males and females (logarithmic scale). ASR incidence (U.S. Standard) vs. one-year period 1973-97 by stage, stratified by sex (logarithmic scale).	Linear contrasts used to compare earlier and later birth cohort effects.	Table of EAPC 1974-89 and 1990-97 for all ages and in three age groups, stratified by sex. Table of EAPC 1988-97 by age and tumour thickness, stratified by sex.	None	Joinpoint regression used to characterise overall trends in men and women.
37	JNCI	Strickler et al	Pleural mesothelioma (incidence), U.S. SEER (1975-97). Aim was to examine pleural mesothelioma incidence trends among adults in by age in relation to the probability of their exposure to potentially SV40-contaminated poliovirus vaccine 1955-61.	Graphics: ASR incidence (U.S. Standard) vs. three-year period 1977-97 overall and by sex (logarithmic scale). P by A (6 age groups, logarithmic scale).	APC model assuming the 1890-91 and 1892-93 effects equal. Linear contrasts for comparing birth cohort effects that 1) spanned approximately 10 years covered periods during which cohort- specific vaccine prevalence curve was approximately linear (1894-99, 1900-07, 1908-17, 1918-27, 1928-35, 1936-47, 1948-57. 2) contrasted consecutive differences of two-year birth cohorts (1900-01, 1902-03,..., 1960-61).	10-year slope contrasts from APC model by sex	Birth-cohort effects as logarithmic effects from APC model presented together with slope contrasts. Plot of differences between adjacent two-year birth-cohort effects and differences in prevalence of exposure to potentially SV40-contaminated poliovirus vaccine.	The age-specific prevalence of exposure to potentially SV40-contaminated poliovirus vaccine in the U.S. 1961 also given. In setting adjacent cohorts to zero, authors rationale is very low rate of exposure and low incidence in early birth cohorts.

3.6 Summary and recommendations

This chapter has provided a broad overview and critique of the technical issues surrounding the analysis and presentation of cancer trends. It has mainly focussed on usage of the APC model, necessarily so, given its utility and emergence as the standard tool for such data, and the controversies that surround the identifiability problem and what may be described as a reasonable solution to the presentation of age, period and cohort effects.

The diversity of graphical, tabular and model-based analyses applied in recent studies, as demonstrated in the last section, probably reflects the descriptive (imprecise) nature of this form of study and a lack of consensus – between both methodologists and practitioners – regarding a suitable presentation of the model effects. The last point is not likely to be easily remedied given the inherent difficulties in obtaining satisfactory inferences from the full APC model. The present heterogeneity of methods used in APC analyses reinforces the need to address the major issues of concern to better serve future studies, and the following text is a compilation of key observations and recommendations from this chapter. Those items in bold are considered as substantive points that will require attention in the study of trends in practice in Chapters 4-6:

- **No statistical tests should start without a thorough understanding of the observed trends. Graphical approaches can be informative, lending support to the relative importance of period versus cohort. They may also inform the APC modelling approach and interpretation of the subsequent parameters.**
- **Although some guidelines for displaying trends in rates are available, basic characteristics of graphics displayed in publications are largely heterogeneous. Technical issues in producing graphs for peer-reviewed publication are not given sufficient priority at the author or editorial level, despite their demonstrated utility in aiding interpretation and improving comparability between studies:**
    - **Arithmetic and logarithmic scales on the y-axis are in general use in plots of rates over time. Arithmetic scales are appropriate where absolute rather than relative changes in magnitude are the main point of interest. Semi-log displays are of greater utility in trends studies however as they allow a visual description of rates of very different orders of magnitude, and identify relative changes in rates irrespective of baseline values.**

- **Detailed labelling of the Y-axes enables identification of absolute as well as relative changes. The ratio of the Y to X-axis can affect interpretation, and scaling rules are available. The use of the same time scale for period and cohort forces the length and shape of the period and cohort lines to be equivalent, and highlights the relationship between the three time factors and the nature of the identifiability problem.**

- **Trends in age-adjusted rates may mask important changes in the age-specific rates, notably the impact of changes in successive birth cohorts. Comparisons of plots of rates versus period by age and birth cohort by age are the most useful of the possible displays in gauging the relative importance and basic characteristics of trends by period and cohort, and also serve to aid interpretation of subsequent APC model output.**

- **In quantifying recent trends in cancer, the EAPC provides a summary of the magnitude and direction of the trend. To circumvent the arbitrary choice of time period for estimation, joinpoint regression allows identification of sudden linear changes in the trend and estimation of the direction and magnitude of the slope within time segments for which rates are relatively stable.**

- **Deciding whether period or cohort effects are important from graphical depictions of the observed rates is itself an arbitrary process, and interpretation of many cancers is too complex to rely solely on visual techniques. The APC model provides a framework for testing and quantifying the overall time trend and the non-linear effects of age, period and cohort, and indicates whether the graphed trends may be considered real or random.**

- Two-factor models are commonly used to present the effects. Justification of such a model is usually provided on the basis of one or more of the following: i) the model fits reasonably well; ii) there is external support that the model is appropriate; iii) the approach always provides a unique solution. The inherent problem of bias in the effects, should one factor primarily occur as a linear pattern, is usually left unchallenged. There is a further under-appreciation that artefactual changes may arise as linear (unidentifiable) period effects.

- **Clayton and Schifflers' net drift has become as an integral part of APC modelling. It provides an estimate of the rate of change in the regular trend, and enables a test of the relative contribution of period and cohort curvature**

over and above the estimable linear component applicable to both. In doing so, the identifiability problem is seen to arise at the two- as well as the three-factor level.

- Where trends convey minimal period or cohort curvature, the APC model may not provide useful information over and above the reporting of the net drift.
- **Net drift estimates obtained over several decades include trends seen in the distant past, and may not reflect recent trends. The relative magnitude and direction of the net drift for the whole study period as well as a more recent epoch may be compared.**

- The full APC model is often the point of departure for trends analyses. Many methods have been proposed:
  - One solution is to equate two effects of one factor, although this may be considered arbitrary, as often one parameterisation cannot be justified against another.
  - Taking the mean first differences of one factor forces the slopes of one effect to return to the baseline value, thereby placing drift with the other factor. While robust for period, the random variation associated with extreme cohorts can lead to resulting cohort slope of magnitudes that do not closely approximate zero, thus rendering the allocation of drift to period erroneous.
- **Holford introduced a flexible approach that explicitly sets the overall slope of one factor to a designated value. On specifying this magnitude, the values of the other two slopes are immediately estimable, and a unique solution emerges.**
  - **The period component of time trends is often considered the least influential of the three effects, and studies using Holford's method usually obtain unique solutions by estimating the period slope, assuming either a slope of zero or a range of values. Imposing a zero period slope puts no restriction on period curvature, which is estimable.**
  - **Postulation as to the direction of a slope founded on biological or epidemiological evidence may be considered amongst the least arbitrary approaches available, although an erroneous specification will create a bias in each of the effects. One possibility is to define the slope for age to conform to a known age pattern for a given cancer.**

- Second differences identify changes in the magnitude of trends by comparing the position of a particular effect relative to preceding and subsequent ones. The approach is conservative given an absence of any linear information, and the estimates need to be interpreted alongside the observed rates and possibly against several arbitrary model parameterisations. Extensions that allow a comparison of the slopes of the linear trend in two epochs have been proposed.
- The fitted values from the full APC model are seldom shown in studies, but often inform regarding any departures from the observed data.
- Several mathematical approaches have been proposed, but can only provide arbitrary interpretations, given that they are informed purely by mathematical properties rather than biological principles. Other approaches including the introduction of identifiable interactions into the APC model and use of the multistage model to fix age effects have their merits but are in practice difficult to implement.
- Often, particularly in analyses of a large population, the models suffer from overdispersion, whereby the variance in the counts is larger than that of the Poisson assumption. Such circumstances render statistical tests somewhat subjective, although methods are available that take overdispersion into account.
- The potential of extrapolating trends in younger generations into later ages is long established. The APC model provides a framework for making predictions and the resulting estimates do not suffer from a lack of identifiability.
    - Several problem areas exist: the assumption that drift will remain constant in the future period; unrealistic predictions as a result of increase exponentially over time; the need for simple models and narrow prediction intervals. These issues have been explored and recent model specifications have been shown to provide reasonable predictions.

As has become appreciated over the last decades, no single APC method can be considered as superior to all others. No definitive solution is available given that the identifiability problem arises from the simple algebraic relation that defines the three factors. With the aim of reaching an honest and informative solution it is reasonable to focus on what is identifiable from the model, and apply our current understanding of the biology and epidemiology of the cancer under investigation in the population under study. The next three chapters of the thesis aim to do this, by considering the recommended graphical and statistical techniques to trends in several cancers in multiple populations. Chapter 4 describes an analysis of trends in the incidence of cervical squamous cell carcinoma and

cervical adenocarcinoma in 13 European countries, Chapter 5, an analysis of endometrial cancer incidence trends in the same 13 European countries, as well as corresponding mortality trends in 28 European countries. Finally, Chapter 6 includes an equivalent trends analysis of testicular germ cell cancer incidence and testicular cancer mortality, and a comparison of cohort-specific trends in the two main histological subtypes of germ cell tumours of the testis.

4 Analyses of temporal trends of cervical cancer in Europe

4.1 Introduction to the chapter

This broad aim of this chapter is a detailed description and evaluation of time trends of cervical cancer incidence in Europe. The focus is on the trends in the main histological subtypes of cervical cancer. The analysis takes advantage of the sufficient time span of high quality cancer registry data available in 13 countries on the continent.

4.1.1 Why analyse trends in cervical cancer?

Cervical cancer is the third most common cancer in women under 65 in Europe after breast and colorectal cancer, with almost one in 100 European women developing the disease before this age [263]. The monitoring of time trends of cervical cancer incidence and mortality in European populations is essential for two reasons. Firstly, the implementation and organisation of cytological screening programmes in Europe varies considerably from country to country [308], and temporal analyses of rates by calendar period among targeted age-groups is fundamental in the evaluation of the effectiveness of organised programmes, and may allow some assessment of the impact of opportunistic screening, where it is prevalent. Exposing contrasting trends in populations with longstanding and highly organised screening programmes with those where programmes have either not been implemented or are considered ineffective, provides compelling visual evidence for the need for immediate action to remedy the situation [309].

A second area of interest in the study of cervical cancer trends involves the changing prevalence of infection with HPV, established as the virtually necessary cause of cervical cancer [310,311]. The monitoring of disease rates among successive generations provides a means to examine changes in the central modifier of risk – levels of persistent infection with high-risk HPV types – as a result of changing patterns of sexual behaviour among birth cohorts [309].

4.1.2 Why analyse incidence?

Incidence is an appropriate statistic for evaluating the impact of the screening test, as cytological screening can detect cervical cancer precursors and aims to reduce the incidence of invasive disease, leading to a subsequent reduction in mortality. While mortality may still have advantages over incidence in terms of longer time series and greater availability with larger population coverage (often national), these are offset by several difficulties associated with their use.

Firstly, the quality of diagnostic information is a major hurdle: there has been a historical failure to distinguish cancers of the uterine cervix, instead they have often been assigned

the code "malignant neoplasm of the uterus, part not specified". These "unspecified" deaths, as a proportion of all uterine cancer mortality, vary considerably among European countries, and for some (such as Italy), they represent over 50% of all uterine cancer deaths [312]. Importantly for the study of time trends, there has been a tendency for the unspecified proportion to decrease over calendar time. The problem is exacerbated by the structure of the 8th revision of ICD and a differing precision of mortality data transmission at the national level, rendering a combined category of "corpus uteri and uterine cancer, unspecified" in the WHO mortality databank [312].

A second interpretational uncertainty with mortality trends stems from its characterisation as a function of both incidence and case fatality. Improving survival rates with time may distort trends in mortality and subsequent interpretation when used as a proxy for changing incidence. The favourable long-term trends in stage at diagnosis and survival as a result of better treatment – as observed in Sweden [313] – would indicate that such a characteristic is present in the cervical cancer mortality trends in several European countries.

4.1.3 Why analyse trends by histology?

Studying cervical cancer incidence allows examination of trends according to the main histological subtypes, cervical squamous cell carcinoma and cervical adenocarcinoma, important as they substantially differ in terms of screen detection and possibly their aetiology. Cervical squamous cell carcinoma is the main histological subtype, representing 75-90% of cervical neoplasms in western countries [18]. Adenocarcinomas are rarer, but the proportion of cases with this histology is higher in low risk than in high risk countries [18], possibly as a result of screening. Susceptibility to detection by cytology has been considered much greater for cervical squamous cell carcinoma than for adenocarcinoma, as reported by Mitchell *et al* in a regional case-control study in Australia in 1995 [314]. More recently (in 2003), Mitchell and colleagues have commented that such a distinction may be becoming less apparent, as an understanding of precursors to adenocarcinoma emerges, and methods for detecting endocervical lesions improves [315,316].

Persistent viral infection with the high-risk types of HPV is established as an almost-necessary cause of both cervical cancer subtypes [310,311], although they may differ in the predominant HPV types involved. There is some evidence of heterogeneity in the cofactors associated with the two histological subtypes [317-321], particularly the effects of smoking for which risk is elevated for squamous cell carcinoma but not for adenocarcinoma according to several recent studies [319,321].

4.1.4 Main objectives of the trends analyses

Analyses of incidence trends of cervical squamous cell carcinoma and cervical adenocarcinoma in European women of screening age allows exploration of the varying impact of, and further need for, primary and early detection prevention strategies in each of the 13 countries examined. For each subtype, the main objective is an evaluation of trends related to:

- the effectiveness of cytological screening in Europe, characterised at present by a broad range of screening policies and implementation strategies [308];
- changing risk patterns amongst European women, likely related to a changing population prevalence of high-risk HPV types.

Before this work is presented and discussed, some background on the epidemiology and screening of cervical cancer and its histological subtypes is given below.

4.2 Review of cervical cancer epidemiology and screening

4.2.1 Descriptive epidemiology

Cervical cancer, the second most common cancer amongst women worldwide, is responsible for almost 10% of all new female cancers. Almost half a million new cases of cervical cancer were estimated to have occurred worldwide in 2002, the vast majority – over four-fifths – in developing countries. The highest incidence rates were observed in Latin America, the Caribbean, Sub-Saharan Africa, and South and South East Asia. Cervical cancer tends to be less common in most of Europe, North America, Japan, Australia and New Zealand. The disease comprised about 4.5% of all cancers among European women in 2002, ranking seventh most common cancer in terms of the absolute number of cases.

The worldwide geographic variation is in part a reflection of the extent to which the Pap test has been available and routinely introduced as a screening tool historically, with low rates often in countries where cytological screening has been successful in reducing incidence (in some economically developed countries), and high rates in countries and areas where intervention has been largely absent (in most developing countries). The impact of screening can be readily observed by comparing the age-adjusted rates of cervical cancer in Western populations in the pre-screening era with those seen in developing areas today (Figure 4.1). Before the advent of cytological programmes in the 1960s and 1970s, the incidence in much of Europe, North America, and Japan was similar to that currently estimated in developing countries in 2002 [221]; the rates in pre-screening periods in the U.S. [84], in Northern Europe e.g. Denmark [169] and neighbouring German city Hamburg [169], for instance, are of the same order of magnitude as current incidence estimates in Eastern Africa, the region

presently with the highest cervical cancer rates in the world. It should also be noted that not all countries in Europe could be considered as low-risk in 2002. Estimated rates in Romania and Slovenia are, for example, three to four times those of their European counterparts, and they are also higher than overall rates estimated for developing countries combined (Figure 4.1).

Gustafsson and colleagues [221] were able to categorise the age profile of cervical cancer in international populations and in periods before the Pap test could have had an effect, into fitting one of two reference curves. Figure 4.2 demonstrates that in the absence of screening, the incidence of cervical cancer begins to rise around the age of 25, with risk rising rapidly between the ages of 30 through 40 to reach a peak rate of incidence around age 45-49 in many western populations, but often later in developing countries [221]. Rates thereafter decline, although the downward slope is of lesser magnitude than the increase seen in younger women. As would be expected, the age pattern profoundly changed following the advent of screening programmes [322].

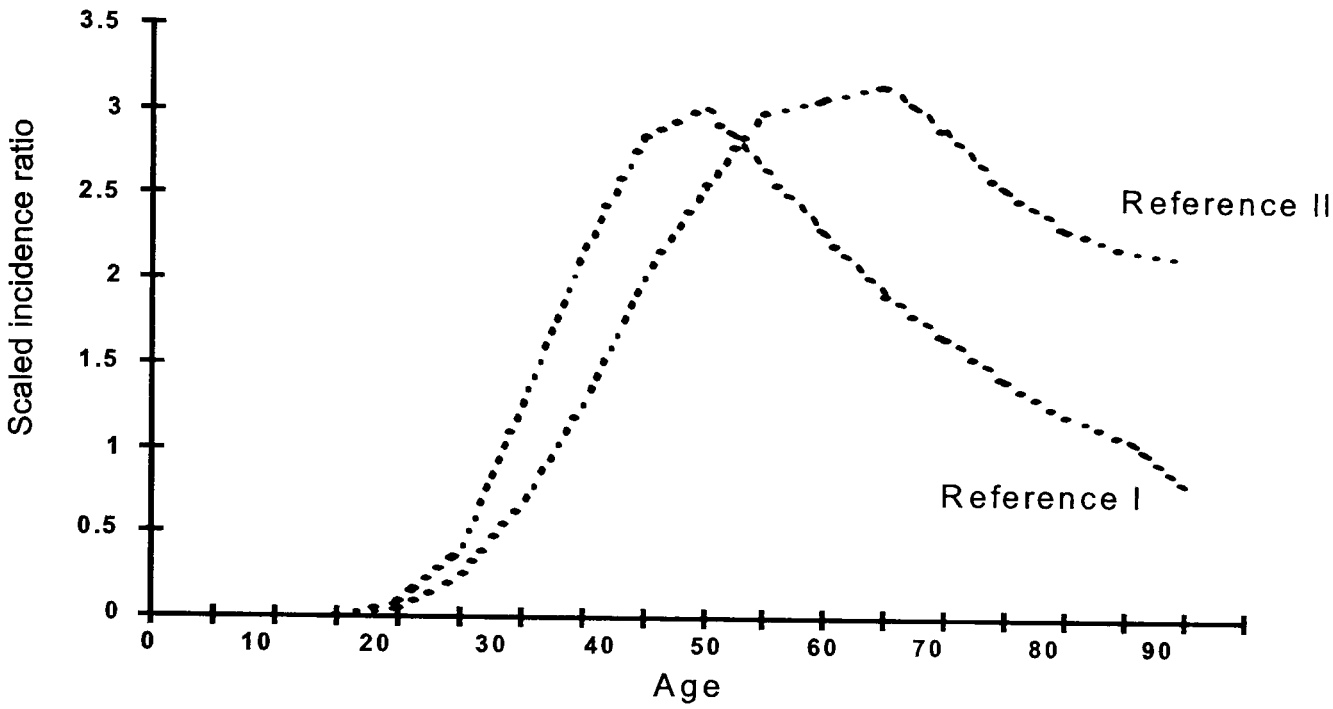
Most incident cases of cervical cancer are squamous cell carcinomas. Adenocarcinomas are rarer, but the proportion of adenocarcinomas cases is higher in low incidence areas than high risk areas [323]. This may be due to the initiation of screening programmes, as screening by cytology is considerably more effective in preventing squamous cell cancer than adenocarcinoma (see 4.2.3.1).

Mortality rates are substantially lower than incidence rates, although the geographic variability is similar. Some 273,000 cervical cancer deaths occurred globally in 2002 [18]. Reasonable prognosis is seen in low-risk higher resources settings; in the U.S., average five-year relative survival for all races is 73% for cases diagnosed 1995-2001 [29] and 62% in the European registries for cases diagnosed 1990-94 [138]. In developing countries, where many cases present at a relatively advanced stage, survival is fair, the most recent five-year estimate put at 49% [324]. Among the lowest survival figures are those in Eastern Europe; in Poland, the five-year survival estimate is 48% for those diagnosed in the early-1990s [138].

As the disease predominantly affects relatively young women, it is a major cause of lost years of life in many developing regions. A recent study estimating age-weighted years of life lost (YLL) due to the different major causes of death found cervical cancer responsible for the loss of 2.3 million years of life, the biggest single cause of YLL from cancer in developing areas [325]. Further, the disease made a more substantial contribution to lost years of life than tuberculosis, maternal conditions or AIDS in Latin America, the Caribbean and Eastern Europe.

Figure 4.1: Cervical cancer age-standardised incidence rates in selected countries in 2002 (as reported in GLOBOCAN 2002 [263]) and in pre-screening populations as reported in the Volume I of CI5 [18] and Dorn and Cutler [84]

Figure 4.2: Reference curves for the age profile of cervical cancer incidence. Curves are scaled ratios based on rates in international populations in periods prior to cytological screening, assigned to one of the two references types. Adapted from Figure 4 of Gustafsson et al [221]



4.2.2 Aetiology

Variations in cervical cancer incidence with respect to demographic variables such as social class, marital status, ethnicity and religion have long implicated a role for sexual activity. In 1974, Beral proposed a causative role for a sexually transmitted agent on the basis of the similarity of cohort trends in cervical cancer and gonorrhoea infection in young women in England and Wales [89]. Epidemiological studies in the decades that followed showed consistent associations between risk and early age of initiation of sexual activity, increasing number of sexual partners of females or of their sexual partners, and other indicators of sexual behaviour [326]. The discovery of HPV type 16 emerged from its presence in the majority of cervical cancer biopsies in 1983 [327], and within the last 10-15 years, supported by the emerging molecular technology, it has been demonstrated beyond doubt that virtually all cases of cervical cancer harbour (as currently estimated) one of 15 oncogenic types of HPV DNA [310,328,329], types 16, 18, 31, 33, 35, 39, 45, rf51, 52, 56, 58, 59, 68, 73 and 82. From an update of the Bradford Hill criteria, a comprehensive evaluation of the association between HPV and cervical cancer has also demonstrated causality [311].

Previously established risk factors for cervical cancer related to sexual activity have had to be re-evaluated in the light of HPV as the necessary cause of cervical cancer, given that they may have been acting as proxies of HPV exposure or were cofactors given the

presence of HPV [309]. Currently, after careful adjustment of oncogenic infection, the residual effects of several additional factors have been noted. Recent pooled analyses of studies have revealed that cofactors may modify the probability of HPV exposure and infection, and the residual effects of high parity [330], oral contraceptive use (although effect of cessation is undetermined) [320,330], tobacco smoking [321,330] and *Chlamydia trachomatis* exposure [331] on cervical cancer risk have been reported. The progression of HPV infection to pre-invasive and invasive cervical cancer may be increased among HIV-carriers and AIDS patients, possibly related to an absence of screening and the severity of immunosuppression [309].

4.2.2.1 Differences in main histological subtypes

A recent meta-analysis of six case-control studies indicated that adenocarcinoma and squamous cell carcinoma share many risk factors including surrogates for persistent oncogenic HPV infection such as the number of sexual partners, early age of first intercourse, and an early age of first birth, as well as the use of oral contraceptives [332]. While some heterogeneity in risk factors has been noted in a U.S study [317,333,334], the only consistent finding across studies refers to smoking, which has been reported to moderately increase the risk of squamous cell carcinoma, but not adenocarcinoma [319,321,332,335].

Adenocarcinoma has been shown to be more associated with the acquisition of HPV type 18 than squamous cell carcinoma, which in turn is more associated with HPV-16 than adenocarcinoma [328]. Reasons for this specificity are at present unidentified [311]. It may point to a lower overall prevalence of high-risk HPV DNA in adenocarcinoma compared to squamous cell carcinoma, as observed in a number of studies e.g. [336], indicative of a subset of women whom developed the disease through mechanisms unrelated to HPV infection. However, explanations related to artefact are probable. The testing of inadequate samples, sampling errors of HPV detection in biopsies, and misclassification of adenocarcinomas of the endometrium as of the cervix may all lead to such biased findings [318]. Recent studies are now estimating the proportion of adenocarcinoma harbouring high risk HPV types as close to 100% [318].

4.2.3 Cytological screening practices in Europe

Cervical cancer is a highly preventable disease; it is detectable at a (usually prolonged) premalignant phase and has a suitable screening test in the Pap smear. Epidemiological studies have revealed that cervical cancer cases typically have been less adequately screened than controls (women free of the disease). Where population-based screening has

been implemented and routinely practiced, large declines in both cervical cancer incidence and mortality have been reported [193,337-339]. A recent IARC evaluation concluded that there was sufficient evidence that screening women aged 35 to 64 for cervical cancer precursors by conventional cytology every three to five years within high-quality programmes reduces incidence of invasive cervical cancer by at least 80% among those screened [309]. In spite of this, there are large variations in current screening policies in Europe and in organisational aspects of established programmes [308,315]. Table 4.1 summarises, for selected countries and for regions covered by registries within countries, basic characteristics of the screening programmes [308]. The populations correspond to areas where there is long-term population-based cancer registration, and for which the data are considered of high quality.

4.2.3.1 Differences in main histological subtypes

Screening using the Pap test has been shown to effectively detect squamous cell carcinoma in early stages, although reports have considered it much less effective at detecting adenocarcinoma [314,340,341]. Recent work by Mitchell and colleagues however has suggested the efficacy of cytological examinations in finding adenocarcinoma has improved during the 1990s, and may have been responsible for some reductions in adenocarcinoma around this time. They observed decreases among Australian women who had a pap smear with endocervical material within one year, or with an increasing number of pap smears with an endocervical component [316].

It is possible that an increasing ability to detect endocervical lesions in cervical screening may arise from the improved diagnostic yield obtained on utilising the extended tip spatula or the Cervex (endocervical) brush, or a combination of both [342], as well as an understanding and recognition of adenocarcinoma in situ [343]. Nevertheless, in the Province of Florence, Italy, the extended tip spatula has been in common use since the 1980s, and has had little impact on the increasing adenocarcinoma rates in women aged under 55 [344]. In a further case-control study in the same reigon, the cytobrush did not appear to offer any significant protection from adenocarcinoma [341].

Table 4.1: Overview of screening policy* in countries and regions where cervical squamous cell carcinoma incidence trends are presented- reported year of onset, age range targeted and recommended screening interval

European Area	Incidence Population	Year of onset of organised screening programme, type of screening system, area covered	Age range targeted (year programme began)	Recommended screening interval with normal result (years)
Northern	Denmark	1967 (achieved 90% coverage of women aged 23-59 years by 1997 [345]	23-59 (1986)	3 (some counties 5 years in >45 or 50)
	Estonia	No screening programme	No screening programme	No screening programme
	Finland	1963 (national coverage)	30-60 (1993)	5
	Norway	1995, pilot 1992 (programme in one county 1959-1977)	25-69 (1992)	3
	Sweden	1967-73 in different counties, Gothenburg 1977	23-60 (1999)	3 in ages 23-50; 5 in ages 51-60
	United Kingdom	1988 (national coverage)	20-64 (1988, reviewed 2003)	3-5 (currently 3 in ages 25-49 and 5 in ages 50-64)
Eastern	Czech Republic	Opportunistic since 1966 (screening in two districts, beginning 2004)	Not specified (1966)	1
	Slovakia	- (intention to initiate programme)	25-64 (--)	3
Southern	Italy	Parma (1998) Ragusa (No data) Torino (1992) Varese (No data)	Parma: 25-64 (1998) Ragusa: 25-64 (1996) Torino: 25-64 (1992) Varese: 25-64 (1996)	3 3 3 3
	Slovenia	Opportunistic until 2003	20-64 (2003)	3
	Spain	Catalonia (opportunistic until 1993)	Catalonia: 20-64 (1993)	3-5: initially 2 smears 1 year apart. Then 3 years in ages 20-34 and 5 years in ages 35-64
Western	France	Bas-Rhin (1994) Doubs (1993) Isére (1990)	Bas-Rhin: 25-65 (1990) Doubs: 20-65 (1993) Isére: 50-69 (1990)	3 3 (after 2 normal exams with 1 year interval) 3
	Switzerland	Opportunistic (no data)	18-69 (no data)	3

* **Based on data** from the European Cervical Cancer Screening Network (ECCSN) questionnaire survey. Adapted from Table 1 of Antilla *et al*, 2004 [308].

4.3 Review of temporal studies of cervical cancer in Europe

4.3.1 Cervical cancer incidence and mortality

Overall, rates of cervical cancer incidence and mortality have declined in the last 40 years in Western Europe [8,35]. Mortality declines predated the introduction of screening, and these have been ascribed loosely to factors related to increasing socioeconomic levels such as improvements in genital hygiene, reduced parity, and a reduction in the prevalence of sexually-transmitted disease [346]. More recently, the beneficial effects of cytological screening programmes at the population level have been quite evident.

The most familiar to investigators studying the impact of cytological screening at the population level have been the temporal studies in the Nordic countries, for which high quality national registry incidence data have been available since the 1950s. The comparisons of incidence and mortality trends between the five countries enabled quantification of the effectiveness of screening in absolute and relative terms, given the contrasting national policies in relation to its implementation [193,309,338]. The declines in incidence were allied to the coverage and extent of the organised programmes [309], and were most marked in the age groups targeted by these programmes [322]. The largest decreases were observed in Finland, with its highly successful screening programme reducing cervical cancer mortality from a peak rate of 6.6 per 100,000 in the late 1960s to 1.2 in 1991, a reduction of 80%. Respective declines of 65% and 55% were observed in Sweden and Denmark over the same period, countries partially covered with organised programmes. The decline was of a lesser order in Norway (41%), where an organised programme was only introduced in 1995. Opportunistic screening had increased throughout the period in all four countries [309].

Although screening in North East Scotland has been shown to be effective – a mortality decline of 63% was noted between 1968 and 1991 [339] –the programme was considered much less so in England as a result of a lack of coverage and follow-up. Since the introduction of an organised national programme in the late 1980s and a corresponding upsurge in coverage within the following five years, the re-launched programme has, given the recent marked declines, been considered a notable success [187,347,348], with recent estimates suggesting the programme has prevented up to 5,000 deaths per year in England and Wales [349].

In spite of the overall declines in crude or age-adjusted incidence and mortality, increases have been reported among young women. The phenomenon was first described in England and Wales by Hill and Adelstein [350], where successive generations of women born since

the mid-1930s were at increasingly high risk, and subsequently by others [189,351,352]. Similar observations have been seen elsewhere in Europe including Belgium [228,353], Scotland [339], Slovenia [354], Slovakia [355], Spain [356], and in several countries of Eastern Europe [346]. These are considered to be due to changes in sexual habits and increased transmission of HPV among younger generations. Even in Finland, marked increases in incidence in younger women (below 55 years of age) have been observed since 1990 [357]. A number of factors have been considered responsible including increased transmission of HPV [357], shortfalls in screening attendance [357], and the inferior quality of cytological laboratory procedures during the 1990s [358].

4.3.2 Squamous cell carcinoma incidence

As squamous cell carcinoma represents the vast majority of cervical cancers, the time trends (and their interpretation) are usually analogous to those observed for cervical cancer overall. A large international study of cervical squamous cell carcinoma trends in 25 countries by Vizcaino and colleagues found declines in incidence in younger (aged 25-49 years) and older (aged 50-74) women in most European countries [252]. Several recent studies have reported trends in cervical squamous cell carcinoma in relation to the effectiveness of national screening programmes. A Swedish study reported little or no increase in risk in cervical squamous cell carcinoma in young women due to effective screening, and stable trends in young women with a levelling off of risk in cohorts born since the mid-1940s [359]. Exceptions to the decreases were observed in the international study: increases were seen among young women resident in the U.K., Slovenia, and Slovakia [252]. In the U.K., a number of recent reports have however communicated that the improved programme has successfully countered observed rises in rates of cervical squamous cell carcinoma [187,348,360].

4.3.3 Adenocarcinoma incidence

Studies in the last twenty years in Finland [357], Italy [361], the Netherlands [362], Norway [363,364], Sweden [359,365] and the U.K. [189,366] have reported increasing rates of cervical adenocarcinoma relative to squamous cell carcinomas. Most noted increasing rates among younger women, particularly under the age of 40. As a result, adenocarcinoma may comprise up to 25% of cervical cancer cases in the respective Western countries [18].

The differential in the temporal profile of the two main subtypes of invasive cervical cancer is in keeping with the proposal of a relative inability of cytological screening to reduce the rates of invasive adenocarcinoma [18]. The Swedish study reported steady increases in period-specific risk from 1975 to 1992, while in England and Wales, incidence rates in women

under 40 were reported to have reached a maximum by the late 1980s [366]. As the increases appear to affect relatively recent generations of women from many countries [253], they may reflect a changing prevalence of oncogenic types of HPV among these younger cohorts, the effect of which on squamous cell tumours has been diminished by screening programmes.

4.4 Study I: APC trends in cervical squamous cell carcinoma incidence

The text in this section describes an original analysis with discussion of the incidence trends of cervical squamous cell carcinoma in 13 European countries, with particular emphasis on the period and cohort effects resulting from the use of the APC model. A version of this section has recently been published in a peer-reviewed journal [367].

4.4.1 Data sources and data quality

Registered new cases of cervical cancer and corresponding population data were extracted from EUROCIM [160] for women aged 30-64 (see 2.8 for details and standard inclusion criteria). Cervical squamous cell carcinoma was classified according to the ICD-O-2 morphology codes 8051-8076 [131]. The time-span of available registry data in the 13 countries varied from 15 to 45 years (Table 4.2).

There are specific issues that concern interpretation of time trends of carcinoma of the cervix, including changes over time in the proportions of unspecified cervical cancer and unspecified cervical carcinoma, and in the prevalence of hysterectomy. Carcinomas of squamous cell origin coded as 'uterus unspecified' (<1% of all uterine cancer cases) were included as cervical squamous cell carcinoma. No attempt was made to reattribute the unspecified carcinomas and cancers, as has been performed elsewhere [189]. The reasoning was that the unspecified group constituted <10% of all cervical cancer cases, and therefore would not materially affect the trends in cervical squamous cell carcinoma.

There have been large variations in the prevalence of hysterectomy in European countries and in populations over time [368]. Hysterectomy in Europe is not as common a procedure as it is in the US, where over 30% of postmenopausal women may have undergone hysterectomy [368]. Recent evidence suggests that, adjustment for hysterectomy affects the magnitude and direction of trends in endometrial cancer in Finland [130] , although the impact on cervical cancer was less profound. The effects on trends in hysterectomy were not taken into account in the present analysis due to a lack of data for different countries in different periods and ages. The incidence of hysterectomy has been increasing in Finland [130], Denmark [369] and England and Wales [23], and the unadjusted trends presented here may underestimate the true temporal pattern in some populations.

Table 4.2: Cervical squamous cell carcinoma: populations included, estimated percentage change in the regular trend, model characteristics and summary of the identifiable attributes of the period and cohort trends, by country within area

European Area	Country	Period*	Incidence†	Person-years†a	ASR (0-74) 1993-7 Per 100,000†	Overall trend (%)‖ 95% CI	Recent trend (%)¶ 95% CI	APC model‡	Residual deviance§	d.f. §	p-value§	Ref. type**	Direction (mid-year) period trend††	Direction (mid-year) cohort trend‡‡
Northern	Denmark	1979-1998 (4)	225	1,216,706	11.8	-2.4 (-2.8 to -2.0)	-3.3 (-4.6 to -1.9)	APC	12.7	10	0.24	I	- (*)	+ (1949)
	Estonia	1971-2000 (6)	99	337,550	16.7	-0.6 (-1.0 to -0.2)	2.8 (0.0 to 5.8)	AC	34.6	24	0.07	II	0 (*)	+ (1936)
	Finland	1955-1999 (9)	65	1,225,829	3.1	-4.7 (-4.8 to -4.5)	8.2 (3.8 to 13.4)	APC	78.2	35	<0.05	I	- (1967)	+ (1945)
	Norway	1953-1997 (9)	185	933,595	11.8	-1.1 (-1.2 to -0.9)	-1.2 (-2.9 to 0.6)	APC	69.3	35	<0.05	I	- (1975)	0 (1943)
	Sweden	1964-1998 (7)	215	1,943,275	6.9	-4.2 (-4.3 to -4.0)	-0.8 (-2.3 to 0.9)	APC	71.4	25	<0.05	I	- (*)	0 (1934) 0 (1954)
	United Kingdom[e]	1978-1997 (4)	1360	11,982,152	6.9	-2.3 (-2.5 to -2.2)	-5.6 (-6.0 to -5.1)	APC	51.2	10	<0.05	I	- (1985)	+ (1933)
Eastern	Czech Republic	1985-1999 (3)	651	2,366,652	17.2	-0.6 (-1.1 to -0.2)	-2.0 (-2.8 to -1.1)	APC	9.5	5	0.09	I	0 (*)	0 (1945)
	Slovakia	1968-1997 (6)	384	1,180,261	18.1	1.5 (1.2 to 1.8)	1.1 (-0.2 to 2.6)	APC	38.9	20	<0.05	I/II	- (1985)	+ (1938)
Southern	Italy[b]	1983-1997 (3)	119	1,118,959	6.3	-1.4 (-2.5 to -0.2)	-0.8 (-2.9 to 1.7)	AD	14.5	13	0.34	I/II	- (*)	+ (1948)
	Slovenia	1985-1999 (3)	126	475,358	14.0	3.5 (2.1 to 5.0)	5.3 (2.5 to 8.5)	AC	5.4	6	0.49	I/II	0 (*)	+ (1940)
	Spain[c]	1983-1997 (3)	72	692,076	6.1	0.7 (-0.8 to 2.4)	1.0 (-1.8 to 4.2)	AC	9.0	6	0.18	II	0 (*)	+ (1938)
Western	France[d]	1978-1997 (4)	115	896,132	8.0	-4.2 (-4.8 to -3.7)	-3.8 (-5.5 to -1.9)	APC	24.1	10	<0.05	I	- (*)	0 (1938)
	Switzerland[e]	1983-1997 (3)	73	702,021	6.4	-3.7 (-4.8 to -2.5)	-0.5 (-3.1 to 2.4)	AP	20.5	12	0.06	I	- (*)	0 (1948)

* data available according to period of diagnosis, figure in parentheses represent number of five-year periods available in the analysis
† average annual number of cases/person-years obtained from most recent five-year period
|| EAPC based on the trend parameter from the net drift for the whole study period (95% CI: 95% confidence interval)
¶ EAPC based on the most recent two five-year periods (95% CI: 95% confidence interval)
‡ refers to the most parsimonious final model providing a good fit: AD: Age+Drift; AC: Age+Drift+Cohort; AP: Age+Drift+Period; APC: Age+Drift+Period+Cohort
§ to determine the goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom determined by the model (see Appendix). $p<0.05$ denotes the full APC model does not yield an adequate fit
** age curve of reference type used (see Subjects and Methods)
†† estimated direction of trends by period of diagnosis (+: positive trends, -: negative trend 0: stable trend or difficult to interpret). Major changes in the direction noted in parentheses as the mid-year of the five-year period (* denotes change throughout study period)
‡‡ estimated direction of trends by birth cohort (-: negative trend 0: stable trend or difficult to interpret). Major changes in the direction noted in parentheses as the mid-year of the 10-year birth cohort
a aggregation of England, Scotland
b aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin
c aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza
d aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn
e aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich

4.4.2 Methods: characterising age, period and cohort effects

4.4.2.1 Evidence of a steady state age curve

For most epithelial cancers, risk increases as a power of age [61], and this has been interpreted in terms of a multistage model for carcinogenesis [245,350]. Cervical cancer is an exception in that risk increases until around the age of menopause, and reaches a plateau and declines thereafter. As infection with HPV has been identified as a necessary aetiologic agent in cervical cancer [310,311], the underlying age pattern may be linked to the natural history of HPV infection and its accompanying carcinogenic mechanisms.

Gustafsson and colleagues analysed age-specific cervical cancer incidence rates, selecting populations where screening activity was either minimal or had not become common [221], since the age distribution in post-screened populations changes markedly [322]. After scaling the rates to account for differing orders of magnitude, Gustafsson *et al* [221] found most populations fitted one of two reference curves (Figure 4.2).

Reference curve type I, including Denmark, the Netherlands, Norway, Slovenia and Sweden, was characterised by an onset at about age 25, a rapid rise between 30 and 40 and a peak at ages 44 to 49 years. After the peak, the decline in subsequent age groups was fairly rapid. *Reference curve type II* included Finland, and had an onset at approximately the same age, but a slower rise to a peak at an age around 53 years, followed by a decline similar to reference type I. Data from the U.K. did not fit either curve, probably due to the effect of large variations in risk by birth cohort distorting the cross-sectional curves [350,352].

Gustafsson and colleagues showed that birth cohort trajectories could generate cross-sectional age curves similar to both reference types dependent on the direction and magnitude of the birth cohort trend [221]. These curves must largely reflect cervical squamous cell carcinoma incidence, given that in unscreened populations in Europe, cervical squamous cell carcinoma comprises around 90% of all cervical neoplasms.

4.4.2.2 Interpretation of period and cohort effects

The relationship of cervical cancer incidence to age was assumed to be determined by the natural history of the disease and to be constant over time. Trends in incidence with time could then be partitioned into the effects of birth cohort and period of diagnosis on fixing the age slope using Holford's method, for which the age structures closely resembled each of the Gustafsson reference curves (see 4.4.2.4).

For cervical squamous cell carcinoma, period effects can be viewed as representing the effects of cytological screening, given the intervention should deflect trends downwards across targeted age groups over the same period of time. Cohort effects are usually defined as proxies for changing patterns of risk attributable to ill-defined environmental causes in successive generations of women. For cervical cancer, they point to modifications in the population prevalence of persistent infection with oncogenic types of sexually-transmitted HPV [311,326].

4.4.2.3 Fitting the APC model

Birth cohorts were obtained by subtracting age (the midpoint of five-year age band) from period (the central year of the five-year period of diagnosis). To distinguish the effects of time period and birth cohort on the time trends in each population, the full APC model of {3.6} was fitted according to the procedure described in 3.3.3. The goodness-of-fit of the APC model and its submodels, as well as tests for the overall slope and effects of period and cohort curvature, were obtained using the analysis of deviance of nested models, as suggested by Clayton and Schifflers [63,68].

The net drift term, reported as the EAPC, was utilised to convey the magnitude of the regular trend [63], as discussed in 3.4.1.1.3. A distinction was made between the *overall trend* – the net drift over the whole time period available – and the *recent trend* – the relative change in the last two five-year periods. A two-sided 95% CI for each estimate was also calculated.

The identifiability problem was highlighted by partitioning the age, period and cohort effects in terms of their linear and curvature component parts, according to the method of Holford [66] described in 3.4.2. A single solution was obtained on the basis of assumptions on the age slope α_L, as set out below.

4.4.2.4 Obtaining identifiable period and cohort parameters

The non-identifiability problem was circumvented by specifying *a priori* age-specific curves of cervical squamous cell carcinoma analogous to the reference types suggested by Gustafsson *et al* [221]. Starting with $\alpha_L = 0$, the APC model was refitted with age slope increases of 0.2% per year, until the ratio of the age parameters in the last (60-64) to first (30-34) strata (β_J / B_1) were equal to or greater than i) 1.5; ii) 4.9; and iii) 3.2. The first two ratios (hereafter referred to as type I and type II) match the ratios (and hence resemble the age curves) proposed by Gustafsson *et al* [221]. The ratio was lowered to 1.2 to obtain more plausible type I curves for the Czech Republic, Denmark and Sweden, since a ratio of 1.5 produced curves showing a progressively increasing risk after age 50. A third (type I/II) was

the average of the type I and type II ratios and served as an intermediate age curve. As an example, Figure 4.3 displays three sets of age, period and cohort effects for Slovakia produced by fixing the age structures to resemble types I, II and I/II. Assuming particular magnitudes of the age slope from the full APC model yielded unique period and cohort slopes additional to the identifiable curvature of each factor.

4.4.2.5 Presenting a single set of parameters

As Figure 4.4 demonstrates, each age curve yielded a set of unique period and cohort curves differing with respect to period and cohort trends, and interpretation of the respective impact of screening and changing risk. A less arbitrary (but informative) final set of chosen parameters required an informed decision on the plausibility of the age effects, rather than assumptions regarding the effects of screening or changes in risk factors.

From the three sets estimated for each country, a single set of age, period and cohort parameters was selected on the basis of the plausibility of the age curves and the level of agreement between the model parameters and the observed age, period and cohort trends. As well as presenting the risk patterns in terms of age, period and birth cohort effects, the second differences [68] acted as identifiable indicators of local departures from the linear trend, enabling detection of major changes (accelerations or decelerations) in the period and cohort trends. An attempt was also made to indirectly assess the contribution of the period slope (assumed to be driven by screening) to the Holford's drift, as defined in 3.4.2, essentially equivalent to Clayton and Schifflers' net drift described in 3.4.1.1.3.

The age effects in each country were antilog-transformed to rates per 100,000 person-years to enable absolute comparisons. The period and cohort effects were reparameterised to rate ratios with reference points $P-1$ and $A+P-6$ respectively, and hence the resultant midpoints of baseline risk were country-dependant, varying from 1990-93 for period, and 1938-41 for birth cohort. To indirectly assess the contribution of the period slope to Holford's drift, a comparison of β_L with $\beta_L+\gamma_L$ was made, via the specification of α_L.

Figure 4.3: Cervical squamous cell carcinoma incidence trends, Slovakia 1968-1997, with age reference 'type I' (dashed line), 'type II' (dotted) and type I/II (solid) imposed. Age is on a rate scale. The reference points for period and cohort rate ratios are marked

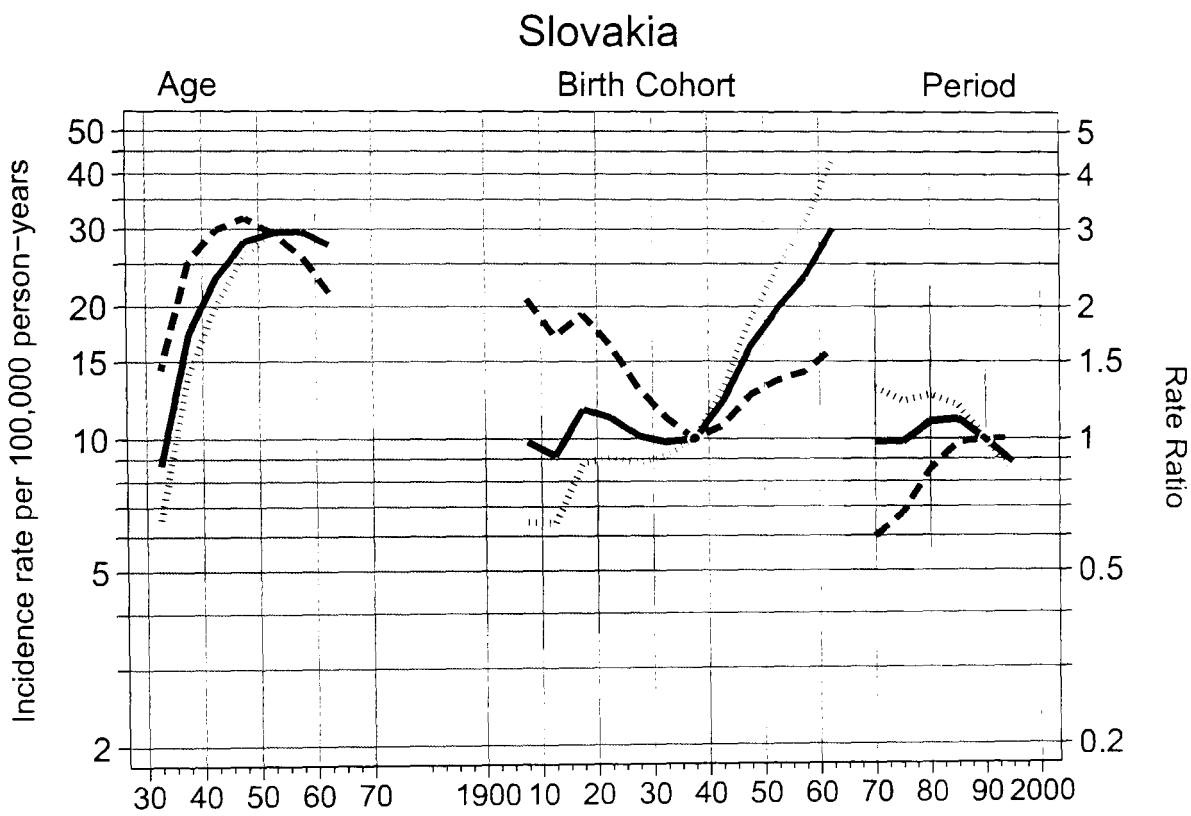
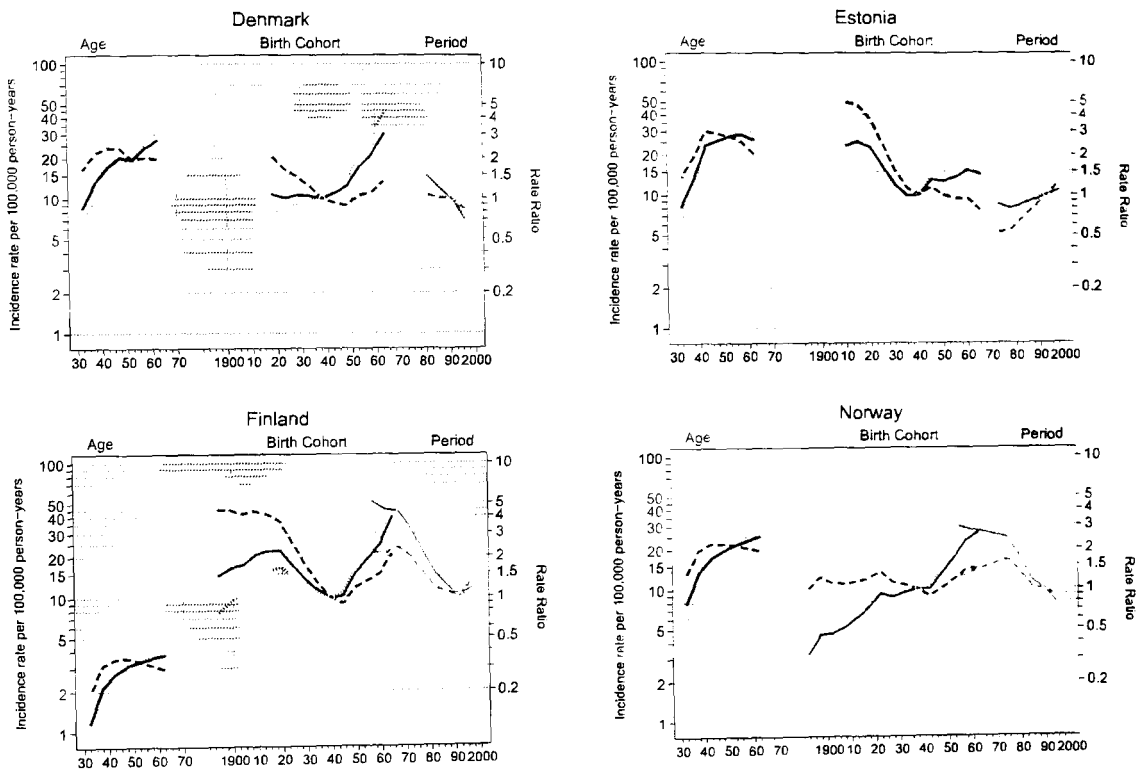
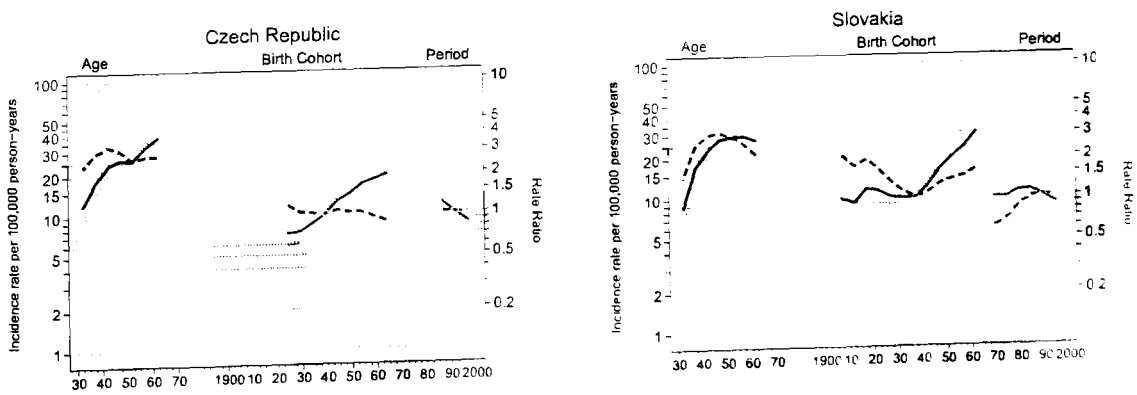


Figure 4.4: Cervical squamous cell carcinoma incidence trends in 13 European countries for women aged 30-64. Trend based on all three reference curves of 'type I' (dashed line), 'type II' (dotted) and type I/II (solid). Age is on a rate scale. The reference points for period and cohort rate ratios are marked

N Europe



E Europe



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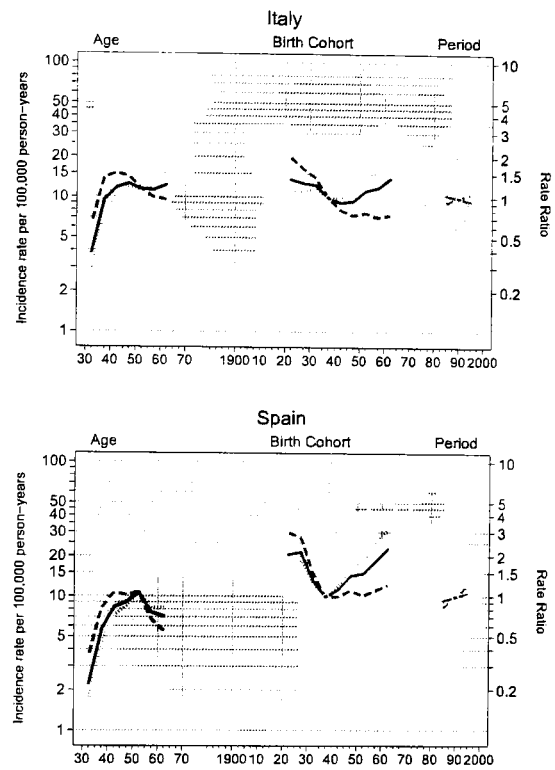

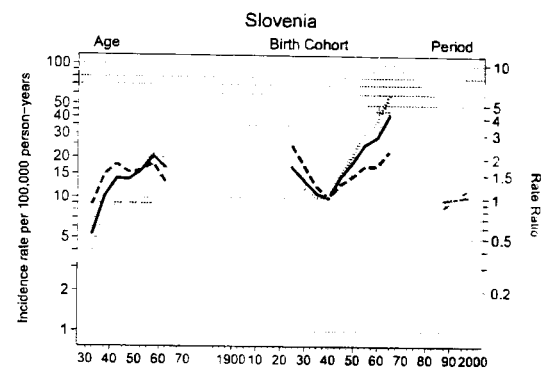

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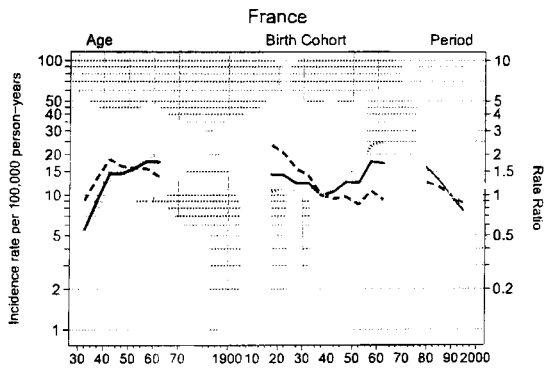
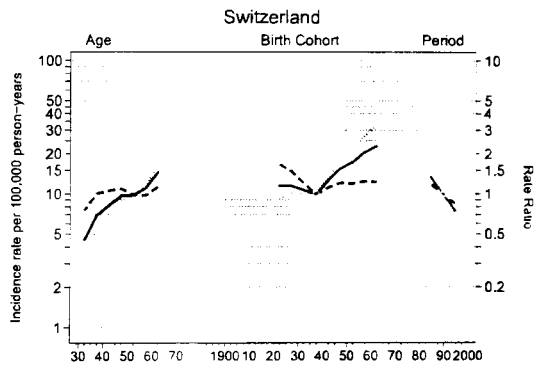


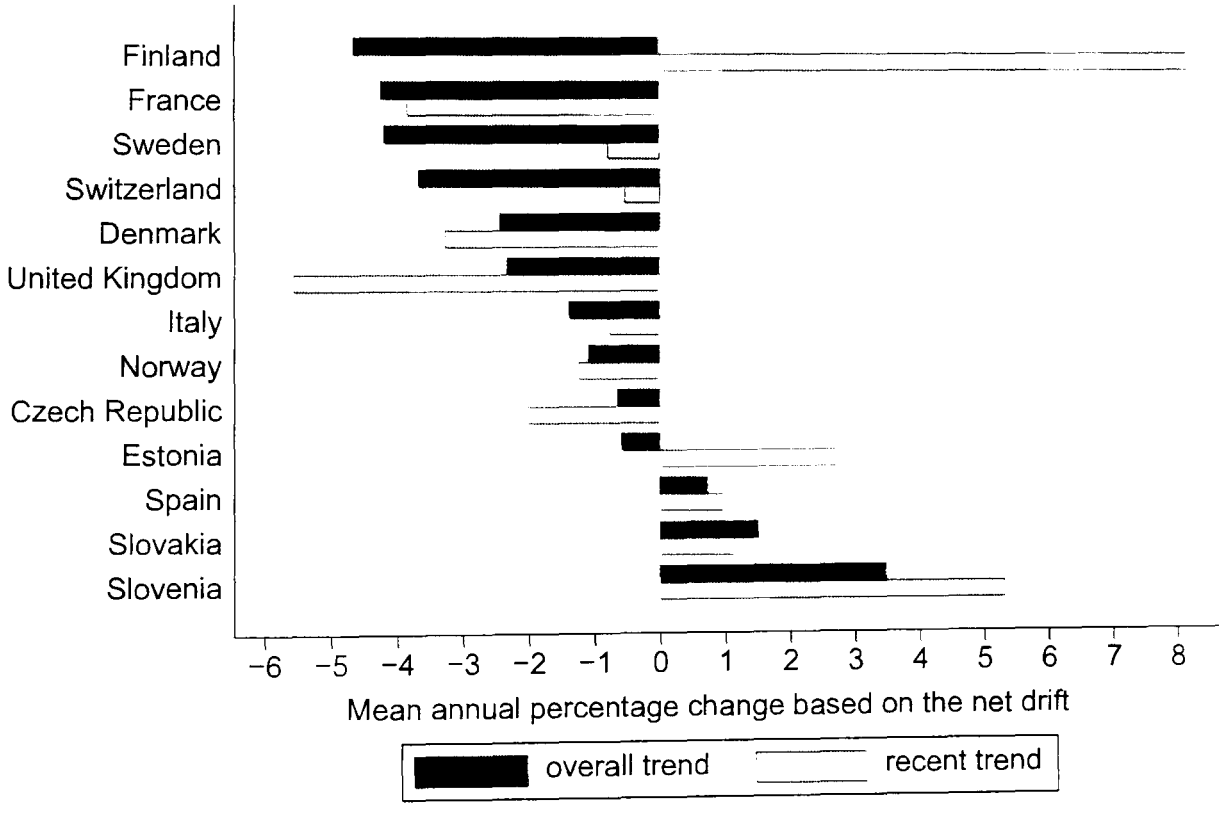


4.4.3 Results: description of trends

4.4.3.1 Regular trend

Figure 4.5 and Table 4.2 show the regular trend in each country across the whole study period, and within the most recent decade. There were large mean decreases in cervical squamous cell carcinoma in a number of Northern and Western European countries over the whole time period - around 4% per year in Finland (95%CI: -4.8% to -4.5%), France (95%CI: -4.8 to -3.7%), Sweden (95%CI: -4.3% to -4.0%) and Switzerland (95%CI: -4.8% to -2.5)%. Average declines of over 2% per annum were seen in Denmark (95%CI: -2.8% to -2.0%) and in the U.K. (95% CI: -2.5% to -2.2%). In contrast, mean annual increases have been observed in Slovenia of 3% per year (95%CI: 2.1% to 5.0%), and in Spain and Slovakia, with non-significant positive trends of 0.7% (95%CI: -0.8% to 2.4%) and 1.5% (95%CI: -0.2% to 2.6%) per annum, respectively.

Figure 4.5: Regular trend over the whole study period and in the last two periods: cervical squamous cell carcinoma incidence in 13 European countries for women aged 30-64, sorted by magnitude of overall trend, expressed as the EAPC.



For countries with a limited span of data, recent trends were of similar magnitude to the overall trends, although some interesting discrepancies emerged between countries with longer periods of observation (Figure 4.5). In Sweden, the (non-significant) decline of 0.8%

per annum (95%CI: -2.3% to 0.9%) in the 1990s was modest compared to the 4.2% (95%CI: -4.3% to -4.0%) decrease over the whole period (1964-1998). In Finland, the direction as well as the magnitude of the trend changed, with a large drop in cervical squamous cell carcinoma of 4% per year over several decades replaced by increases of over 8% (95%CI: 3.8% to 13.4%) per year in the 1990s. The decrease of 5.6% (95%CI: -6.0% to -5.1%) per year in the U.K. between 1988 and 1997 was double that of the decline from 1978-97.

4.4.3.2 Observed trends by age, period and cohort

Figure 4.6 displays the observed rates versus age, period and cohort. As a result of inherent random variation and a combination of forces acting on the trends, there was some difficulty in visualising the trends and appropriating the effects to period or birth cohort. Some notable observations were the following: parallelism of the age-specific decreases by period of diagnosis in Finland from the 1960s; a similar observation in Sweden, but in successive birth cohorts born since the end of World War I; and substantial increases in rates in Estonia, Slovakia and Slovenia rates among consecutive generations born since the early-1940s.

4.4.3.3 Period trends from the APC models

A more comprehensible exposition of the trends is given in Figure 4.7, based on the chosen single set of APC model estimates for each country. In Northern European countries, there was clear evidence of large period-specific declines in cervical squamous cell carcinoma, most notably in Sweden and Finland since the mid-1960s, but also in Norway since the mid-1970s, in the U.K., since the mid-1980s, and in Denmark throughout the study period available (Table 4.2). Within these countries, some indication of accelerations in the declining trends was seen in Norway and Sweden from the 1980s, and clearer evidence of an increasing trend in Finland in the 1990s.

Estonia was an exception within Northern Europe: no trend was discernible in the period parameters. In France and Switzerland (Western Europe), and in Italy (Southern Europe), there were negative period trends in recent periods, whereas in Spain and Slovenia, no such trends were apparent. In Eastern Europe, the trends were slightly different: period effects were largely flat in the Czech Republic, but in Slovakia, a deceleration in cervical squamous cell carcinoma incidence was suggested, detectable from the mid-1980s.

4.4.3.4 Birth cohort trends from the APC models

Figure 4.7 indicates a good correspondence in the birth cohort patterns in several European countries. The declines in risk in generations born in the first three decades of the twentieth century have often been replaced by successive increases in risk in women born thereafter. The timing of the change varied between countries, but in each of them, the escalation of

risk began in generations born in the early 1930s through to the late 1940s (Table 4.2). In Northern Europe, this was evident in cohort trends in Denmark and Finland, but in Estonia and the U.K., the generational increases started a little earlier. The increasing cohort parameters in Norway and Sweden were open to less inference, with a deceleration in the trend in the most recent generations suggested.

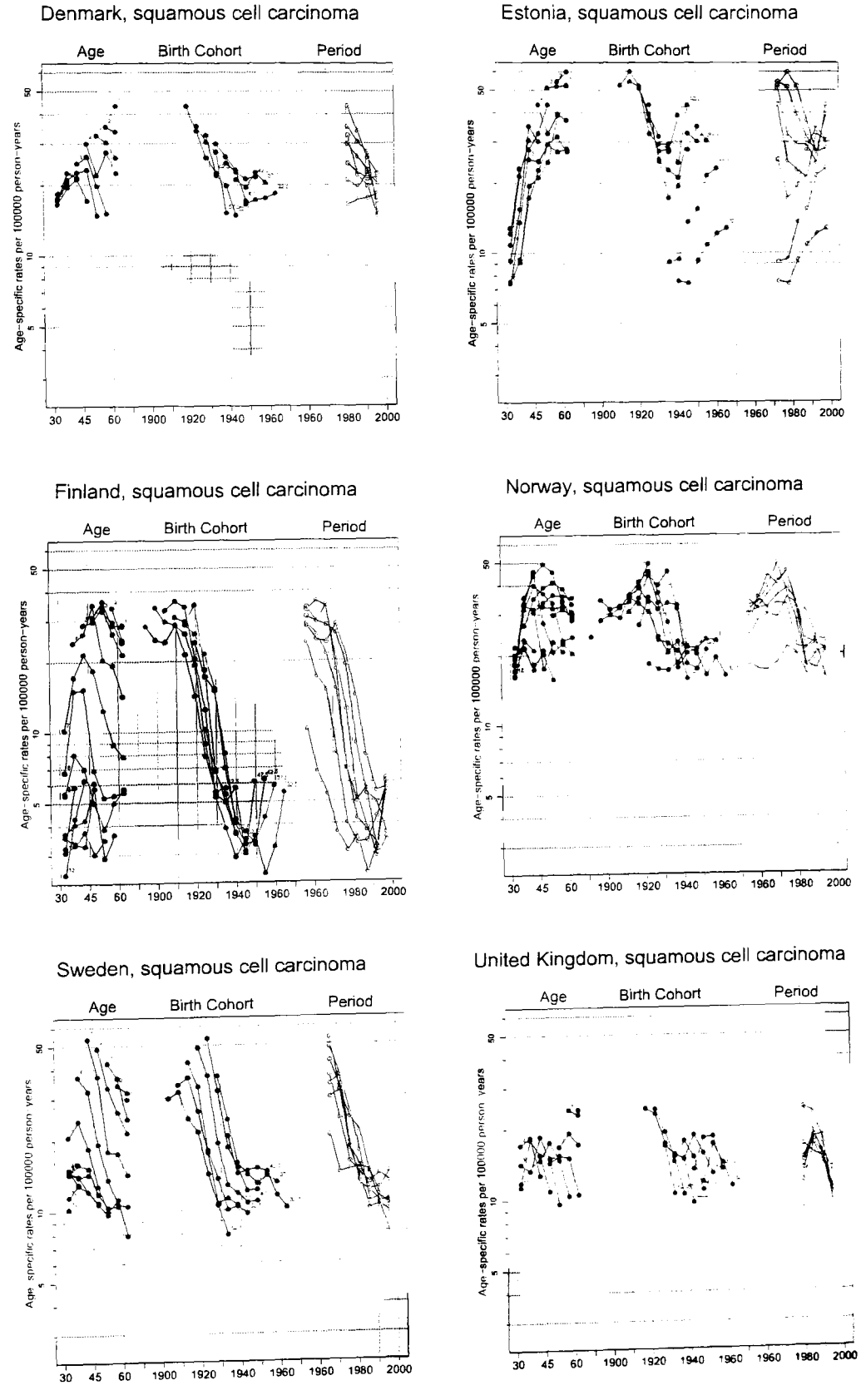
In several Southern and Eastern European countries, increases in risk were observed in women born from around 1940 in Spain, Slovakia and Slovenia. A similar but less marked trend was seen in Italy that started slightly earlier, while in the Czech Republic, little change in risk was seen in successive cohorts. In France and Switzerland, rather constant levels of risk among recent generations have followed the declines observed in cohorts born in the 1920s and 1930s.

4.4.3.5 The contribution of period slope to Holford's drift

Figure 4.8 compares the contribution of the period slope to Holford's drift. The bottom left quadrant includes nine countries in which the downward trend in cervical squamous cell carcinoma is accompanied by a fall attributed to a linear period effect. The negative period slope took up most of the negative regular trend where the observations were reasonably close to the superimposed $y = x$ line, with the extent of the period-specific reduction large in certain countries (e.g. Sweden and Switzerland) and minimal in others (e.g. the Czech Republic). Four countries were characterised by increasing regular trends (the upper quadrants of Figure 4.8), accompanied by period slopes of negligible magnitude. The increase was most notable in Slovenia.

Figure 4.6: Observed trends in cervical squamous cell carcinoma incidence in 13 European countries for women aged 30-64 by region. Left to right: rates versus age by cohort (indices of cohorts indicated), rates versus cohort by age (midpoints of age groups indicated), rates versus period by age. Rates are on a logarithmic scale

N Europe



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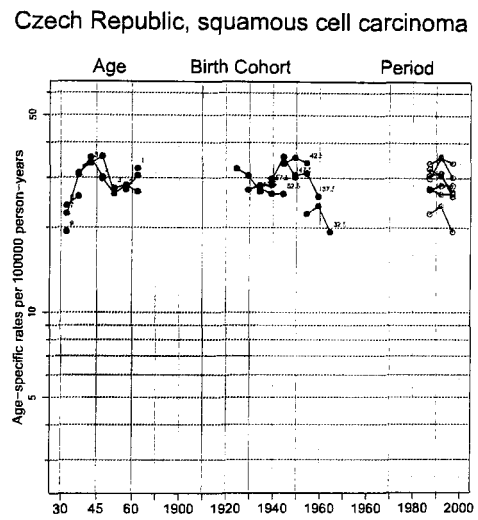

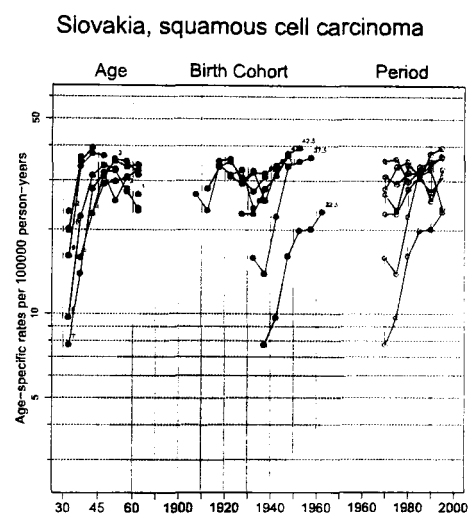

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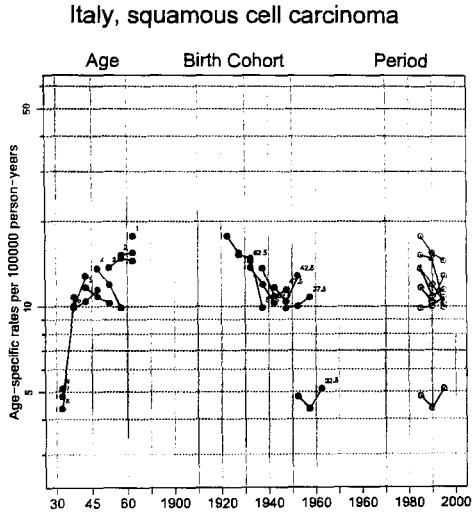

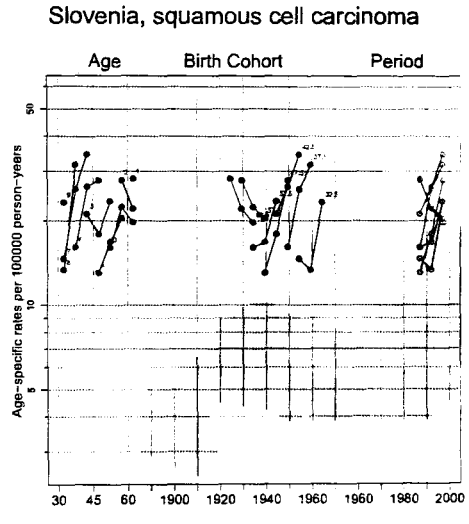

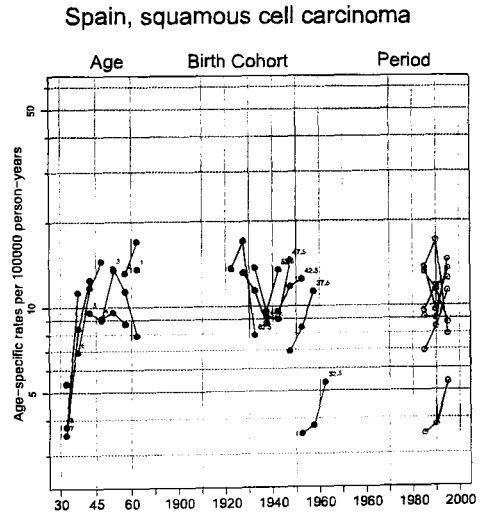

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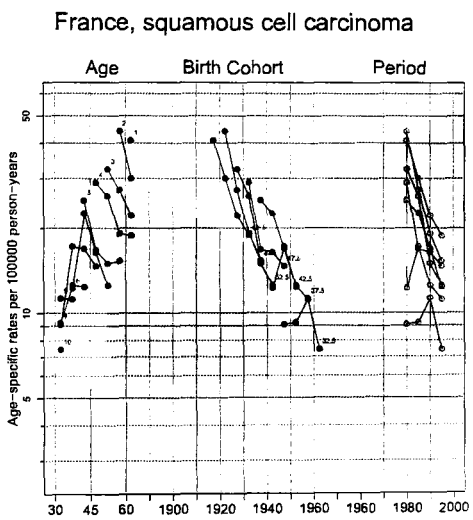


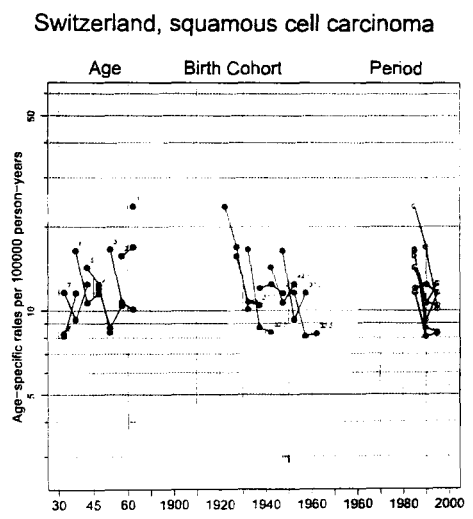
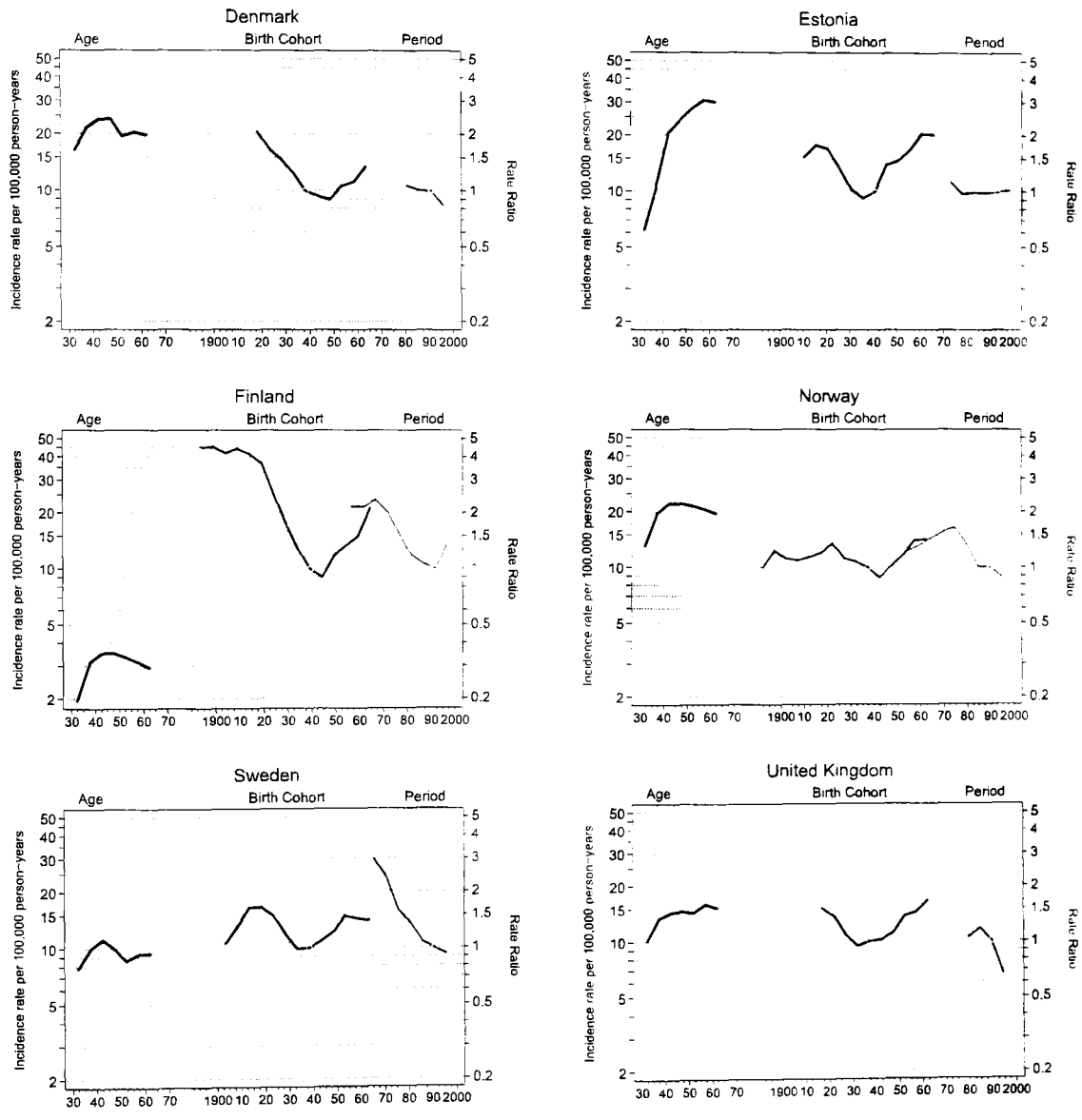


Figure 4.7: Cervical squamous cell carcinoma incidence trends in 13 European countries for women aged 30-64. Age is on a rate per 100,000 scale. The reference points for period and cohort rate ratios are marked

N Europe



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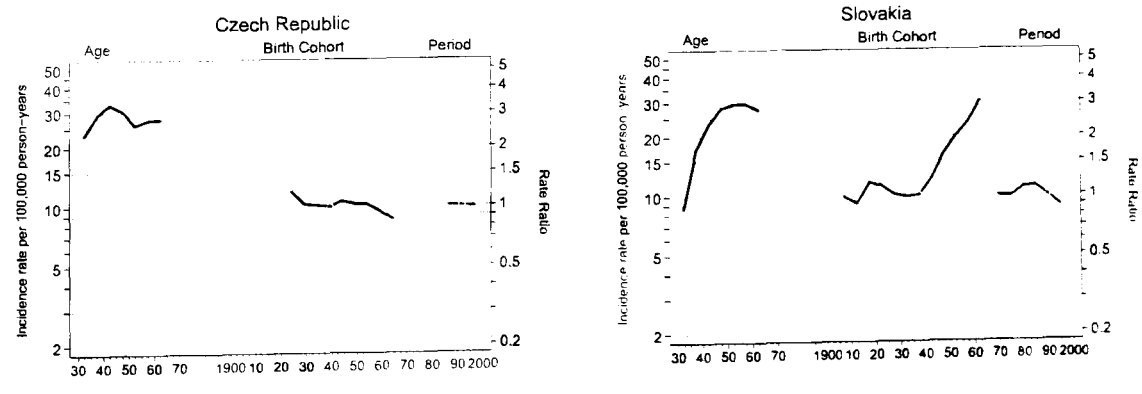

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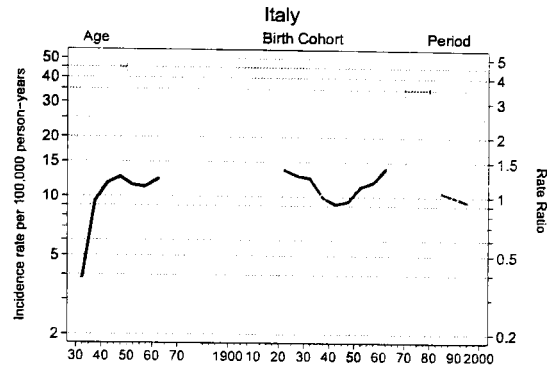

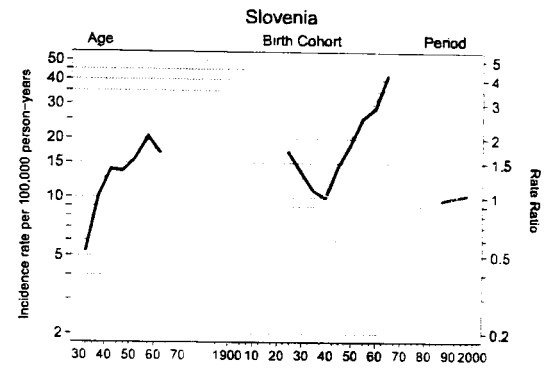

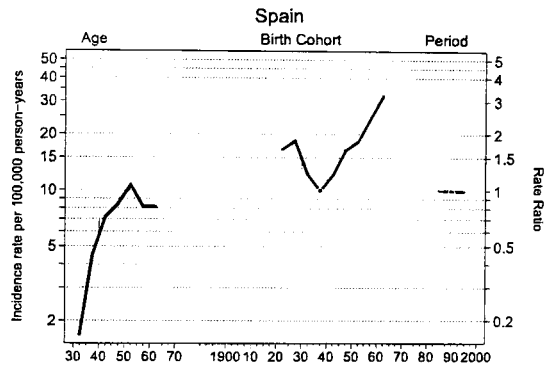

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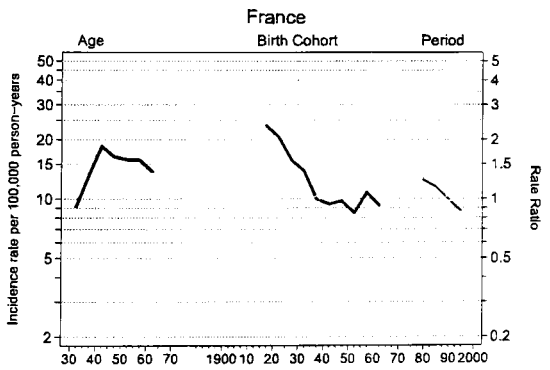


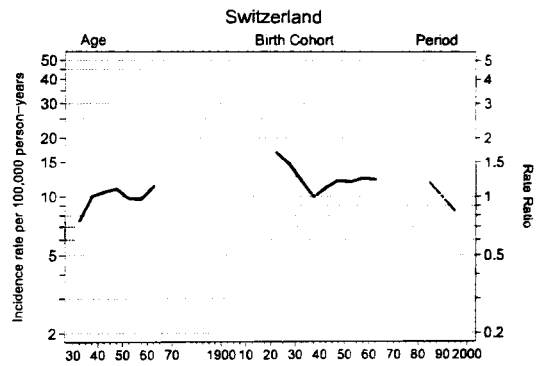
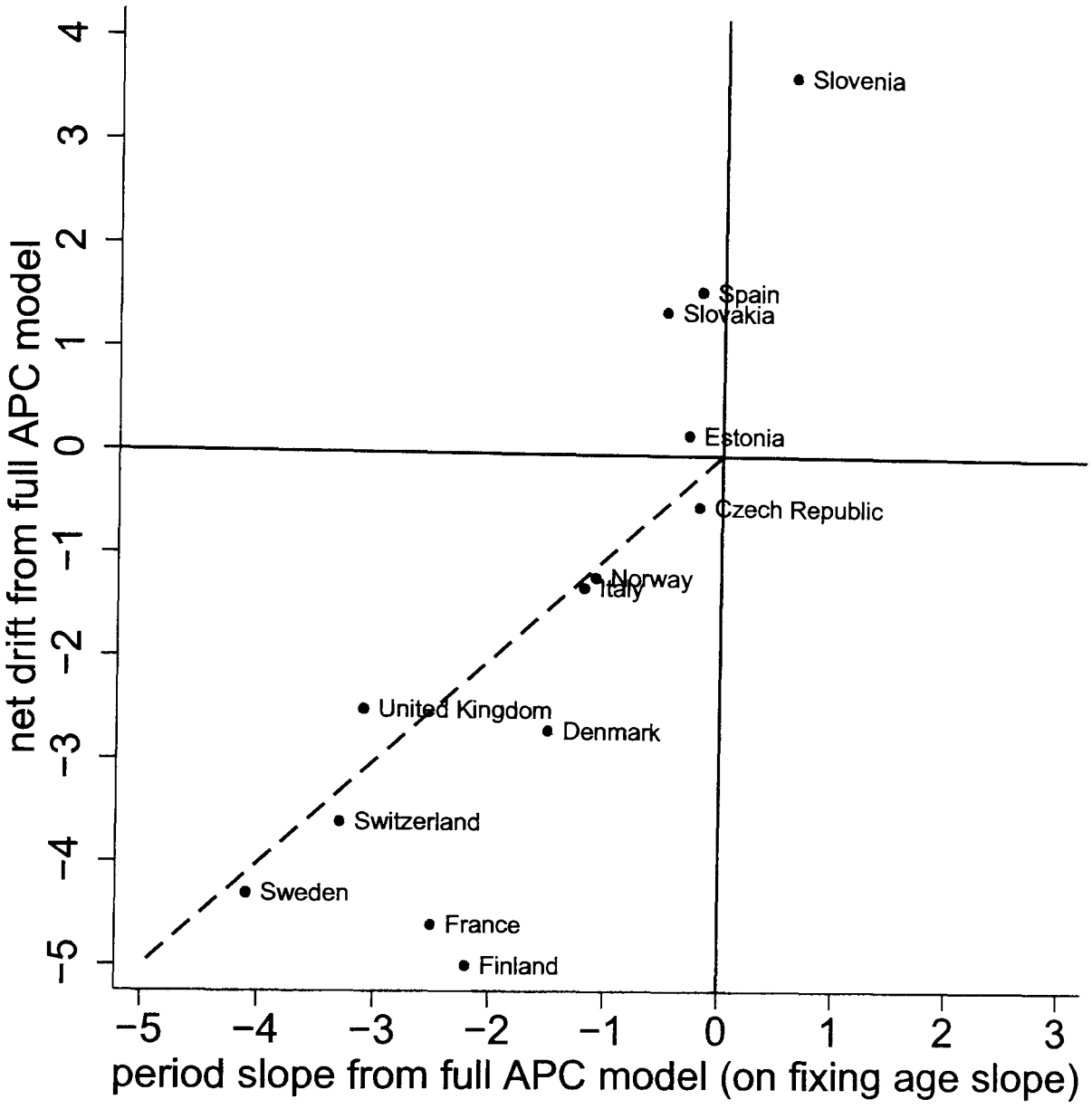


Figure 4.8: Comparison of the net drift and the contribution of the period slope alone. Both are generated from the full APC model and expressed as the EAPC in cervical squamous cell carcinoma incidence in each country



4.4.4 Discussion of main findings

There has been a major decline in the incidence of cervical squamous cell carcinoma over time in a number of European countries. Figure 4.8 demonstrates that in most of them, the decreased incidence is accompanied by a decline in the period slope, implying that it is the consequence of the implementation of effective cytological screening. The absolute and relative magnitudes of the period and cohort slopes between countries should be interpreted with caution as they are dependant on both the available period of observed data (in relation to the initiation of screening), and the initial parameterisation that yielded the particular set of estimates presented.

Nevertheless, in most of the countries in which the period slope is of lower magnitude than the sum of the period and cohort slopes, notably in Finland and France, there were also declines in risk by birth cohort during the study period. In Finland, the moderation of the magnitude of the period slope relative to Holford's drift could be a consequence of the availability of data for over a decade before screening was officially implemented, thereby diminishing its effect. There was almost no reduction in incidence by time period in four countries, implying the absence of effective screening for these women, who are at increasing risk in successive generations. The most obvious examples were Spain and Slovenia, where respective increases of 1% and over 5% per year were observed during the 1990s.

In light of the results, one can broadly dichotomise the European countries in terms of their historical screening activity and its impact on period-specific risk, as well as in term of changing aetiology, as described by trends in risk according to birth cohort.

4.4.4.1 Countries with decreases in period risk, possibly increasing cohort risks

There is clear evidence that screening has been effective in reducing the incidence of cervical squamous cell carcinoma in women in Finland (at least up to the early 1990s) and Sweden since the 1960s, reflecting the implementation of nationally organised programmes in 1963 and 1964, respectively [193,359,370]. In Denmark, the incidence data go as far back as 1979, and the declining period trend was evident throughout. Regional screening was introduced in 1967 in Denmark, initially covering 40% of the population [193,371]. Screening was introduced in Norway in a single county (5% of the population) in the same year [193], and declines in cervical squamous cell carcinoma incidence by period have been occurring since around 1975. A coordinated screening programme has been in operation since the mid-1990s [372], and therefore the declines are probably a result of the increasing levels of opportunistic screening, at least since the time of the period decline.

In the U.K., incidence has been falling since the 1980s, particularly so during the 1990s, likely a result of improvements to the National Health Service Cervical Screening Programme from 1988 [187,189,348,349,373,374]. Period-specific declines in risk were also evident throughout the study period in both France and Switzerland; in France, regional screening programmes were implemented in the early to mid-1990s in three of the six registry areas represented in this analysis. Underlying the period-specific changes in risk in these populations, there are changes in risk of cervical squamous cell carcinoma according to generation. Increasing cohort effects are most likely to be the result of changing sexual mores, resulting in an increased transmission of oncogenic types of HPV with corresponding increases in prevalence of persistent infection and dramatically increased risk [89,375,376].

However, the possibility that women may have been screened differently from one cohort to another needs also to be considered.

Generation-specific increases in risk were evident in Finland in women born since 1945. The increasing incidence among Finnish women below 55 years of age since 1990 has been remarked on previously, and attributed to changing sexual lifestyles and increased transmission of papillomaviruses in younger generations of women [357], and to shortfalls in screening attendance [357]. A more recent study examining several Finnish cytological laboratories suggested that additional explanations were possible, linked to the quality and criteria of lab procedures during this time [358]. In Denmark, some increases in cervical squamous cell carcinoma were seen in women born since 1950, while in the U.K, there were increases in cohorts born since the mid-1930s, as previously reported [189], although incidence rates in women under 55 appeared to be deflected downwards by period-related screening effects. Modest cohort-specific increases in risk in were observed in Sweden in generations born since 1940, suggested to be a consequence of organised and opportunistic screening efforts addressing these cohorts [359]. Further, there has been little or no increase in cervical squamous cell carcinoma rates in young women in this country.

There were no cohort-specific increases in risk among recent generations of women in France and Switzerland. It may be that women in these countries have had different experiences with respect to exposure to aetiological factors than other European women. On the other hand, screening has been mainly opportunistic in these countries, and may have been accepted by successive generations of women (rather than women of all ages, at a given period). In this instance, screening effects on risk would appear as a cohort effect, and counter any underlying increase.

4.4.4.2 Countries with minor changes in period risk, increasing cohort risks

A decline in risk by period was small in Italy throughout the study period (1983 onwards) and in Slovakia since around 1985. This may reflect sporadic screening at low intensity rather than organised screening effects, given that the declines occurred before any regional screening programmes were in place in Italy, while screening policy in Slovakia is currently at the planning stage. In the Czech Republic, Estonia, Spain and Slovenia, there was little or no trend in the period slope, in accordance with the minor screening efforts in these countries.

In a number of these countries there were accelerating incidence trends amongst recently born generations. There were large increases in cohort-specific risk in Slovenia, Slovakia and Spain and, to a lesser extent, in Estonia, from around 1940, and in Italy, beginning

slightly later. The Czech Republic was an exception, in that there appeared to be almost no change in the cohort-specific trends, but, as with several countries, these remain difficult to interpret given the short period of observation. Most disturbing are the substantial cohort-led increases of cervical squamous cell carcinoma in countries where no programmes are in place. The prime example is Slovenia, where the recent regular increase amounts to over 5% per annum.

4.4.4.3 Modelling concerns

A solution to the non-identifiability problem involved considering *a priori* evidence of a constant pattern of age-specific risk over time. From a set of three candidate age curves, similar to those identified in unscreened populations by Gustafsson and colleagues [221], a fixed age slope was determined by taking into account the credibility of the age curves from a biological viewpoint, and on assuming the APC model was correctly specified, supporting evidence that the resultant period and cohort effects were not in disagreement with the observed age-specific trends. Although this does provide a unique solution, the true age-specific risk cannot be directly observed, and the estimates were interpreted with appropriate caution.

The model was employed primarily as a descriptive tool to interpret period- and cohort-specific risk patterns across Europe, although the deviance statistics in Table 4.2 indicated the full model did not fit the data in several countries. Overdispersion, whereby the variance in the counts of incidence is larger than that of the Poisson assumption, is a likely determinant, given the large number of events being analysed at the national level [198]. Additionally, one may speculate that other complex factors than the effects of screening and changing risk patterns, such as spatial effects at the sub-national level, and heterogeneity in the quality or completeness of cervical cancer registration, may also have contributed.

4.5 Study II: APC trends in cervical adenocarcinoma incidence

Incidence trends in the other main histological subtype of cervical cancer, adenocarcinoma, were studied in European women in the same 13 countries, again utilising the APC model. However, additional complexities were anticipated in the study of adenocarcinoma trends that motivated a reappraisal of the methods used in presenting those for squamous cell carcinoma. The increasing capability to diagnose adenocarcinoma and its impact on the trends was a critical issue for this less common histology. Indeterminate knowledge of the biological age curve for adenocarcinoma, and the lack of impact of cytological screening on trends in Europe, had also to be considered. A version of the text in this section has been recently published in a peer-reviewed journal [377].

4.5.1 Data sources and data quality

Registered cases of adenocarcinoma and corresponding population data were obtained from EUROCIM [160] (see 2.8 for details and standard inclusion criteria). Cervical adenocarcinoma was classified according to the ICD-O-2 morphology codes and includes adenosquamous carcinoma [131]. The same countries and years were used as for the squamous cell carcinoma analysis (Table 4.3). To provide a broad description of the trends and their impact both on younger and older women, data on all subjects aged under 75 were analysed.

As with the previous analysis, the rates are unadjusted for the known variations in the prevalence of hysterectomy in European countries over time [368]. The trends presented in this section therefore may be attenuated relative to the true temporal patterns upon adjustment for the prevalence of hysterectomy in each population.

4.5.1.1 Increasing specificity of subtype

As with squamous cell carcinoma, cancers of the cervix uteri with unspecified or ill-defined histology were not reallocated to specified histological subtypes. The prior reasoning that the unspecified group could not have made a sizable impact on the trends was not an acceptable assumption for adenocarcinoma however, given that the rates of cervix unspecified and the proportions of all cervical cancer combined, in some countries, was of the same order of magnitude as the adenocarcinoma rates (Tables 4.4 and 4.5).

Analyses were performed on the original data on the grounds that there was insufficient external information on which to base a rule for reallocation. In particular, the strong assumption that the unspecified group represented a random sample of those subjects with histology specified was not considered as justified. As way of an example, in Finland, a sudden drop in the number of unspecified cases was observed in 1968, likely due to structural changes in the way pathology data was coded, with the quality of the data pre-1968 considered of relatively poor quality in general. The Finnish data is therefore regarded at its most reliable if only cases coded as adenocarcinoma are included, and more recent trends were the focus of evaluation. The present analysis adhered to this criterion for all 13 countries, and the evaluation of recent trends was given priority.

Table 4.3: Adenocarcinoma of the cervix: populations included in the analysis, recent age-standardised rates, the estimated percentage change in the regular trend, and model characteristics and characteristics of cohort trends, by country within area

European Area	Country	Period (No. of years)*	Annual number of cases †	Person-years†	ASR (0-74) 1993-97 per 100,000†	Overall trend (%)‖ 95% CI	Recent trend (%)¶ 95% CI	APC model‡	Residual deviance§	d.f.§	p-value§	Direction (Year) Cohort trend**
Northern	Denmark	1978-1998 (21)	73	2.4	3.0	0.7 (-0.2 to 1.5)	0.4 (-0.7 to 1.6)	A	18.7	21	0.60	+ (1945)
	Estonia	1968-2000 (33)	10	0.7	1.0	-0.6 (-1.8 to 0.6)	1.0 (-1.8 to 3.9)	A	35.0	35	0.47	+ (1935)
	Finland	1953-1999 (45)	39	2.4	1.4	-0.2 (-0.6 to 0.2)	2.6 (1.0 to 4.3)	AC	47.9	42	0.25	+ (1945)
	Norway	1953-1997 (45)	55	2.0	2.6	2.1 (1.7 to 2.5)	1.1 (-0.4 to 2.7)	AC	36.5	42	0.71	+ (1930)
	Sweden	1960-1998 (39)	82	4.0	2.0	1.6 (1.3 to 2)	0.4 (-0.6 to 1.5)	AP	40.0	36	0.30	+ (--)
	United Kingdom[a]	1974-1997 (24)	591	25.1	2.2	3.2 (2.9 to 3.5)	2.4 (1.9 to 2.8)	APC	14.0	10	0.17	+ (1940)
Eastern	Czech Republic	1985-1999 (15)	104	5.0	1.9	1.7 (0.5 to 2.9)	1.7 (0.5 to 3.0)	AD	2.6	13	1.00	+ (--)
	Slovakia	1968-1997 (30)	53	2.6	2.1	2.0 (1.3 to 2.7)	3.4 (1.7 to 5.1)	AC	29.0	24	0.22	+ (1935)
Southern	Italy[b]	1981-1997 (17)	37	2.1	1.4	1.5 (-0.7 to 3.8)	1.6 (-0.8 to 4.0)	AD	12.5	13	0.49	+ (1940)
	Slovenia	1983-1999 (17)	36	1.0	3.0	4.4 (2.4 to 6.4)	4.5 (2.4 to 6.6)	AC	8.2	6	0.22	+ (1940)
	Spain[c]	1980-1997 (18)	20	1.5	1.3	1.9 (-0.6 to 4.5)	2.6 (-0.2 to 5.4)	A	17.7	14	0.22	+ (1940)
Western	France[d]	1978-1997 (20)	27	1.9	1.4	0.5 (-2.0 to 3)	-1.1 (-3.1 to 1.0)	A	14.0	21	0.87	0 (1945)
	Switzerland[e]	1981-1997 (17)	22	1.3	1.5	-1.4 (-3.0 to 0.2)	0.4 (-2.2 to 3.1)	A	3.6	14	1.00	0 (1955)

* data available according to period of diagnosis, figure in parentheses represent number of years available in the analysis
† average annual number of cases/person-years (latter expressed per million) obtained from most recent five-year period. ASR: truncated age-standardised rate in women aged <75 (Europe) in most recent five-year period
‖ EAPC based on the trend parameter from the net drift for the whole study period
¶ EAPC based on the most recent 15-year period
** estimated direction of recent trends by birth cohort (+: positive trend 0: relatively stable trend or difficult to interpret). Time in parentheses is midyear of birth when direction al change in of trend first noted (to nearest five years); -- denotes change in trends not apparent
‡ refers to the most parsimonious final model providing a good fit: AD: Age+Drift; AC: Age+Drift+Cohort; AP: Age+Drift+Period; APC: Age+Drift+Period+Cohort
§ to determine goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom determined by the model (see Appendix). $p<0.05$ denotes the full APC model does not yield an adequate fit
** age curve of reference type used (see Subjects and Methods)
a aggregation of England, Scotland
b aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin
c aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza
d aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn
e aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich

Table 4.4: Time trends in the proportions of (i) cervical adenocarcinoma; (ii) combined categories of unspecified cervical carcinoma and cervical unspecified cancer;(iii) cervical adenocarcinomas if all cervical cases unspecified were truly adenocarcinoma. Proportions expressed as percentage of all cervical cancer cases

		Cervical adenocarcinoma					Unspecified cervical carcinomas and unspecified cervical cancer					Cervical adenocarcinoma if all unspecified cervical carcinoma or unspecified cervical cancers were adenocarcinoma				
European Area	**Country**	**1953-57**	**1963-67**	**1973-77**	**1983-87**	**1993-97**	**1953-57**	**1963-67**	**1973-77**	**1983-87**	**1993-97**	**1953-57**	**1963-67**	**1973-77**	**1983-87**	**1993-97**
Northern	Denmark				12.7%	18.8%				7.5%	2.4%				20.2%	21.2%
	Estonia			5.1%	6.4%	5.6%			15.3%	8.7%	7.6%			20.4%	15.1%	13.2%
	Finland	6.1%	7.3%	11.2%	19.5%	28.4%	16.8%	26.1%	6.4%	5.1%	4.3%	22.9%	33.4%	17.6%	24.6%	32.8%
	Norway	6.7%	6.5%	7.7%	13.7%	17.7%	11.8%	6.6%	3.7%	1.7%	2.9%	18.4%	13.1%	11.4%	15.5%	20.6%
	Sweden		6.0%	7.9%	16.8%	19.6%		7.4%	2.8%	3.2%	4.8%		13.4%	10.7%	20.0%	24.4%
	United Kingdom			8.0%	11.3%	21.0%			26.7%	17.6%	11.1%			34.7%	29.0%	32.1%
Eastern	Czech Republic				7.9%	9.5%				7.4%	5.3%				15.3%	14.7%
	Slovakia			6.3%	7.7%	9.9%			23.5%	4.9%	3.9%			29.8%	12.5%	13.8%
Southern	France				10.7%	13.4%				6.6%	4.7%				17.3%	18.2%
	Italy				11.2%	16.4%				13.3%	8.2%				24.5%	24.6%
	Slovenia				12.2%	16.4%				13.1%	4.1%				25.2%	20.6%
Western	Spain				11.5%	16.1%				21.8%	7.2%				33.3%	23.3%
	Switzerland				12.9%	18.0%				1.4%	1.3%				14.3%	19.3%

Table 4.5: Time trends in the crude rates (per 100,000 person-years) of (i) cervical adenocarcinoma; (ii) combined categories of unspecified cervical carcinoma and cervical unspecified cancer;(iii) cervical adenocarcinomas if all cervical cases unspecified were truly adenocarcinoma

		Cervical adenocarcinoma					Unspecified cervical carcinomas and unspecified cervical cancer					Cervical adenocarcinoma if all unspecified cervical carcinoma or unspecified cervical cancers were adenocarcinoma				
European Area	**Country**	**1953-57**	**1963-67**	**1973-77**	**1983-87**	**1993-97**	**1953-57**	**1963-67**	**1973-77**	**1983-87**	**1993-97**	**1953-57**	**1963-67**	**1973-77**	**1983-87**	**1993-97**
Northern	Denmark				3.5	4.2				2.1	0.6				5.6	4.8
	Estonia			1.6	1.7	1.6			4.8	2.3	2.2			6.5	4.0	3.8
	Finland	1.6	2.0	1.6	1.5	2.1	4.3	7.3	0.9	0.4	0.3	5.9	9.3	2.5	1.9	2.4
	Norway	1.9	2.0	2.5	3.0	3.8	3.3	2.0	1.2	0.4	0.6	5.1	4.0	3.7	3.4	4.4
	Sweden		2.1	1.7	2.8	2.9		2.6	0.6	0.5	0.7		4.7	2.3	3.3	3.6
	United Kingdom			1.7	2.6	3.2			5.8	4.0	1.7			7.5	6.5	4.9
Eastern	Czech Republic				2.4	2.8				2.3	1.5				4.7	4.3
	Slovakia			1.6	2.1	3.0			6.1	1.3	1.2			7.7	3.4	4.1
Southern	Italy				1.8	2.1				2.1	1.1				3.9	3.2
	Slovenia				2.8	4.3				3.0	1.1				5.8	5.4
	Spain				1.5	1.8				2.7	0.8				4.2	2.6
Western	France				2.3	2.0				1.4	0.7				3.7	2.7
	Switzerland				2.0	2.1				0.2	0.2				2.2	2.3

4.5.2 Methods: characterising age, period and cohort effects

Trends in adenocarcinoma incidence were analysed using the APC model; the effects of birth cohort and period of diagnosis were evaluated to examine the extent to which changes in risk in successive generations were evident, and whether the diverse cytological screening policies presently in Europe [308] had any recent impact in reducing adenocarcinoma incidence, respectively.

An attempt was made to fix the age structure to that that was assumed for squamous cell carcinoma, in order to leave the period and birth cohort parameters free and thereby allowing an independent assessment of their effects. However, other *a priori* assumptions on the effect of period-specific risk were also examined. The first involved a similar analysis of the age, period and cohort effects to that carried out for squamous cell carcinoma (see 4.5.2.2.1). The second approach analysed the temporal data at a finer resolution, in five-year age-classes but one-year periods, the APC model smoothing the trends via cubic splines and the specification of knots at defined points on the age, period and cohort scales (see 4.5.2.2.2).

4.5.2.1 Evidence of a steady state age curve for adenocarcinoma

Figure 4.9 displays the trends based on the same three solutions obtained for squamous cell carcinoma assuming that the three alternatives for steady state age curves were also relevant for the representation of adenocarcinoma trends. As for squamous cell carcinoma, contrasting interpretations of the period and cohort effects could be made dependant on the particular age curve selected. Curves of reference type I tended to produce positive slopes for period (and accordingly, rather flat or decreasing cohorts slopes), while type II age curves often generated increasing positive cohort slopes, and minor or decreasing period slopes.

A single set of age, period and cohort estimates is displayed in Figure 4.10, obtained by utilising the same reference curve as that chosen for squamous cell carcinoma, that is, on the basis of an equivalent ratio of the first and last age parameters, yielding three reference types. The imposed assumption was that the chosen biological age curve for adenocarcinoma was similar to that of squamous cell carcinoma, implying the selected curve in each country was a reasonable description of cervical cancer, regardless of histological subtype. Interestingly, the parameters displayed emphasises period-specific increases in all countries except Switzerland, with the rises evident in most countries over the whole period of observation. Cohort-specific increases were also apparent in most

countries, in cohorts born since the 1940s; exceptions were Sweden, the Czech Republic and Switzerland.

4.5.2.2 Zero period slope as indicator of screening inefficiency

An alternative solution applied Holford's method to fix the overall period slope to zero (see 3.4.2.1), perhaps appropriate given the accumulated evidence of a lack of screening effect, at least historically. It was assumed that screening operated purely as a period effect, no other period-related factors were in operation, and, where effective screening was in operation, the effect was recent and one that would not alter the linear component of the period effect from its set value of zero. Holford's method still provided estimates of period curvature despite deactivation of the linear part of the effect. The result of a recent, relatively sudden ability to screen-detect adenocarcinoma (as postulated [316]) could therefore be observed in the non-linear period effects. Two approaches were examined, as described below.

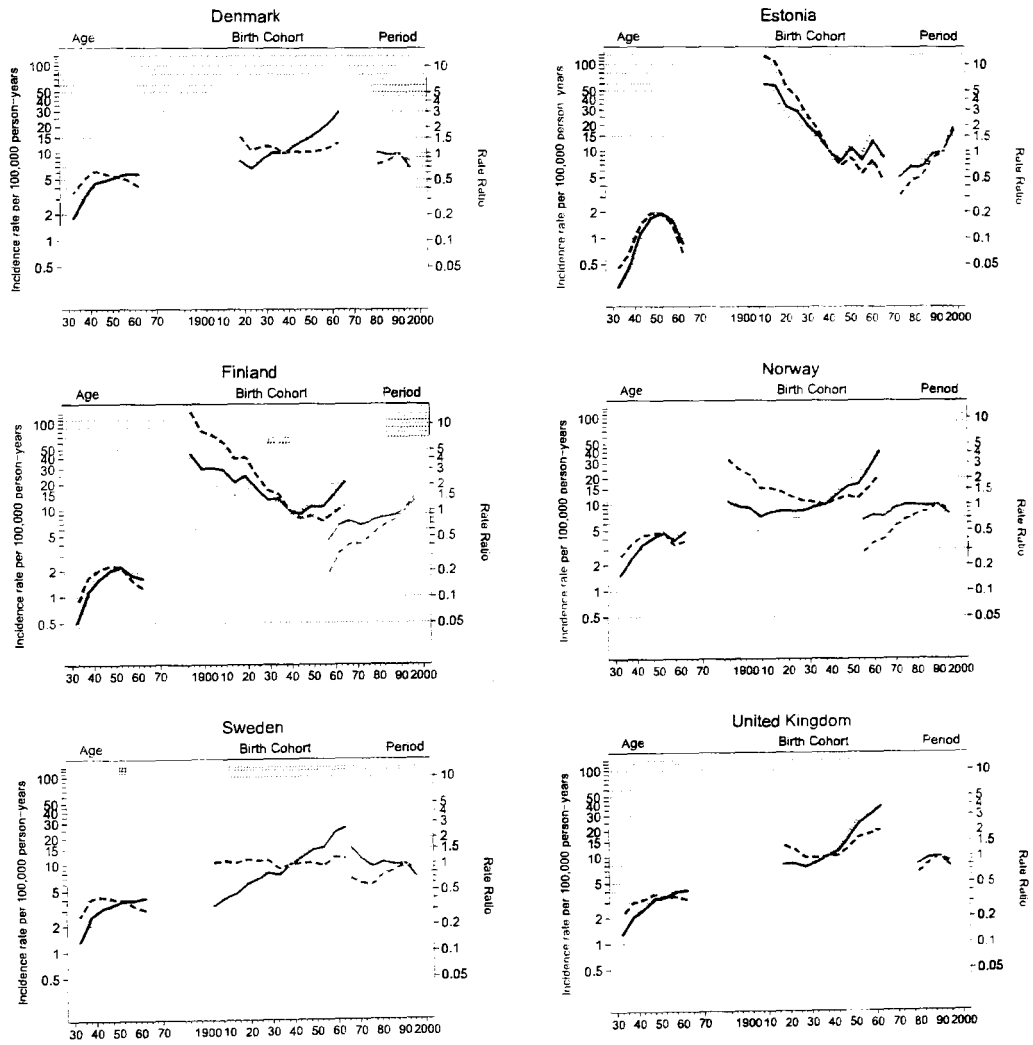
4.5.2.2.1 Trends based on standard modelling approach

The APC model of {3.6} was utilised as before, with non-identifiability highlighted by partitioning the effects into their linear and curvature parts [66], with specification of $\beta_L = 0$ resulting in α_L and γ_L being immediately estimable. The effects were defined and presented in the same way as with cervical squamous cell carcinoma.

Figure 4.11 shows the trends in age, period and cohort in which an identifiable set of parameter estimates was obtained on constraining the overall slope of period to zero. The trends, by nature of the imposed parameterisation of Holford's drift entirely to cohort, brought to attention the generational effects, with an underlying slope equal to its magnitude. The displayed trends contrast with those based on the elected squamous cell carcinoma curve seen in Figure 4.10. The transformation of the period slopes, from mainly positive in Figure 4.10 (obtained on fixing age) to zero throughout in Figure 4.11 (obtained on fixing period), involved a clockwise rotation of the period effects enforcing an equal but opposite rotation (e.g. counter-clockwise) of the cohort effects. The latter in Figure 4.11 are not only increasing in most countries (in keeping with its absorption of the regular trend), but the trends also imply successive increases in adenocarcinoma start earlier – around 1910, or before, in Sweden and Norway.

Figure 4.9: Adenocarcinoma incidence trends in 13 European countries for women aged 30-64. Trend based on all three reference curves of 'type I' (dashed line), 'type II' (dotted) and type I/II (solid), as used for squamous cell carcinoma. Age is on a rate scale. The reference points for period and cohort rate ratios are marked

N Europe



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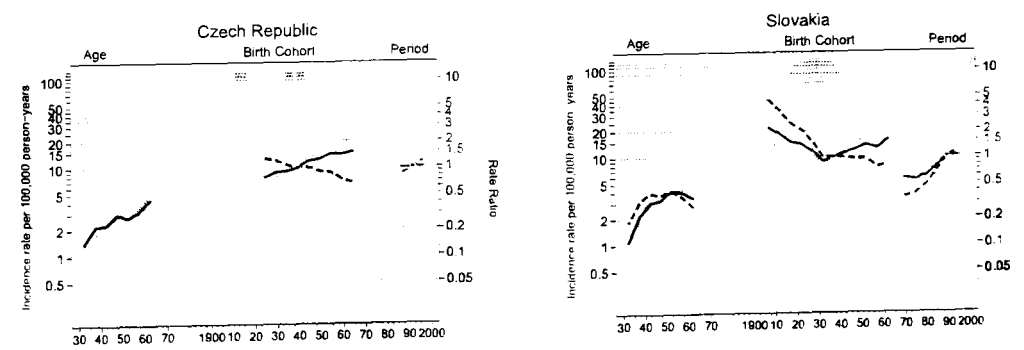
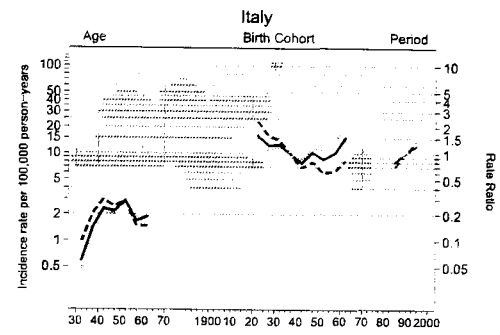
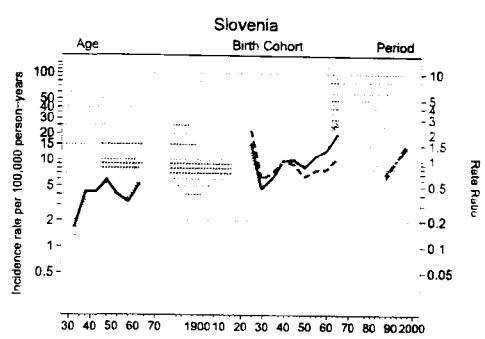
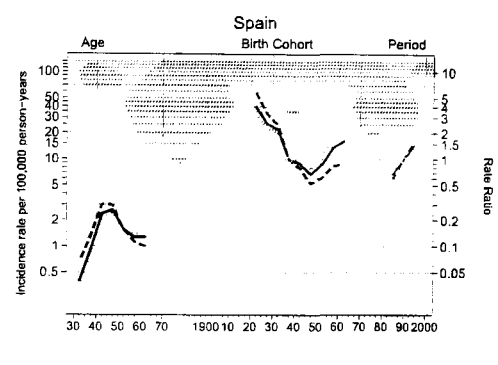


Figure 4.9 cont..

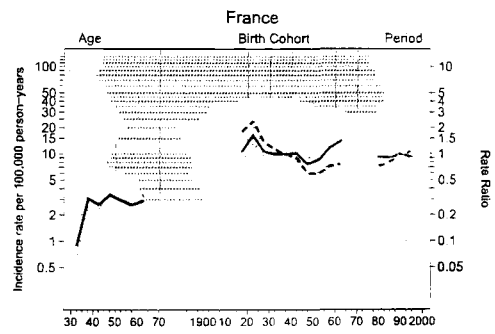
S Europe







W Europe



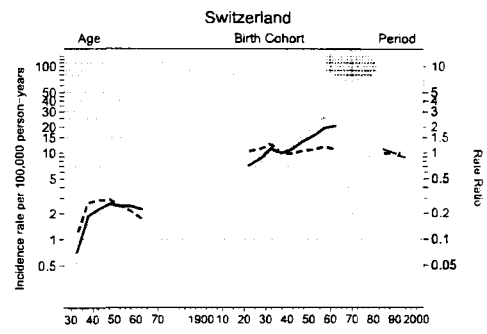
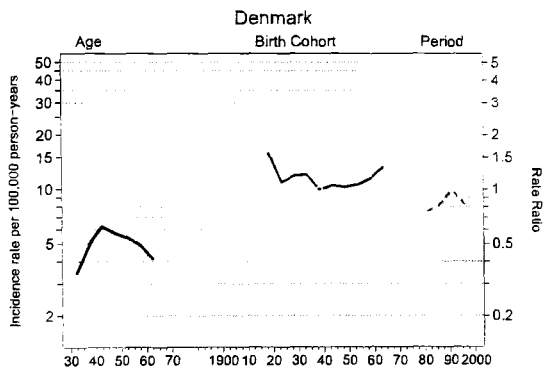
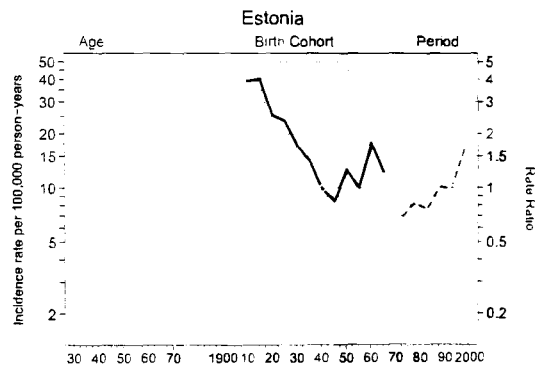
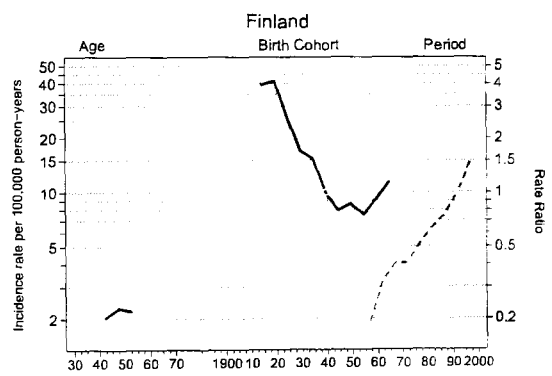


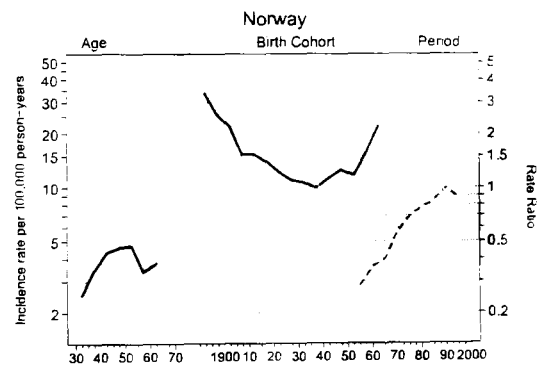
Figure 4.10: Adenocarcinoma incidence trends in 13 European countries for women aged 30-64. Trend based on selected reference curves used for squamous cell carcinoma. Age is on a rate per 100,000 scale. The reference points for period and cohort rate ratios are marked. Rates <2 are not shown

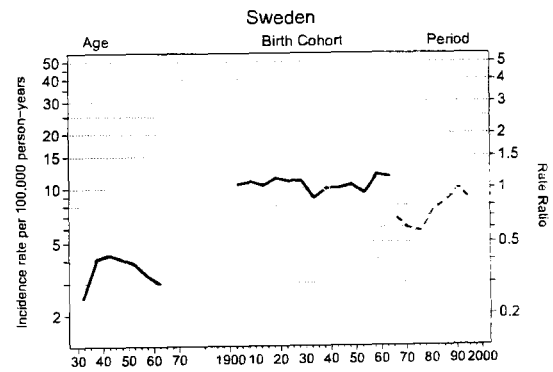
N Europe

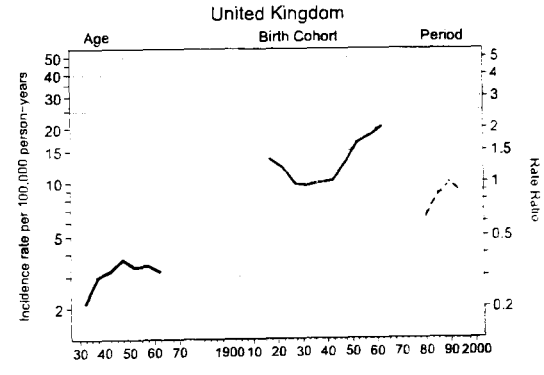




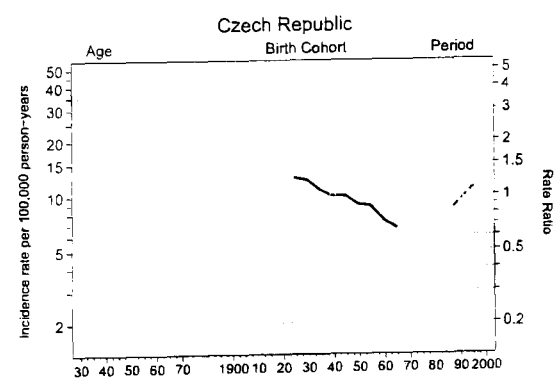








E Europe



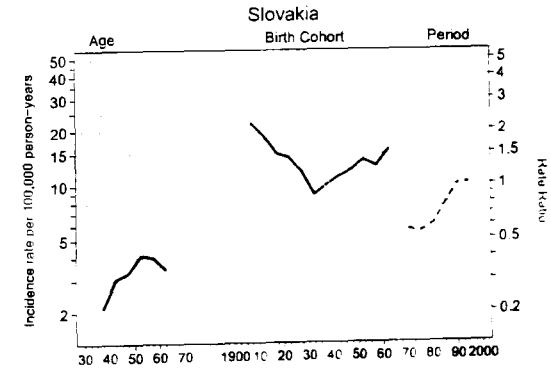
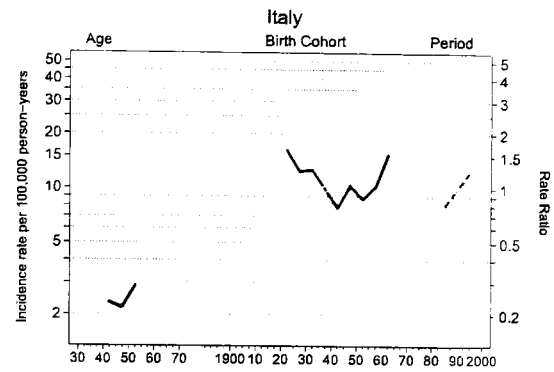
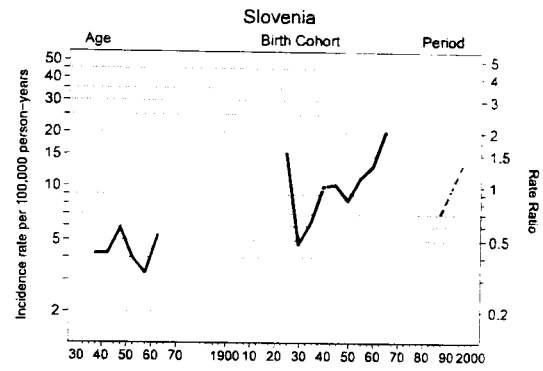
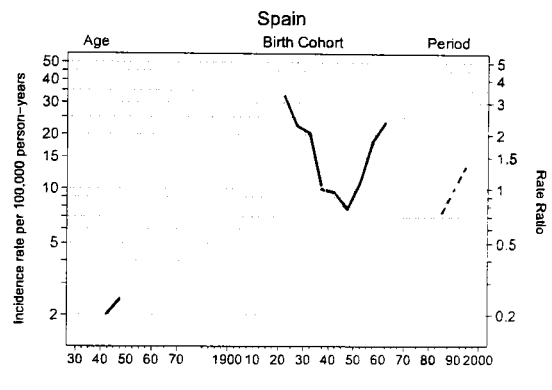


Figure 4.10 cont..

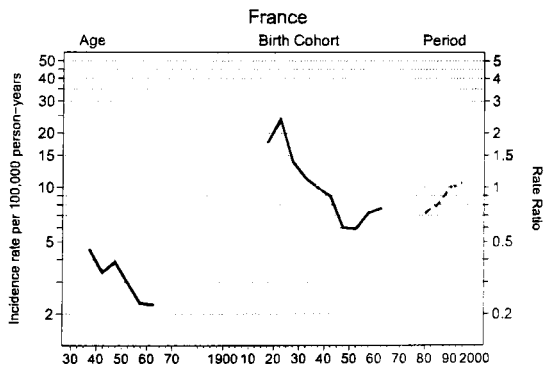
S Europe







W Europe



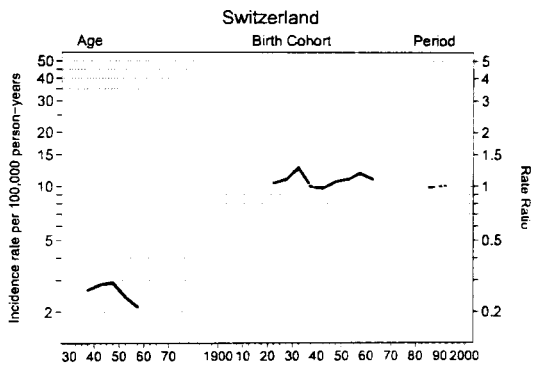
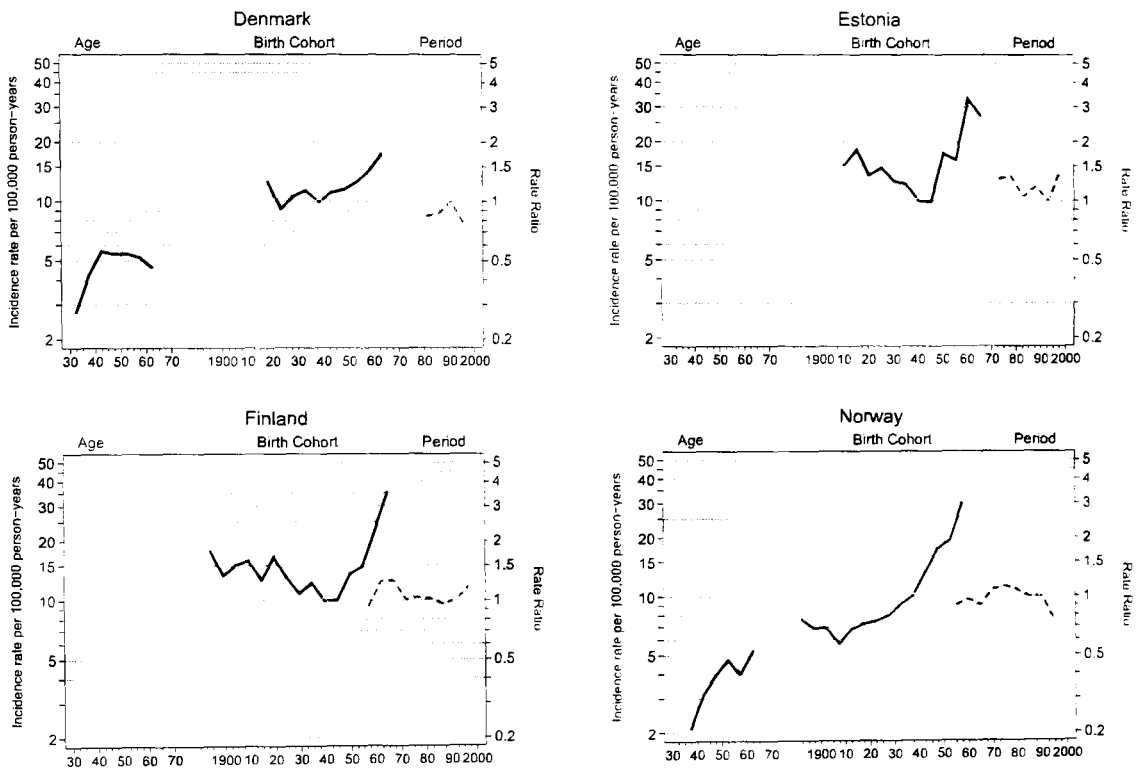
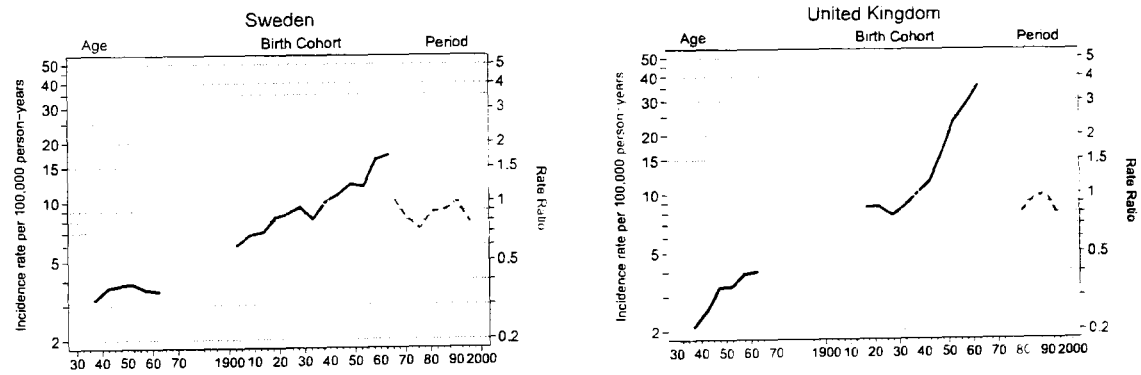


Figure 4.11: Adenocarcinoma incidence trends in 13 European countries for women aged 30-64. Trends obtained on constraining the overall slope of period to zero. Age is on a rate per 100,000 scale. The reference points for period and cohort rate ratios are marked. Rates <2 are not shown

N Europe





E Europe

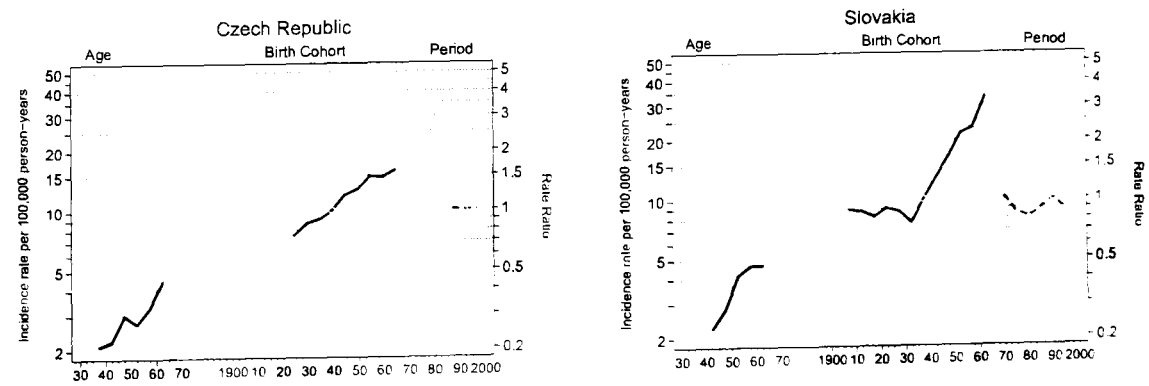
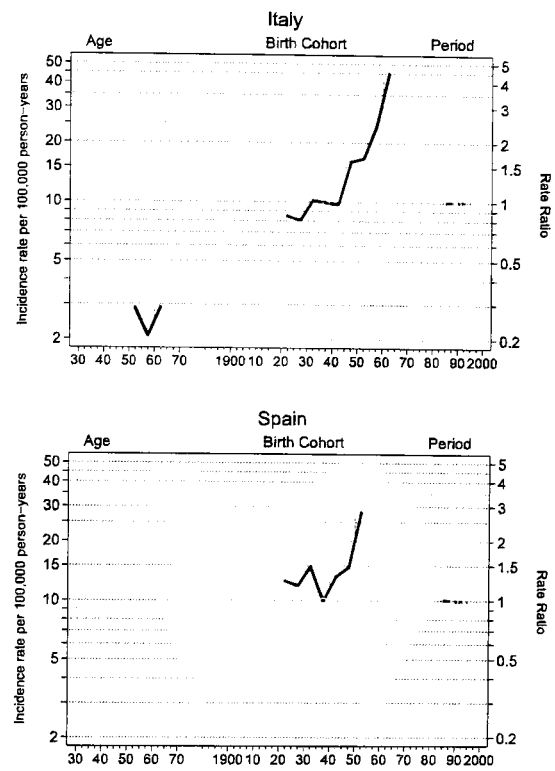
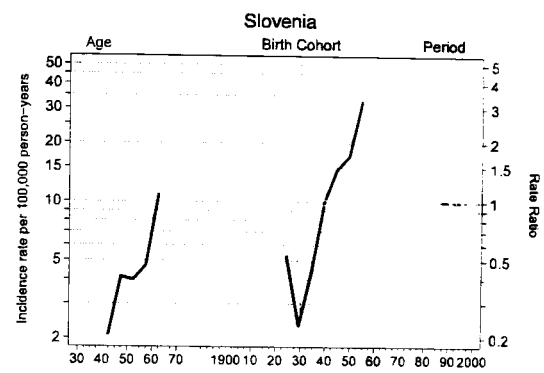


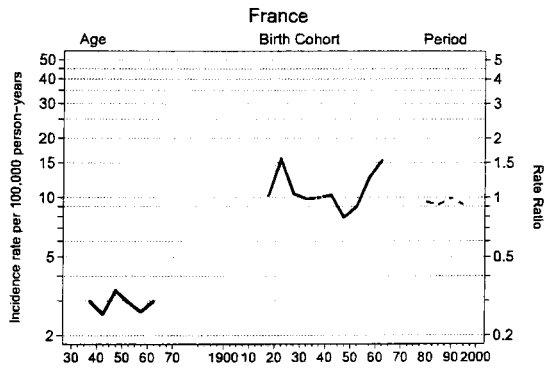
Figure 4.11 cont..

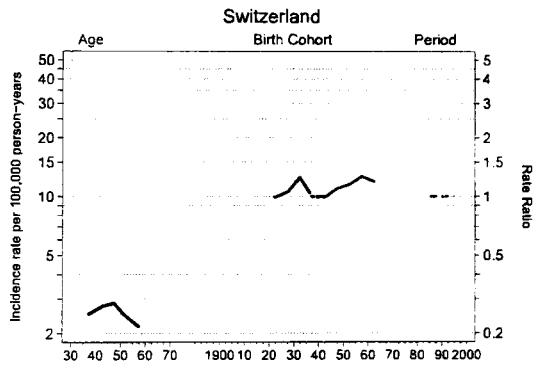
S Europe





W Europe





4.5.2.2.2 Trends based on cubic spline regression

An alternative but related presentation concerned incorporating some form of smoothing of the data by fitting a cubic spline to the data resolution available in EUROCIM [160]. The number of events and person-years corresponded to 5 year × 1 year subsets of a Lexis diagram, and under the assumption of a constant incidence rate λ, the likelihood contribution from each subset is proportional to a likelihood for a Poisson observation d with mean λY. The rates were described as a function of age, period and cohort using a log-linear model, with Poisson errors and a logarithmic link function, as previously. Thus for a given mean age a and mean date of diagnosis p (period), the mean date of birth (cohort) for those diagnosed (and for those at risk) was $c = p - a$. The number of distinct values of a in the dataset was 15, namely 2.5, 7.5,...,72.5, the number of distinct values of p was 48, namely 1953.5, 1954.5,. . . , 2000.5 and hence the number of distinct values of c was 118, namely (1953.5 − 72.5 =) 1881, 1882,...,1998 (= 2000.5 − 2.5).

Country-specific drift estimates for the latest 15-year period were obtained and reported as the EAPC. For a more detailed description, an APC model was used for the rates $\lambda(a, p)$:

$$\log \lambda_{a,p} = f(a) + g(p) + h(c)$$

with f, g and h functions each parameterised with a limited number of parameters. The parametric form for f, g and h was taken as cubic splines; functions that are 3rd degree polynomials in each of a sequence of intervals defined by a set of points (knots). The parameters were constrained to have 0th, 1st and 2nd derivatives identical at the knots. Natural splines were used and constrained to be linear beyond the outermost (boundary) knots using **R** [209]. The knots were chosen as points on the scales for age, period and cohort that divided the number of recorded cases equally in the intervals between knots. To circumvent the identifiability problem an age-cohort model was fitted:

$$\log \lambda_{a,c} = f(a) + h(c)$$

where h is chosen so that $h(c_0) = 0$ for a reference cohort c_0 (in this case the 1945 cohort). This means that $f(a)$ correspond to log-incidence rates in the cohort c_0, and $h(c)$, the rate-ratio of cohort c relative to cohort c_0.

Subsequently, period effects were fitted to the residuals by using a Poisson model for D, but with the log of the fitted values from the age-cohort model as offset. This gives period effects conditional on the estimated age and cohort effects. The fitted values using this

approach were very close to those obtained by maximum likelihood estimation in the full age-period-cohort model. In so doing, the secular trend was explicitly put in the cohort term in a well-defined way. Furthermore, the standard errors of the estimated values of f, g and h could be derived. The resulting period-effect was in practice very close to the "de-trending" approach suggested by Holford [66], as used in 4.5.2.2.1. The age, period and cohort effects are presented together with their associated 95% CI for each of the 13 countries (Figure 4.12), and, where informative, with the observed age-specific period and cohort trends in selected countries.

4.5.2.3 Presenting a single set of parameters

Selecting from the above presentations was a difficult task, a choice between an informative parameterisation on fixing to an age curve that may however be inappropriate, and a less informative display on fixing the period slope to zero, a marker of screening ineffectiveness. Trends in the period and cohort parameters based on fixing age or period gave quite conflicting results and different interpretations to the same datasets.

In selecting a single approach from which to interpret the findings, the fixing of period approach was considered more appropriate, given that the assumption was based on reasonably firm evidence of a historical lack of a screening effect for adenocarcinoma. Further, the cohort effects obtained from such a constraint were perhaps more in keeping with the observed data (although their interpretation, given the variability, may itself be declared as arbitrary). Finally, the setting of $\beta_L = 0$ was in line with several previous U.S. and U.K studies [189,210,366]. Period effects were only required in the description of trends in Sweden and the U.K. (Table 4.3), although their lack of significance in most countries refers only to the non-linear component. By the inherent properties of the non-identifiability, strong linear period effects – like those seen in Figure 4.10 on fixing age – would have remained undetected using the APC model.

Clearly, fixing the age curve, as was argued for in 4.4.2.4 for squamous cell carcinoma trends, would have been the best solution, leaving the period and cohort parameters undetermined and without any *a priori* judgement on their likely impact interfering with the display of model effects. However, knowledge of the age curve of squamous cell carcinoma was assumed on the grounds that it was identical to the documented reference curves established for cervical cancer [221], feasible, given that the histology comprised at least 75% of cervical cancer in the populations studied. The same could not be said for the relatively less common adenocarcinoma, for which the knowledge of the age structure was more limited. Empirical evidence suggests that the peak age of incidence is in fact lower

than that of squamous cell carcinoma. This is discussed in the context of further investigations and the extensions to the considered approaches in 4.6.3.

The results based on cubic spline smoothing (Figure 4.12) are described below in 4.5.3.4 and 4.5.3.5. Given the random variation inherent, encompassing a smoothing effect allowing the available data to be analysed at a higher resolution seemed appropriate, giving a more appealing visualisation of the trends than the standard APC analysis involving five-year age groups and periods. Further, the use of splines is consistent with several other reports [189,210,366].

4.5.3 Results: description of trends

4.5.3.1 Changing rates of adenocarcinoma relative to unspecified cases

The rates of adenocarcinoma have tended to increase in successive decades in most countries studied, although trends were rather stable in Estonia, France and Sweden. In parallel, declines in the rates of unspecified cervical cancer and unspecified cervical carcinoma were observed, notably within the last two decades in Southern Europe but also in the U.K., Denmark and France (Table 4.4 and 4.5). The historical data from Finland, Norway and Sweden indicates that the rates of unknown histology were large, often exceeding those of adenocarcinoma from the 1950s and 1960s; but in the 1970s, unspecified histology rates were vastly reduced, remaining steady (and of a low order of magnitude) thereafter. High rates of unspecified cervical cancer/carcinoma were observed in Slovakia and the U.K. in the mid-1970s, although they decreased rapidly with time in Slovakia. In the U.K., the unspecified rate was still amongst the highest (second only to Estonia) in the mid-1990s. Large declines in unspecified rates were also seen in Southern Europe, notably in Italy and Slovenia from the mid-1980s to the mid-1990s. Conversely, the rates of unspecified were stable and minor in Switzerland in the same time period.

4.5.3.2 Geographical variations in age-adjusted rates

There was a threefold variation in the age-standardised rates of adenocarcinoma in women aged under 75 (Table 4.3). Rates varied from relatively low (1.3 – 1.5 per 100,000) in Estonia, Spain, Italy, France and Finland, through to intermediate (1.9 – 2.2) in Sweden, the Czech Republic, Slovakia and the U.K. The highest rates were recorded in Norway (2.6), Denmark (2.8) and Slovenia (3.5).

Figure 4.12: Age, period and cohort effects of cervical adenocarcinoma incidence for women aged under 75 by country within region (N Europe, panels 1-6; E Europe, panels 7-8; S Europe, panels 9-11; W Europe, panels 12-13). Period effects are estimated as residual effects of period given estimated age and cohort effects. Cohort effects are displayed for generations born up to 1975. Corresponding 95% CI are also displayed

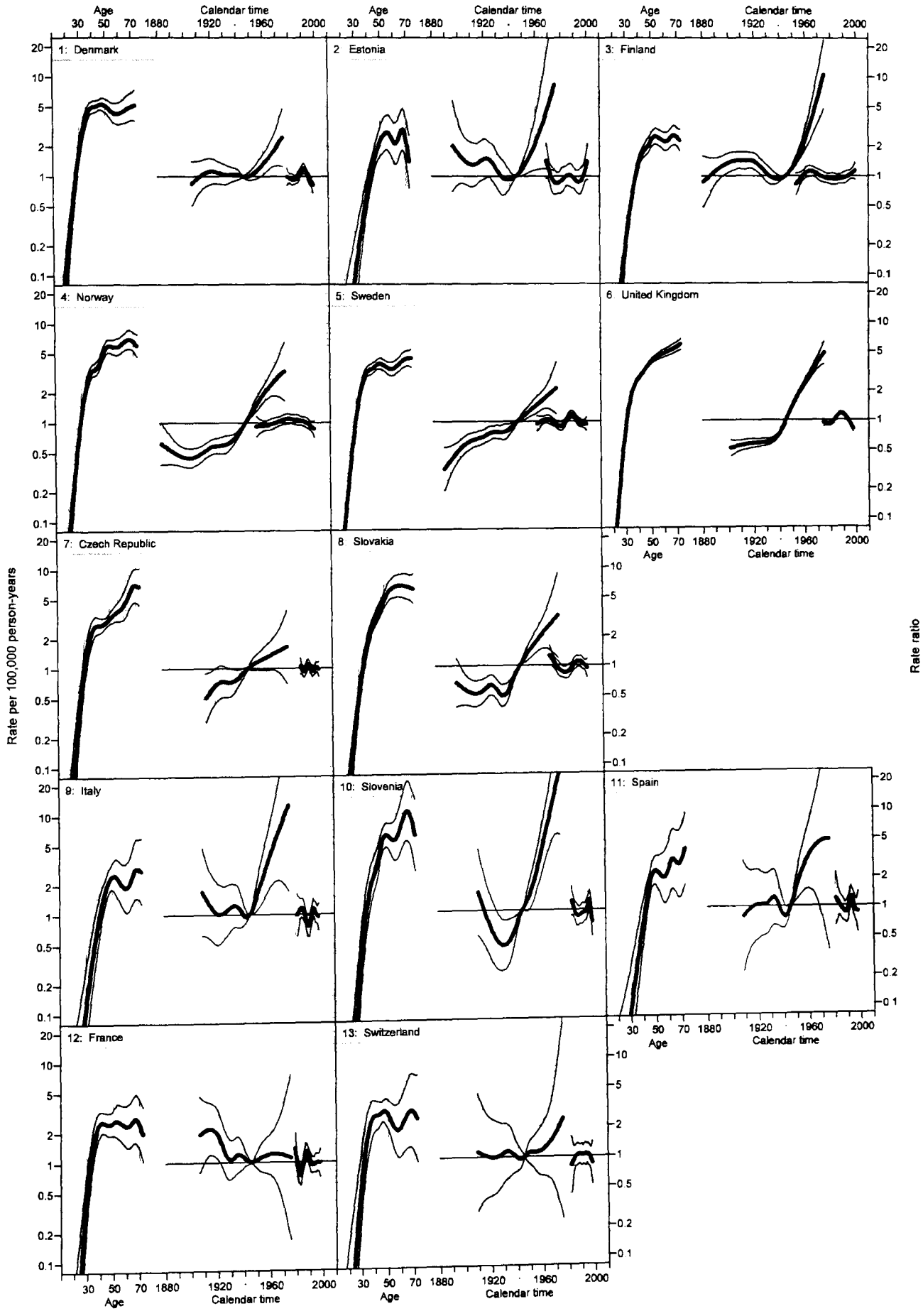
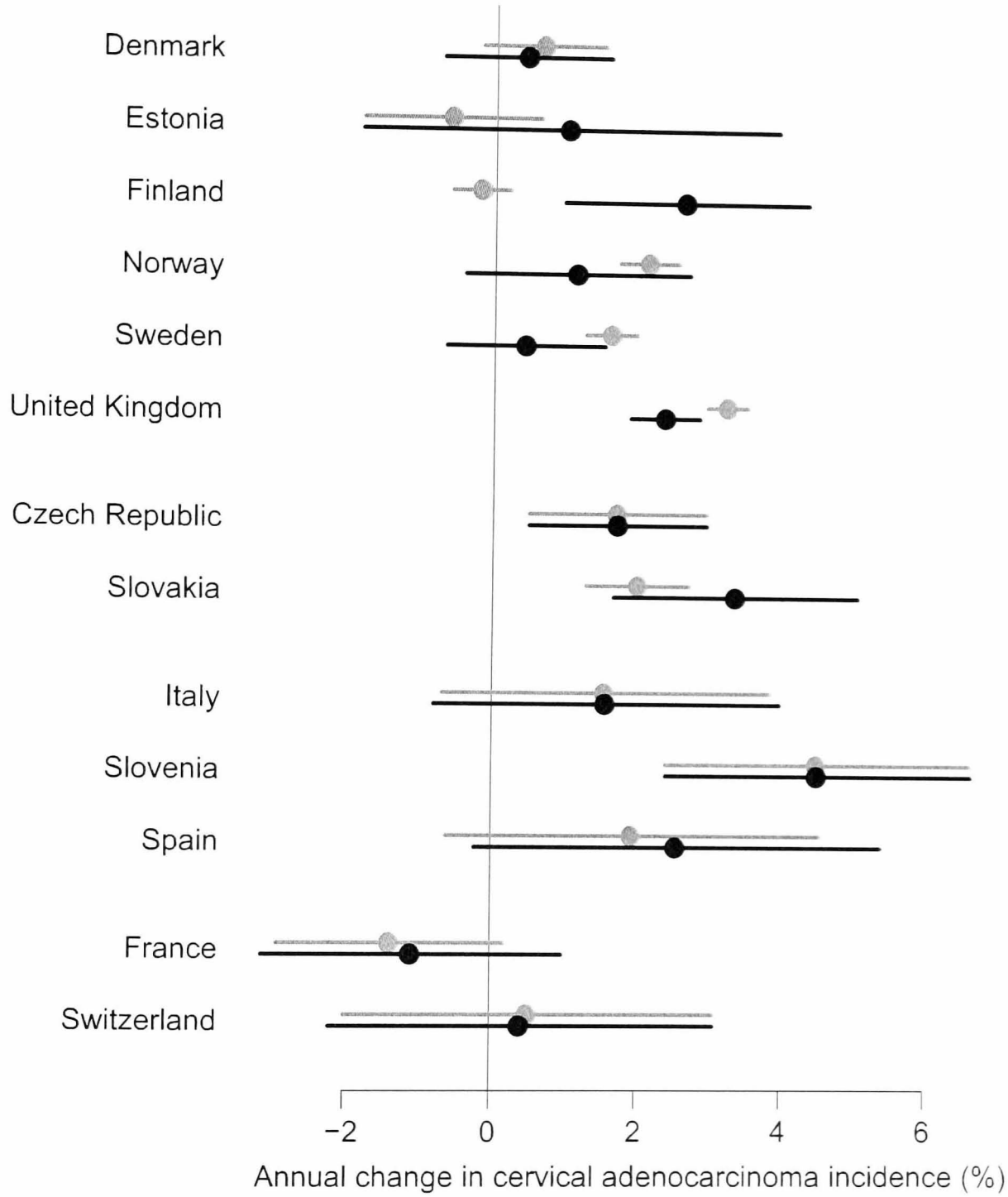


Figure 4.13: Drift estimates and corresponding 95% CI of cervical adenocarcinoma incidence over the entire study period (in grey) and in the most recent 15-year period available (black) in 13 European countries in women aged under 75, expressed as the EAPC



4.5.3.3 Regular trend

Figure 4.13 and Table 4.3 present the EAPC in each European country across the whole study period, and for the 15 most recent years available, based on the age-drift model. Only in France was a mean decline in the recent trend of adenocarcinoma observed, the annual change estimated at -1.1% per year between 1983-97.

The mean rates of increase during the most recent 15-year period were rather modest (≤0.5% per annum) in Denmark, Sweden and Switzerland; they were more substantial in the majority of countries studied. Increases ranged from around 1% to 2% in Estonia and Italy, through to increases of 2.4% in the U.K and Spain, 2.8% in Finland, 3.4% in Slovakia, and 4.6% in Slovenia.

Where the span of data was limited or close to 15 years, recent trends were obviously of similar magnitude to the overall trend, although some discrepancies emerged in Northern Europe, where longer periods of data were available. In Finland and Estonia, the modest overall declines contrasted with recent annual increases. In Norway, Sweden and the U.K., the temporal changes were in opposite directions, with a reduction in the rate of increase observed during the most recent 15 years.

4.5.3.4 Cohort trends from the APC models

Figure 4.12 shows the risk of cervical adenocarcinoma in each country according to age, birth cohort and period of diagnosis. The particular representation of the effects indicates that there were generation-specific rises in almost all European populations. The increases varied by country in terms of both their magnitude and the time at which successive generations were first observed to be at increasingly higher risk of developing the disease. The starting point of the escalation varied from generations born in the early-1930s through to the mid-1940s. The risk of adenocarcinoma was elevated in women born in the mid-1960s compared to those born in the mid-1940s, although the magnitude of the increase varied considerably across countries. Assuming the observed data and model specification are correct, Slovenian women born around 1965 had 7-8 times higher risk of adenocarcinoma compared to those born two decades earlier. In contrast, in France, the relative rate in the later birth period was only about 20% above that in women born around 1945.

In Northern Europe (Figure 4.12, panels 1-6), the increases were seen mainly in women born after around 1940, although the effect was possibly observed earlier in Norway (early-1930s), and later in Denmark (around 1950). The largest rise in risk among recent generations was seen in Estonia and Finland. A lesser degree of acceleration in risk was seen in Sweden than elsewhere in the region. Increases were observed in the Eastern European countries represented (Figure 4.12, panels 7-8).

There were also increases in risk of cervical adenocarcinoma in Southern Europe, although the changing rates of unspecified cancer and unspecified carcinoma call for a cautious interpretation. Among successive generations of Italian and Spanish women, increases from

around 1940 were indicated (Figure 4.12, panels 9-11). In Slovenia, consecutive cohorts born from around 1930 were affected, where the risk rose much more rapidly. In Western Europe (Figure 4.12, panels 12-13), the cohort trends in Switzerland were rather flat up to around 1955, with increasing risk thereafter, although the rates are based on few cases. The generation-specific increase among French women (from around 1945) was minor in comparison to other European countries.

4.5.3.5 Period trends from the APC models

While the assumption of a period slope of zero precluded the possibility to assess the magnitude of trends on this time scale, curvature, in the form of accelerations or decelerations in period-specific risk, were identifiable, and were noted in some countries. Declines in period-specific risk were most evident in the U.K., beginning around 1990 (Figure 4.12, Panel 6), although a decline in Denmark (Figure 4.12, Panel 1) around the same time was also suggested, and in Sweden (Figure 4.12, Panel 5) possibly slightly earlier, during the late-1980s.

4.5.3.6 Consideration of the observed trends

The age-specific trends in Figure 4.14 indicate a stabilisation or decline in rates in women aged over 30 in Denmark, Sweden and the U.K., and these appear more related to period of diagnosis than birth cohort. Cohort-specific increases were also observed in women aged under 30 in Denmark and the U.K., corresponding to generations born from the mid-1960s onwards [377]. In contrast, the observed rates in Swedish women born after 1960 appear to consecutively decline, although, as a result of smoothing, the model parameters displayed in Figure 4.12 do not exhibit such a trend.

4.5.4 Discussion of main findings

This study examined temporal patterns of cervical adenocarcinoma incidence using high quality data from population-based cancer registries in 13 European countries. The interpretation of the trends is clearly complex in light of a number of plausible factors that may explain them. In the next sections, the relative contribution of diagnostic and coding artefacts, a changing distribution and prevalence of risk factors, and the impact of cytological screening, are assessed.

Figure 4.14: Observed trends in adenocarcinoma in 13 European countries for women aged 30-64 by region. Left to right: rates versus age by cohort (indices of cohorts indicated); rates versus cohort by age (midpoints of age groups indicated); rates versus period by age. Rates are on a logarithmic scale

N Europe

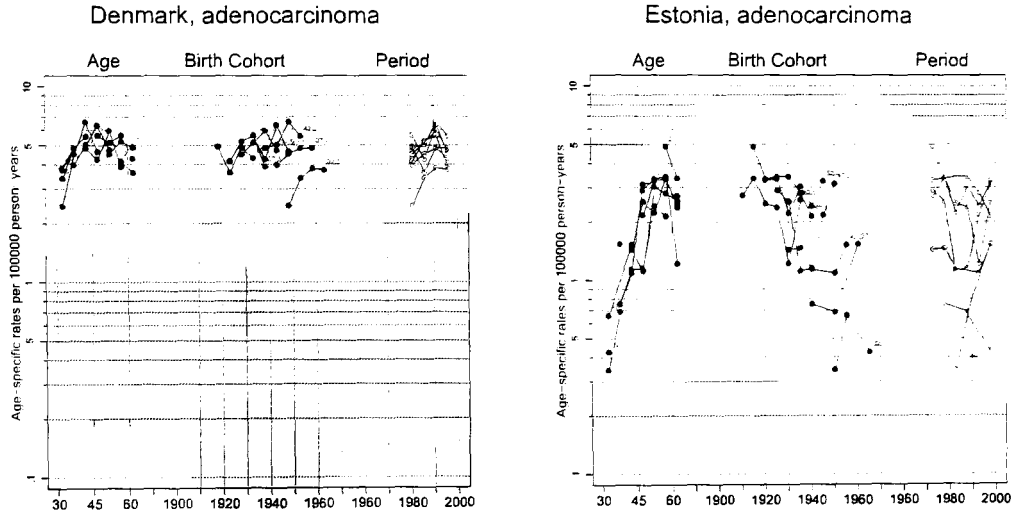


Figure 4.14 cont..

E Europe

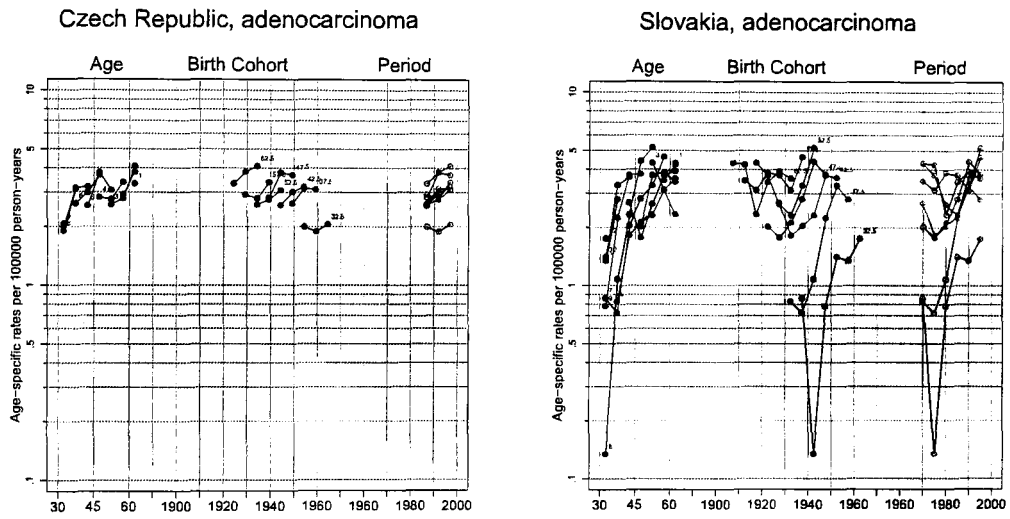
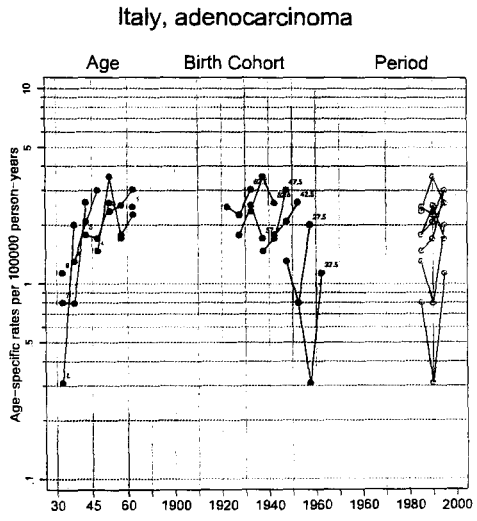
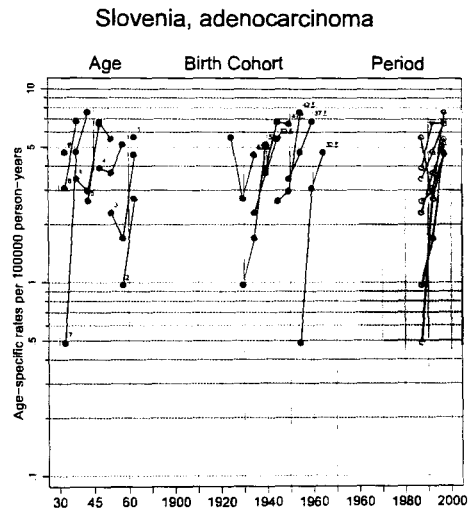


Figure 4.14 cont..

S Europe





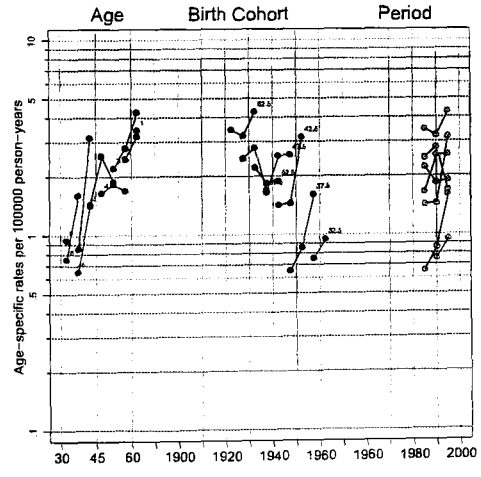
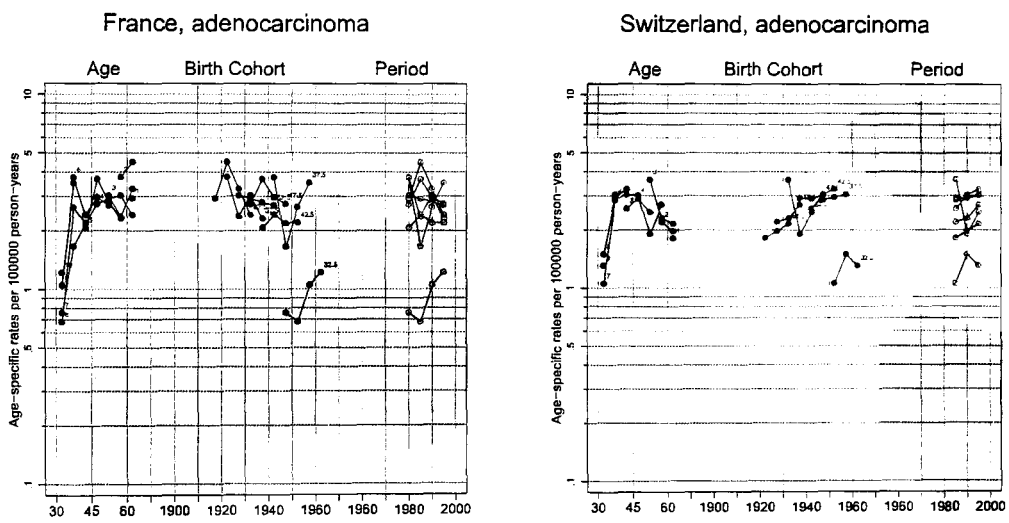


Figure 4.14 cont..

W Europe



4.5.4.1 Are increases due to increasing specificity?

Rising cervical adenocarcinoma rates could reflect an increasing ability to diagnose the disease over time. A recent study from England and Wales apportioned the unspecified cases to adenocarcinoma or squamous cell carcinoma according to their relative proportions by age and period of diagnosis [189]. This approach was not taken in the present analysis, on the grounds that there was insufficient evidence to conclude that age and period-specific proportions of unspecified and specified cases were not in some way interrelated. The present analysis adhered to this criterion for all 13 countries, with a focus on evaluating recent trends.

Caution in interpretation of cervical adenocarcinoma trends must be exercised, particularly where the order of magnitude of both the absolute rates of unspecified cancer/carcinoma and their relative rate of increase were large in comparison to those of adenocarcinoma. Following the alternative scenario that all unknown cases were truly adenocarcinoma, the recent increases in adenocarcinoma rates in Denmark, the Czech Republic, Italy, Slovenia, Spain and the U.K. could be explained by an increasing specificity in pathological diagnosis of subtype with time. The reallocation approach in a recent England and Wales study [189] however, yielded similar results to that of the U.K. as reported in this study, on the basis of the unadjusted data.

An increasing specificity of subtype with time could at least partially explain the adenocarcinoma increase in Denmark. An earlier study reported proportional decreases in unspecified and unknown type, and increases in adenocarcinoma from the period 1943-47 through to 1978-82. However, observed increases in adenocarcinoma rates among recent cohorts were also reported [378].

4.5.4.2 Data and modelling considerations

The main focus has been on the description of trends by birth cohort and identification of deviations by period of diagnosis. To achieve a unique solution from the infinite number possible [68], the period slope was constrained to zero, and assumed to reflect the well-documented historical inability to screen for adenocarcinoma. Other solutions, such as fixing the age structure, as was done for squamous cell carcinoma (4.4), were considered less reasonable for adenocarcinoma. There is little background knowledge regarding the latent age curve for adenocarcinoma, while it is possible that error may be introduced should segments of the age profile be over- or under-compensated by an age-related misclassification of adenocarcinoma.

In some countries the trends are based on relatively few cases and shorter spans of data, this reflecting the current availability of cancer registry data of sufficient quality within Europe. Clearly the description of the period and cohort-specific trends is open to a more unequivocal interpretation for countries where registries have been longstanding and cover larger populations, but exclusion only to countries where cancer trends are more well-documented would remove some of the richness of the findings in this comparison across European areas.

4.5.4.3 Are the increases in risk in recent generations real?

Recent statistically significant increases in cervical adenocarcinoma rates were observed of at least 2% per annum or more in Finland, the U.K., Slovakia and Slovenia. Positive but non-significant trends of a lesser magnitude were observed in most other countries. That cervical adenocarcinoma is rising in recent years in Europe, particularly among young women, has been consistently reported in several countries [189,253,357,359,362-366,379]. Study II establishes that the increases in incidence in many parts of Europe referred mainly to generations born since the epoch 1930-45. The risk in cohorts born in the 1960s relative to the 1940s varied seven-fold, from high incidence in Slovenia to low incidence in France, where, uniquely, the risk appeared to be reasonably stable among recent generations.

An international study of time trends of adenocarcinoma incidence 1973-91 [253] described increasing risk in cohorts born after the mid-1930 in England, Scotland, Denmark, Sweden, Slovenia and Slovakia. The trends reported here replicate these findings, although the data used in this study also spanned the 1990s, and found recent increases in Estonia, Spain, Finland, and Italy, starting in cohorts born between 1935 and 1945, countries previously reported to have either stable or decreasing trends by cohort. The findings for the U.K. are replicated by studies in England and Wales reporting generational increases in adenocarcinoma [189,366]. The authors found risk to be some 14 times greater in women born in the early 1960s relative to those born before 1935.

Persistent infection with sexually-transmitted high-risk HPV types is established as the necessary cause of cervical cancer [310] and its main histological subtypes [311]. The widespread increases in cervical adenocarcinoma in Europe among recently-born cohorts reported in this study and others [189,253,362,365,366] suggest that an increasing number of women are becoming carriers of high-risk HPV types in many European countries. These cohorts may be defined by generational changes in sexual behaviour that increase the risk of HPV infection, among them younger age at first intercourse, increased number of sexual partners, and an increasing risk that each sexual partner is HPV-infected.

4.6 General discussion

4.6.1 Brief summary of main findings

These studies analysed trends in squamous cell carcinoma and adenocarcinoma of the cervix uteri in 13 European countries with high quality incidence data to evaluate the effectiveness of screening against a background of changing risk. APC models were fitted, and the estimated period and cohort effects were considered as primarily indicative of screening interventions and changing aetiology, respectively.

4.6.1.1 Cervical squamous cell carcinoma

In study I, a unique set of estimates was derived on fixing age slopes to one of several plausible age curves, under the assumption that the relation between age and cervical cancer incidence is biologically determined. There were period-specific declines in cervical squamous cell carcinoma in several countries, with the largest decrease seen in Northern Europe. A pattern of escalating risk in successive generations born after 1930 emerged across Europe. In the Western European countries, a decrease followed by a stabilisation of risk by cohort was accompanied by period-specific declines. In Southern Europe, stable period, but increasing cohort trends, were observed. Substantial changes have occurred in cervical squamous cell carcinoma incidence in Europe, and well-organised screening programmes have been highly effective in reducing the incidence of cervical squamous cell carcinoma.

The beneficial effects of organised screening programmes can be deduced from the period-specific decreases in the Nordic countries and in the U.K., which largely confirmed previously published results. The corresponding decline in France and Switzerland was consistent with the effectiveness of spontaneous screening in those countries. There were, however, competing generational increases in cervical squamous cell carcinoma risk in younger women in many countries – irrespective of their screening policy – that deserve particular attention. Most concerning were the future prospects in countries like Slovenia, where there were rapid increases in risk in successive generations of women, and where screening programmes are not in place, and hence a notable absence of any intervention-related declines.

4.6.1.2 Adenocarcinoma

In analysing cervical adenocarcinoma trends, it was necessary to take into consideration the prospects of increasing specificity of subtype – the capability to diagnose the disease – and an inability of cytological screening to reduce cervical adenocarcinoma, against a background of anticipated generational increases a result of persistent HPV infection. In

study II therefore, APC models were fitted using Holford's method as before, but this time assuming a lack of screening effect by fixing the period slope to zero.

Age-adjusted adenocarcinoma incidence rates increased throughout Europe, the rate of increase ranging from around 0.5% per annum in Denmark, Sweden and Switzerland to 3% or over in Finland, Slovakia and Slovenia. The increases first affected generations born in the early-1930s through to the mid-1940s, with risk invariably higher in women born in the mid-1960s relative to those born 20 years earlier. The magnitude of the risk ratios varied considerably, from around seven in Slovenia to almost unity in France. Declines in period-specific risk were observed in the U.K., Denmark and Sweden, primarily among women aged over 30.

While increasing specificity of subtype with time may have been responsible for some of the increases in several countries, the changing distribution and prevalence of persistent infection with high-risk HPV types, alongside an inability to detect cervical adenocarcinoma within screening programmes would accord with the temporal profile observed in Europe. Screening may have had at least some impact in reducing cervical adenocarcinoma incidence in several countries during the 1990s.

4.6.2 Comparison of trends in adenocarcinoma and squamous cell carcinoma

There were necessary differences in the approach to the analyses of squamous cell carcinoma and adenocarcinoma, as a result of the existing knowledge that could be brought to bear regarding the two histologies. The focus of these studies was a broad description of the trends of the two subtypes in Europe, and a limitation was the lack of a quantifiable and systematic comparison between subtypes. These themes are taken up and discussed in 4.6.3.1 and 4.6.3.2.

Despite this concern, some inference of the respective differences in period and cohort trends was possible, and Table 4.6 compares some of the key observations from the above studies. Clearly, there is tremendous variation in the ratio of squamous cell carcinoma to adenocarcinoma rates, and the statistic appears to be a good marker of the extent to which cytological screening has been a success in reducing squamous cell carcinoma, with an increasing degree of screening success measured by a decreasing magnitude of this ratio. Finland, for instance, had a very low ratio as well as a long-standing well-organised programme, whereas former Soviet countries had among the highest ratios, partially reflecting a combined effect of lesser resources and lack of provision for cytological screening.

Table 4.6: Comparisons of cervical squamous cell carcinoma and adenocarcinoma in 13 European countries: age-adjusted rates (Europe), EAPC 1983-97 (net drift), and characteristics of period and cohort trends

				SCC	AdC	SCC	AdC
European Area	**Country**	**Period (No. of years)***	**Standardised Rate Ratio†**	**Direction (Year) Period trend****		**Direction (Year) Cohort trend****	
Northern	Denmark	1978-1998 (21)	4.0	- (*)	- (1990)	+ (1950)	+ (1945)
	Estonia	1968-2000 (33)	15.9	0 (*)	0 (*)	+ (1935)	+ (1935)
	Finland	1953-1999 (45)	2.3	- (1967)	0 (*)	+ (1945)	+ (1945)
	Norway	1953-1997 (45)	4.5	- (1975)	0 (*)	0 (1945)	+ (1930)
	Sweden	1960-1998 (39)	3.5	- (*)	- (1990)	0 (1935) 0 (1955)	+ (–)
	United Kingdom[a]	1974-1997 (24)	3.1	- (1985)	- (1990)	+ (1935)	+ (1940)
Eastern	Czech Republic	1985-1999 (15)	9.2	0 (*)	0 (*)	0 (1945)	+ (–)
	Slovakia	1968-1997 (30)	8.5	- (1985)	0 (*)	+ (1935)	+ (1935)
Southern	Italy[b]	1981-1997 (17)	4.5	- (*)	0 (*)	+ (1945)	+ (1940)
	Slovenia	1983-1999 (17)	4.7	0 (*)	0 (*)	+ (1940)	+ (1940)
	Spain[c]	1980-1997 (18)	4.8	0 (*)	0 (*)	+ (1940)	+ (1940)
Western	France[d]	1978-1997 (20)	5.7	- (*)	0 (*)	0 (1940)	0 (1945)
	Switzerland[e]	1981-1997 (17)	4.3	- (*)	0 (*)	0 (1950)	0 (1955)

SCC: squamous cell carcinoma; AdC: adenocarcinoma
* data available according to period of diagnosis, figure in parentheses represent number of years available in the analysis
† Ratio of truncated age-standardised rates (European standard) of squamous cell carcinoma vs. adenocarcinoma , women aged 75, 1993-97
** estimated direction of recent trends by (+: positive trend 0: relatively stable trend or difficult to interpret). Time in parentheses is year of birth when change in direction of trend first noted (to nearest five years); – denotes change in trends not apparent; * denotes no change in trend apparent.
a aggregation of England, Scotland
b aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin
c aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza
d aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn
e aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich

4.6.2.1 Comparisons of trends in relation to cytological screening

The beneficial effects of organised screening programmes on reducing the incidence of squamous cell carcinoma may be deduced from the period-specific (non-linear) decreases in the Nordic countries and in the U.K. (Table 4.6), which largely confirms previously published results. Period-related declines were noted for eight of the same thirteen countries, in line with the initiation of organised screening programmes, and in France and Switzerland possibly consistent with the effectiveness of spontaneous screening.

Possible instances of a period-specific downturn in adenocarcinoma were seen in Denmark, the U.K. and Sweden, although any such screening effect was recent, during the 1990s. Cytological screening may thus have had a protective effect on adenocarcinoma, as supported by recent studies in the U.K. and Australia [316,366]. A recent Swedish study described a lack of screening effect, citing uniform increases in period-specific risk from around 1975 to 1992 [359], although the risk was in fact quite stable from 1983. In England and Wales, incidence has been reported to have possibly peaked in the late 1980s in young women (aged 25-39) [189,366]. The present analysis is in broad agreement with this finding, and would imply some beneficial effects of screening within the last decade, although substantial increases in adenocarcinoma were observed in younger women during the same period in the present analysis.

4.6.2.2 Comparisons of trends in relation to risk patterns

There is some support for the idea of homogeneity across the cohort-specific trends of each subtype in Europe. The cohort-specific increases in Italy, Spain, the U.K., Norway, Estonia, Slovakia, Finland and Slovenia in adenocarcinoma described in this study, are in accordance with the temporal patterns conveyed for squamous cell carcinoma, with risk of both subtypes accelerating among consecutive generations born in the 1930s and 1940s. The rapid increases in the drift estimates of adenocarcinoma noted in Finland and Slovenia in recent years reasonably match those observed for squamous cell carcinoma. The more moderate generational increases in adenocarcinoma in the Czech Republic, Sweden and Switzerland also largely parallel those of squamous cell carcinoma trends, as does the noted absence of an increase in recent generations in France of either subtype. The cohort-specific trends are however difficult to fully interpret for countries where the span of available data is short.

An increasing capability to correctly assign the histology of cervical cancer cases is unlikely to account for the increases in squamous cell carcinoma, which still represent the vast majority of cervical malignancies (75% to 90%), and may be excluded in explaining much of increasing adenocarcinoma trends in certain countries where the unspecified proportion was small relative to adenocarcinoma and/or the unspecified trends were rather stable. That European women born in successive generations experienced an increasing risk of both major histological forms of cervical cancer within the same time window – during the 1930s and 1940s – points to a homogeneity in the risk factors chiefly responsible for the increases, presumably linked to changes in sexual activity and risk of HPV infection.

4.6.3 Reconsideration of methods and further exploration

The two papers published in relation to the work described in 4.4 and 4.5 in a peer-reviewed journal [377,380] focused on the results from a single set of parameters, the methodologies for which were described in 4.4.2.5 and 4.5.2.3, respectively. In circumventing the non-identifiability problem, the estimates presented were not unique and other parameterisations could have been selected. However, a degree of plausibility was ascertained by bringing to bear external information for both squamous cell carcinoma and adenocarcinoma; the trends may therefore be thought of as broadly representative of the effects of screening and HPV infection in these countries.

The present study used an analytical approach to the description of time trends of squamous cell carcinoma and adenocarcinoma to better understand the evolution of cervical cancer in Europe, the factors involved, and the prospects for prevention. Holford's approach to the problem allowed a qualitative comparison of the differences and similarities of the non-linear effects of period and cohort between the two histologies. Beyond the scope of the work presented in this chapter, are further studies that attempt to better quantify and reinforce some of the observations laid out here. These considerations are briefly discussed below.

4.6.3.1 A more integrated approach

There is substantial evidence that the two histological subtypes share many risk factors, with possible exceptions including smoking and oncogenic infection with certain HPV types. Assuming the histological subtypes are biologically equivalent, a more integrated approach might involve a joint analysis of squamous cell carcinoma and adenocarcinoma and a more elaborate version of the APC model. One possibility would be to collapse the data from the two histologies and analyse cervical cancer trends as a whole, fixing the age curves as previously in 4.4. A binary variable for histology could be incorporated into the model allowing more comparable and quantifiable answers as to whether the histological trends differed over time, according to period and birth cohort, and whether the introduction of screening changed the temporal profile.

Ideally, one would, as before, model the age effects of cervical cancer directly, leaving the period and cohort parameters free. It is worth noting the variability of the peak age of incidence noted for cervical cancer within European countries in pre-screening populations – ranging from ages 42 to 62. Should the true age curve for cervical adenocarcinoma diverge from that of total cervical cancer, the possibility of wrongly attributing the period and cohort trends is distinct possibility.

A future exercise might involve introducing data on screening practices in Europe (such as year of implementation and estimated coverage). By explicitly including such covariates in the APC models, further quantification of the screening effects on incidence is possible, as is the prediction of the estimated numbers of cases that screening has prevented. This would necessarily lead to a modelling approach of further complexity however, and possibly the inclusion of unverifiable assumptions given the lack of reliable data regarding screening policies in some European countries (see 4.6.3.2).

4.6.3.2 A more quantitative approach to the impact of screening

An obvious public health question would be to ask, in each of the 13 countries, how many cases of cervical squamous cell carcinoma and adenocarcinoma has screening prevented, and how many will be prevented in the future. Several recent reports using data from England and Wales have attempted such a quantification [189,349,366]. In estimating the number of cases prevented in the past, one must specify an appropriate model; the age-cohort model for instance might seem like an obvious choice for adenocarcinoma, yet Table 4.3 indicated the terms in the models varied by country. The lack of complexity in the models for some countries indicates the presence of a form of non-identifiability – an inability to reject simpler models due to low power [381].

In addition, information on the historical screening processes in each country and their effectiveness would need to be ascertained. However – as already established [308] – it is problematic to determine precise data on organised screening practices. There is also a lack of knowledge of the amount of opportunistic screening in Europe [308]. In estimating that 100,000 of the eight million British women born between 1951 and 1970 will be saved from premature death by the cervical screening programme, Peto and colleagues [349] assumed that opportunistic screening already accounted for 40% of the prevented deaths in England and Wales, before the successful call-recall system was implemented. It would be difficult to estimate the level with any degree of certainty for most of the countries studied, where rather little is known (or could be reasonably guessed) regarding its impact. The analyses in this chapter would imply that screening in France and Switzerland has been mainly opportunistic, although data on the extent of this practice are not available. Efforts to make future predictions would also require some assumptions on the future levels of screening [366].

4.6.3.3 Trends in HPV

There are few studies reporting trends in HPV incidence or prevalence either overall or by subtype, and these have been cross-sectional in nature. Increases in the incidence and

seroprevalence of HPV-16 have been reported in Finland in women aged in their twenties [382], while in Sweden, the main increases in HPV-16 during the period 1969-89 occurred during the 1970s and early-1980s, in women aged under 35 [383]. It has been suggested that the lifetime number of sexual partners is the strongest marker for oncogenic HPV infection, whereas a history of condyloma is associated more with acquiring benign HPV types [384]. It may be of utility from a public health perspective to collect the relevant data and examine the prevalence and distribution of HPV and its markers in birth cohorts, as a means to better understand behavioural aspects that place women at a higher average risk of cervical cancer in certain countries relative to others.

4.6.3.4 Influence of unspecified groups on histological trends

The trend analyses did not take explicit account of unspecified carcinomas and cancers, while other analyses have reallocated this group to known proportions of histological subtype [189]. A comparison of the two approaches is warranted and an appraisal of the degree to which the trends in the unspecified group are gradual, possibly impacting on the period slope, undetected by the APC model. This might require exclusion to countries with long series of the highest quality data, such as is available in the Nordic countries.

4.6.3.5 Comparison of incidence and mortality trends

Given that there is an algorithm for reallocating the rubric "site unspecified" to deaths from either cancers of the cervix uteri or corpus uteri [312], it would be interesting to compare incidence and mortality trends, particularly in reference to the possible differential effects of screening in describing prevention or avoidance of death. Knowledge regarding the known improvements in treatment, both in the distant past and more recently, could help elucidate any observed differences in the secular trends.

4.6.4 Future prospects for prevention

Screening, together with changing sexual mores, largely explain the respective changes in period- and cohort-specific patterns in cervical squamous cell carcinoma in the European countries studied. The increasing risk among more recent cohorts is of obvious concern, particularly in countries where no screening programmes are currently in place. For cervical adenocarcinoma, the effects of screening, although part-enforced by the model specification, appeared negligible in most countries, although a downturn was observed in several of them where national programmes were in operation during the 1990s. This provides at least some confirmatory evidence that cytological screening is detecting more pre-invasive adenocarcinomas than in previous decades. Opportunistic screening clearly plays a role, but an undefined one in terms of its effectiveness.

The homogeneity of trends in adenocarcinoma and squamous cell carcinoma by birth cohort is consistent with the notion that they share a similar aetiology irrespective of the differential capability of screen detection. The increasing risk in successive generations of subtypes suggests the major driver is an increasing prevalence of persistent oncogenic HPV infection, and possibly, its cofactors. The observation of differing risk patterns in young cohorts in countries with relatively similar societal structures (the Czech Republic and Slovakia) is an interesting finding deserving further research.

HPV screening for high risk HPV types – probably in combination with cytological screening – may maximise the possibilities of having early lesions detected and treated. Recent trials evaluating the efficacy of virus-like-particle vaccines in prevention of persistent infection with HPV types 16 and 18 in young women have been shown to be highly efficacious [385,386]. There is therefore some expectation that cervical cancer generally, and adenocarcinoma of the cervix in particular, may be preventable by HPV vaccination. Cytological screening will continue to play an essential role in preventing occurrences of, and deaths, from cervical cancer in the decades to come. There are many lower-resource countries with high rates, notably in Eastern Europe, where there is an unequivocal need for preventative action. Reaching currently unscreened groups, which are concentrated essentially in lower socioeconomic categories, is also an important task.

5 Analyses of temporal trends in endometrial cancer in Europe

5.1 Introduction to the chapter

This chapter aims to describe and evaluate time trends of endometrial cancer incidence and mortality in Europe, with an emphasis on explication of the factors responsible for the incidence trends with the aid of APC models. To achieve these objectives, the analysis involves the same high quality cancer registry data series available in the 13 European countries used in Chapter 4.

The incidence and mortality observations analysed in this chapter strictly comprise cancers of the corpus uteri. In the following text it is used interchangeably with the term "endometrial cancer", a longstanding practice [387] given the vast majority of cancers of the uterine corpus are adenocarcinomas arising from the endometrium, the epithelial cells that line the uterus.

5.1.1 Why analyse trends in endometrial cancer incidence?

Rapid increases in incidence of endometrial cancer amongst postmenopausal women reported in the U.S. in the early to mid-1970s [387-390] brought the substantial risk conferred by HRT via the intake of oestrogen to progesterone to the attention of the medical and scientific community, and to the public at large. No such extreme rise occurred in Europe at that time or thereafter. Instead, steady increases were observed in many countries. Some of the highest incidence rates of endometrial cancer worldwide are found in Europe [18], and rates vary only by a factor of two between countries [323].

The disease mechanisms and risk factors for endometrial cancer are more established than for other cancers, and surveillance of incidence trends effectively monitors the changing profile of the established risk determinants. Endometrial cancer has a multifactorial aetiology however, and one that differs according to menopausal status leaving assessment of the impact of specific risk factors a complicated task. In this regard, comparisons of trends across European populations, potentially heterogeneous with respect to the prevalence and distribution of certain factors that may be responsible for the neoplasm, may shed light on the particular components that drive trends in certain countries.

The disease occurs predominantly after the menopause. In premenopausal women, endometrial cancer is relatively rare, and where data on incidence are available, observed trends are mainly decreasing [312]. COC provide long-lasting protection [391], as do several reproductive factors including high parity and a late age at first birth. In postmenopausal women, intake of postmenopausal oestrogens without the protective effect of progestins increases risk. High serum levels of endogenous oestrogens, menstrual history (early

menarche, late menopause, anovulation), nulliparity, early age at last birth, and obesity [392-394] may increase risk. An estimated 39% of all cases in the European Union was attributable to excess body weight in 1995 [395]. Smoking has been consistently reported to confer a decreased risk of endometrial cancer in postmenopausal women [396].

5.1.2 Why analyse trends in endometrial cancer mortality?

The prevalence of endogenous hormone use in a particular country, both in terms of COC and HRT, is dependant on its availability, and as such, has a very different profile across populations, with prevalence high only in several richer countries. Mortality is an important indicator in establishing the contrasting risk profile of endometrial cancer in Eastern Europe – where long series of incidence data are unavailable in most countries. In several Eastern countries, five-year relative survival has been estimated to be 10-15% lower than the 78% European average [397].

As well as problems associated with using mortality as a surrogate of incidence, there are major problems interpreting endometrial cancer trends as a result of substantial variations in the accuracy of death certificates in specifying cancer of the uterus [312]. Many deaths are recorded as uterine cancer unspecified, rather than attributed to either cervical or corpus uteri cancer. A somewhat unsatisfactory practice in analysing cervix and endometrial cancer mortality trends involves restricting analyses to trends in subgroups considered largely unaffected by the problem e.g. cervical cancer in premenopausal women (few endometrial cancer cases) and a combination of cervix and corpus uteri trends in postmenopausal ages. The alternative is an assignment of unspecified deaths to the main sites; a recent algorithm was therefore used that reallocates unspecified uterine cancer deaths to cervix uteri and corpus uteri [312], enabling a comparison of cross-sectional trends across Europe in pre- and postmenopausal women.

5.1.3 Main objectives of the trends analyses

The objectives are twofold. The first involves putting together a comprehensive synthesis of the major geographical and temporal variations in endometrial cancer incidence and mortality, with an emphasis on determining the variations in the rates of change in the age-adjusted secular trends in pre- (aged 25-49 years) and postmenopausal (aged 50-74 years) women. The results are described in light of both established and postulated risk factors for endometrial cancer. The second aim is to examine in more detail the age-specific incidence trends of endometrial cancer across European countries with high quality cancer registry data and sufficient time series, with a view to a comparative description and interpretation of

the contribution of period and birth cohort effects and their relation to the risk determinants that drive the trends.

5.2 Review of endometrial cancer epidemiology

5.2.1 Descriptive epidemiology

In 2002, almost 200,000 endometrial cancers were diagnosed worldwide [263]. The disease occurs mainly in Western countries, with rates high in Northern America, Europe (particularly Northern and Eastern Europe) and Oceania, intermediate in Southern and Central America, and predominantly low in Africa and Asia. About two-fifths of the worldwide burden of endometrial cancer occurs in Europe, representing one in every 18 new female cancers and ranking as the fourth most common neoplasm in women after breast, ovarian and colon cancer, and ranking above cervical and lung cancer [263]. Incidence rates are high to intermediate relative to other world regions, differing twofold amongst European populations [323]. Prognosis is relatively good – relative survival at five years in European areas covered by registries is between 63% and 78%, with the poorer survival estimates observed in several Eastern European areas [397]. The 18,000 deaths estimated in Europe per annum is comparatively low, ranking as the tenth most common cause of cancer death in women. Variations in mortality in Europe reflect both cancer incidence and survival, with variations between European countries suggested as a result of disparities in patient management [398]. Trends in survival suggesting improvements in prognosis are generally restricted to women over 65 [138].

5.2.2 Aetiology

The epidemiology of endometrial cancer in Western countries is fairly well understood. Family history of endometrial cancer is associated with an increase in risk [392], while high parity and late age at last birth is considered to confer long-lasting protection [392]. The role of obesity as a risk factor in both pre- and postmenopausal women is also firmly established [394] and there is additional evidence – albeit limited – that physical activity has a protective effect [394].

Use of COC confers a long-lasting protection against endometrial cancer, particularly among long-term users [391]. HRT is an important risk factor in countries where their prescription has been common practice in recent decades [392]. Risk increases markedly with use of oestrogen-only and sequential oestrogen-progestin HRT, although it may be mitigated by the continuous addition of progestins [399,400]. There is also substantive evidence that smoking is protective [396]. The risk factors involved are discussed in more depth later in this chapter in relation to interpreting the results (5.4.4 and 5.5.4).

5.3 Review of temporal studies of endometrial cancer in Europe

Temporal patterns of endometrial cancer came to widespread attention following the rapid rise in incidence amongst postmenopausal women in the U.S. in the early 1970s [387]. The observation of a concomitant increase in the prescription of HRT led to the hypothesis that high levels of oestrogens unopposed by progestins predisposed women to an elevated risk of endometrial cancer [399]. The subsequent prohibition of HRT with oestrogens in the U.S. led to prompt declines in endometrial cancer rates [401]. That the downwards trends continued throughout the 1980s despite an increasing HRT prescription rate in the 1980s is explained by the reductive or protective effect of a reduced dose of oestrogen in combination with added progesterone [402,403].

The profoundly steep rise seen in endometrial cancer was not a feature of temporal patterns in Europe. Instead, incidence trends in many European populations increased for several decades up to the early 1980s [8,404,405], with subsequent declines reported in several countries [152,406-409]. Widespread use of combined oestrogen-progesterone HRT from the 1970s onwards, together with the widespread use of combined oestrogen-progestin contraceptives introduced during the 1960s – which markedly reduce a women's corpus uteri cancer risk – have been suggested as important factors responsible for the favourable trends. Mortality rates have generally been shown to be decreasing with time in most European populations [8,405].

Although a number of reports have emerged from the U.S. [387,390,410,411], there have been relatively few such studies examining trends of endometrial cancer in European populations. Where they have been studied, incidence has been reported to have been increasing for several decades up to the early 1980s [8,404,405], while subsequently some declines have been reported in East Germany [408], Sweden [406], Switzerland [409] and England and Wales [152,407].

5.4 Study I: joinpoint trends in endometrial cancer in Europe

This section describes the geographical and temporal variations in endometrial cancer incidence and mortality, with an emphasis on determining the variations in the rates of change in the age-adjusted secular trends in pre- (aged 25-49 years) and postmenopausal (aged 50-74 years) women via the joinpoint regression model [183]. The results are described in light of both established and postulated risk factors for endometrial cancer and their assumed prevalence and distribution in Europe. A version of this section has been recently published in a peer-reviewed journal [412].

5.4.1 Data sources and data quality

5.4.1.1 Incidence

The incidence and population datasets were extracted from the EUROCIM [160] (see 2.8 for details and standard inclusion criteria). Table 5.1 provides details of the cancer registries used in this analysis. The time-span of observations in the final dataset varied from 11 to 47 years. Incidence data pre-1960 were not considered. The analysis was restricted to the five-year age groups comprising the age range 25-74.

5.4.1.2 Mortality

Mortality data coded as cancer of the cervix uteri (ICD-9 180), corpus uteri (ICD-9 182), and uterine cancer unspecified (ICD9 179) was extracted from the WHO mortality database (see 2.8 for details and standard inclusion criteria). There are large variations in the accuracy of death certificates specifying cancer of the uterus in Europe [312], with many deaths recorded as uterine cancer unspecified, rather than attributed to either cervical or corpus uteri cancer. For some countries, the proportion is over 50% of all uterine cancer deaths, although there is a tendency for the proportion to decrease with calendar time [312].

Therefore, an algorithm proposed by Loos *et al* [312] was implemented that reallocates unspecified uterine cancer deaths to the two primary sites on the basis of age- and time-specific distributions of cervix and corpus uteri cancer from representative populations with consistently high quality data. Further, the method reassigns deaths that were combined at the 3-digit level in ICD-8 to their original coding as corpus uteri or unspecified, allowing credible time trends for corpus uteri cancer in postmenopausal women, previously unavailable for a number of countries [312]. The time-span of observations in the final dataset varied from 16 to 34 years (Table 5.2). Only mortality data from 1969 onwards were considered, as there was a lack of consistent data in many countries in prior years corresponding to the ICD-7 revision.

5.4.1.3 Data quality

5.4.1.3.1 Changing proportions of uterus otherwise unspecified

There is substantial misclassification of cancer of the corpus uteri as site unspecified in some countries, and the reallocation procedure attempted to estimate the true rates of endometrial cancer by country, age and time period [312]. The algorithm dealt not only with problems of varying coding precision over time, but also with the combined category of corpus uteri and unspecified, when the data were not reported at a sufficient level of detail, as was common in a number of Eastern European countries. Unspecified deaths were reallocated on a country-specific basis, according to proportions of cervix or corpus uteri

from well-matching reference populations associated with high and long-term precision of coding. The method indicated that many of the large differences were a consequence of data incompleteness and could be corrected by applying the reallocation. The procedure was considered generally valid, at least in terms of the plausibility of the reallocated temporal patterns compared to those observed within populations similar in terms of socio-economic structure and screening policies [312].

5.4.1.3.2 Changing rates of hysterectomy

The prevalence of hysterectomy in the European countries must be considered in interpreting the geographical and temporal patterns of endometrial cancer. There are known to be some variations in hysterectomy rates in European populations over time [368,413]. In Finland for instance, the age-adjusted prevalence of hysterectomy increased from about 13% in the late 1980s to over 20% a decade later [368]. While a number of methods have been proposed for correcting incidence and mortality rates of uterine cancer [368,414,415], hysterectomy data were not available at a sufficient level of detail to adequately present adjusted rates in most of these countries. A special survey has been called for to adequately address this issue [130].

The denominators in this study are thus unadjusted person-years at risk – based on the country and age-specific population data for all women – rather than just those with their uteruses intact. A lack of adjustment has the potential to seriously bias the direction and magnitudes of these estimates, particularly among older women. It is possible, for example, that the apparent levelling off of rates or even declines – seen in incidence trends in recent years among postmenopausal women in several Northern and Western countries – is an artefact of increasing population prevalence of hysterectomy [130]. Caution is also urged in interpreting recent mortality trends demonstrating these characteristics [130].

Table 5.1: Endometrial cancer incidence: populations and recent stable trend in pre- and postmenopausal women

			Ages 25-49				Ages 50-74			
European Area	**Country**	**Period available (year span)**	**Incident cases***	**Person-years†**	**Stable period¶**	**Stable trend 95% CI¶**	**Incident cases***	**Person-years†**	**Stable period¶**	**Stable trend 95% CI¶**
Northern	Denmark	1978 – 1998 (21)	33	953,576	1978 – 1998	-1.9 [-3.1, -0.7]	381	708,540	1978 - 1998	-1.1 [-1.6, -0.6]
	Estonia	1968 – 2000 (33)	16	246,027	1968 – 2000	+0.4 [-0.4, +1.2]	134	218,207	1968 - 2000	+1.1 [+0.8, +1.4]
	Finland	1953 – 1999 (47)	57	900,917	1953 – 1999	-0.4 [-1.1, -0.4]	470	733,776	1953 - 1999	+1.5 [+1.4, +1.7]
	Iceland	1955 – 2000 (40)	6	47,417	1955 – 2000	-1.3 [-3.0, +0.3]	18	28,402	1955 - 2000	+1.1 [+0.2, +2.0]
	Norway	1953 – 1997 (45)	52	789,483	1979 – 1997	-0.7 [-2.1, +0.7]	304	525,730	1978 - 2000	+2.2 [+1.8, +2.6]
	Sweden	1960 – 1998 (39)	43	1,488,299	1972 – 1998	-4.3 [-4.8, -3.8]	870	1,196,116	1985 - 1998	+1.7 [+1.1, +2.2]
	United Kingdom[a]	1974 – 1997 (24)	317	9,885,453	1974 – 1997	-1.2 [-1.6, -0.9]	2964	6,944,200	1992 - 1997	+2.5 [+1.5, +3.5]
Eastern	Czech Republic	1985 – 1999 (15)	139	1,819,411	1985 – 1999	-1.8 [-2.5, -1.0]	1152	1,459,422	1985 - 1999	+0.8 [+0.2, +1.4]
	Poland[b]	1986 – 1996 (11)	72	1,018,194	1986 – 1996	-3.5 [-6.7, -0.1]	440	730,002	1986 - 1996	+3.4 [+1.0, +5.8]
	Slovakia	1968 – 1997 (30)	77	973,987	1992 – 1997	-6.6 [-14.5, +2.2]	470	630,722	1973 - 1997	+1.8 [+1.5, +2.2]
Southern	Italy[c]	1981 – 1997 (17)	56	766,773	1981 – 1997	-2.6 [-5.5, +0.4]	406	753,060	1981 - 1997	-0.8 [-1.5, -0.0]
	Slovenia	1983 – 1999 (17)	28	384,589	-	-	191	277,887	1983 - 1999	+2.1 [+1.3, +2.8]
	Spain[d]	1980 – 1997 (18)	39	659,032	1980 – 1997	+0.2 [-2.0, +2.5]	285	504,290	1988 - 1997	+2.5 [+0.6, +4.5]
Western	France[e]	1978 – 1997 (20)	52	741,584	1978 – 1997	-1.9 [-3.4, -0.5]	262	501,845	1978 - 1997	-0.3 [-1.0, +0.3]
	Germany, Saarland	1970 – 1997 (28)	16	210,559	1970 – 1997	-2.2 [-4.2, -0.2]	116	166,488	1970 - 1997	-0.0 [-0.4, +0.4]
	Switzerland[f]	1981 – 1997 (17)	39	551,868	1981 – 1997	-1.6 [-3.8, +0.6]	276	451,643	1981 - 1997	-0.8 [-2.0, +0.4]
	The Netherlands[g]	1986 – 1997 (12)	18	329,731	1989 – 1997	-2.6 [-9.8, +5.3]	153	242,837	1986 - 1997	+0.8 [-0.3, +1.9]

* number of new cases in latest year available.
† person-years at risk (unadjusted for hysterectomy) in latest year available.
¶ EAPC based on joinpoint regression for the most recent period available for which authors consider the trends representative of the observed patterns; - denotes regression not possible due to sparse data, or fitted trends unstable.
a aggregation of England, Scotland
b aggregation of Cracow City, Lower Silesia, Warsaw City
c aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin
d aggregation of Tarragona; Granada, Murcia, Navarra, Zaragoza
e aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn
f aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich
g aggregation of Eindhoven, Maastricht (IKL)

Table 5.2: Endometrial cancer mortality: populations and recent stable trend in pre- and postmenopausal women

			Ages 25-49				Ages 50-74			
European Area	**Country**	**Period available (year span)**	**Deaths***	**Person-years†**	**Stable period**	**Stable trend 95% CI¶**	**Deaths***	**Person-years†**	**Stable period**	**Stable trend 95% CI¶**
Northern	Denmark	1969 - 1999 (31)	1	952,442	-1.9 [-4.5, +0.8]	1969 – 1999	67	716,716	1969 – 1999	-1.2 [-1.7, -0.7]
	Estonia	1981 - 2002 (20)	0	242,650			27	217,763	1993 – 2002	-3.9 [-8.1, +0.6]
	Finland	1969 - 2002 (34)	1	880,973	-2.2 [-4.3, -0.1]	1969 – 2002	62	763,982	1982 – 2002	-0.5 [-1.5, +0.6]
	Iceland	1969 - 2002 (34)	0	49,868	-	-	5	27,706	-	-
	Ireland	1969 - 1999 (31)	4	669,300	-5.1 [-7.5, -2.5]	1969 – 1999	26	396,700	1969 – 1999	-2.8 [-3.2, -2.3]
	Latvia	1969 - 2000 (32)	5	419,877	-	-	81	378,502	1969 – 2000	+1.3 [+0.4, +2.1]
	Lithuania	1980 - 2002 (23)	4	633,978	-	-	83	506,944	1980 – 1995	+0.1 [-1.1, +1.4]
	Norway	1981 - 2002 (20)	0	802,936	-0.7 [-3.2, +1.9]	1981 – 2002	63	547,974	1981 – 2002	-0.9 [-1.3, -0.4]
	Sweden	1969 - 2001 (33)	2	1,481,243	-2.7 [-6.0, +0.6]	1969 – 2001	132	1,233,237	1987 – 2001	+0.7 [-0.4, +1.9]
	United Kingdom	1969 - 1999 (31)	25	10,639,800	-8.5 [-11.8, -5.1]	1985 – 1997	531	7,705,000	1969 – 1991	-1.7 [-2.2, -1.4]
Eastern	Belarus	1981 - 2001 (19)	0	1,889,143	-	-	262	1,419,621	1988 – 2001	+0.6 [-0.5, +1.8]
	Bulgaria	1970 - 2002 (33)	26	1,369,374	-2.7 [-7.4, +2.3]	1990 – 2002	162	1,263,327	1987 – 2002	-2.6 [-3.8, -1.3]
	Czech Republic	1986 - 2001 (16)	13	1,829,141	-0.3 [-4.2, +3.8]	1986 – 2001	200	1,491,580	1986 – 2001	-2.0 [-2.8, -1.2]
	Hungary	1970 - 2002 (33)	14	1,831,979	-0.8 [-2.6, +1.1]	1982 – 2002	201	1,572,680	1970 – 2002	-1.6 [-1.9, -1.4]
	Poland	1970 - 1996 (27)	0	7,062,100	-	-	678	4,581,800	1986 – 1996	-1.8 [-2.5, -1.2]
	Republic of Moldova	1981 - 2002 (20)	13	675,023	-	-	67	419,828	1981 – 2002	+1.7 [+0.2, +3.3]
	Romania	1970 - 2002 (32)	31	3,946,395	-	-	246	3,031,621	1996 – 2002	-8.9 [-12.9, -4.8]
	Russia	1980 - 2002 (23)	0	27,471,229	-	-	1880	20,655,545	1980 – 2000	+1.2 [+0.8, +1.5]
	Ukraine	1981 - 2000 (18)	0	9,096,800	-	-	1409	7,585,900	1992 – 2000	-0.6 [-1.9,+ 0.7]
Southern	Croatia	1972 - 2000 (29)	0	788,900	-	-	74	684,700	1972 – 2000	-0.8 [-2.4, +0.9]
	Greece	1969 - 1990 (22)	4	1,887,781	-4.5 [-6.6, -2.3]	1969 – 1990	102	1,542,838	1969 – 1990	-1.3 [-1.9, -0.8]
	Italy	1972 - 2002 (31)	36	10,709,440	-4.2 [-5.3, -3.1]	1972 – 2002	777	8,738,869	1978 – 2002	-3.4 [-3.9, -2.9]
	Malta	1972 - 1997 (26)	0	68,105	-	-	7	54,334	1982 – 1997	-2.6 [-6.7, +1.8]
	Portugal	1972 - 1999 (28)	7	1,887,831	-3.5 [-7.1, +0.2]	1972 – 1999	128	1,440,858	1983 – 1999	-1.5 [-2.4, -0.6]
	Slovenia	1983 - 2001 (19)	5	373,909	-	-	36	282,585	1983 – 2001	-1.3 [-2.8, +0.3]
	Spain	1972 - 2002 (31)	16	7,559,046	-4.3 [-5.4, -3.2]	1972 - 2002	492	5,391,336	1972 – 2002	-2.01 [-2.3, -1.7]
Western	Austria	1985 - 2002 (18)	1	1,519,671	-4.4 [-6.0, -2.7]	1985 – 2002	102	1,095,677	1985 – 2002	-2.2 [-2.5, -1.8]
	Belgium	1972 - 1999 (28)	5	1,864,973	-4.0 [-5.7, -2.2]	1972 – 1999	123	1,382,174	1982 – 1989	-7.1 [-12.5, -1.4]
	France	1972 - 2000 (29)	26	10,698,229	-4.2 [-5.1, -3.4]	1972 – 2000	735	7,574,869	1972 – 1992	-2.3 [-2.8, -1.8]
	Germany	1972 - 2002 (31)	37	15,083,039	-	-	830	12,107,443	1991 – 2002	-2.6 [-3.8, -1.3]
	Luxembourg	1972 - 2000 (29)	0	87,264	-	-	1	55,207	-	-
	Switzerland	1985 - 2002 (18)	0	1,365,126	-5.5 [-9.0, -2.0]	1985 – 2002	73	969,158	1985 – 2002	-3.2 [-3.6, -2.8]
	The Netherlands	1969 - 2001 (33)	14	3,026,925	-3.1 [-4.7, -1.4]	1969 – 2001	151	2,016,626	1969 – 2001	-2.0 [-2.4, -1.5]

* number of deaths in latest year available.
† person-years at risk (unadjusted for hysterectomy) in latest year available.
¶ EAPC based on joinpoint regression for the most recent period available for which authors consider the trends representative of the observed patterns. - denotes regression not possible due to sparse data, or fitted trends unstable.

5.4.2 Methods: joinpoint regression

Annual truncated age-standardised rates (TASR) of corpus uteri cancer incidence and mortality were calculated for women aged 25-49 and 50-74 years (hereafter pre- and postmenopausal are respective synonyms) using the World standard population [168]. The mean TASR during the period 1997-99 – or the latest three-year period if not available – was calculated to provide a synopsis of geographical variations by European country.

To present secular trends in pre- and postmenopausal women by calendar period, regression models [183] were fitted to the TASR for the available data in the two age groups by country, using the Joinpoint software package (Version 2.6) [184]. A logarithmic transformation of the rates and equal variance for each year were specified as options within the program. A maximum number of three joinpoints was specified, leading to the prerequisite minimum of 11 years of data required to achieve meaningful model fits. The program thus searched for changes in the linear trends of incidence and mortality based on regression models with 0, 1, 2 and 3 joinpoints, with the final model selecting the most parsimonious of these. Joinpoint regression can be seen as a descriptive tool for identifying sudden changes in the long-term trend in epochs of time, or "segments", for which rates are relatively stable, avoiding the need to arbitrarily select a base for estimating the direction and magnitude of the slope.

The observed age-truncated rates and the fitted trends between joinpoints are shown graphically by country within European area. The rates are plotted on a log-transformed 2-cycle ordinate (e.g. with a y-scale of 1 to 100), and on an abscissa covering a 40-year span (1960-2000), with a Y:X ratio scaled to be approximately 2:1. Presented with these properties, a slope of 10 degrees portrays a 1% change in the rate per annum, a rule proposed by Devesa *et al* [165] to aid visual inspection.

The EAPC is summarised in tabular form as the best description of the most recent (and stable) trend by country and age group. Using the formula $100\times(\exp(b)-1)$, b is the parameter estimate of the trend for the most recent segment, or for the whole available period, where no joinpoints were found.

As has been recently commented [416], the estimated trend via joinpoint regression can be unduly influenced by the last datapoints, and additionally, some arbitrary fitted slopes can be anticipated for populations where large random variation is present, most notably in mortality trends, and trends in women aged 25-49. In presenting this data, each of the fitted trends from the joinpoint models was preserved in the graphical presentation, but the tabular display of the EAPC was limited to recent trends and those considered to provide a

reasonable description of the observed data. The associated 95% CI provides a gauge of the adequacy of the final model and the degree of random variation inherent in the observed rates.

5.4.3 Results: description of trends

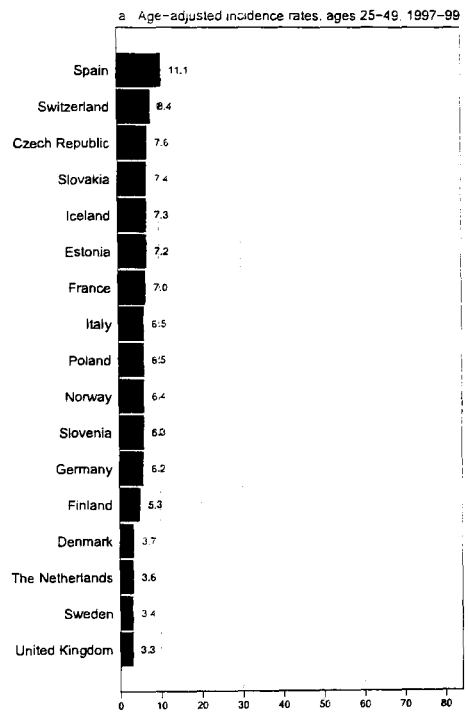
5.4.3.1 Geographical variations

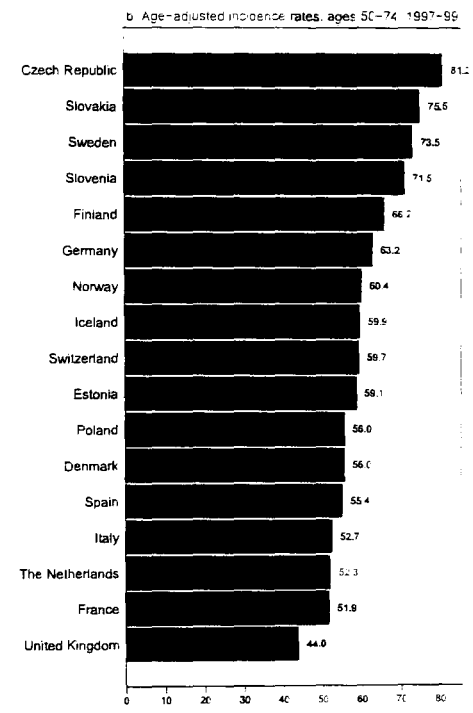
There were clear variations in incidence and mortality rates, and rates among pre- and postmenopausal women in Europe (Figure 5.1). Endometrial cancer incidence was at least 10 times more common in older women than in younger women in most study populations, with even more pronounced age ratios for mortality of up to 30-fold. Mortality rates tended to be four to six times lower than incidence in postmenopausal women, although more striking contrasts were seen in the younger women.

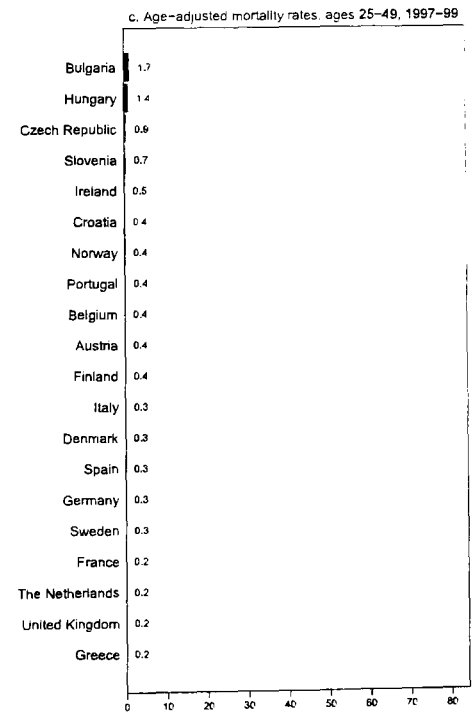
Incidence rates varied threefold in premenopausal and twofold in postmenopausal women among the countries studied. Some consistent patterns emerged across age groups, for example the high rates observed in the Czech Republic and Slovakia among both pre- and postmenopausal women. Additionally to these countries, rates amongst women aged over 50 were elevated in Sweden and Slovenia, but were low in France and the U.K., with the latter country also having the lowest incidence rate of corpus uteri cancer in premenopausal women.

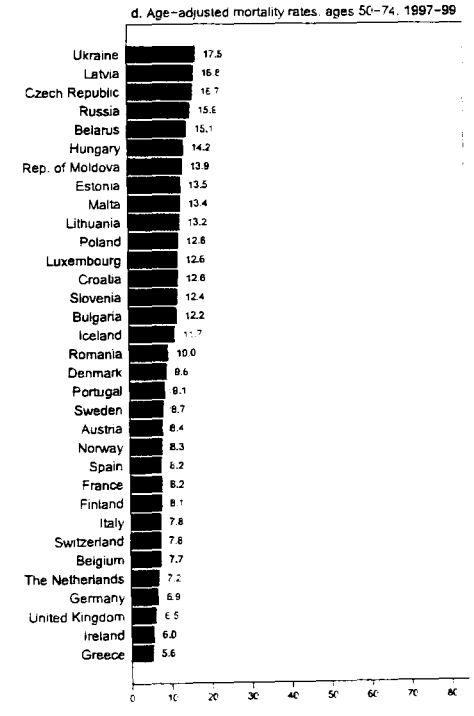
As with incidence, endometrial cancer mortality rates ranged approximately twofold in postmenopausal women. Rates varied more considerably in premenopausal women, and were highest in some Eastern European countries, although these estimates are based on small numbers in most populations. Certainly, the ranking of mortality rates among postmenopausal women conveys a profile more related to European area of residence than was seen for incidence: mortality rates were systematically higher in Eastern Europe, with rates in Ukraine, Latvia, Czech Republic, Russia, Belarus two to three times those seen in postmenopausal women in most Western European countries, where rates were generally low. As with incidence, very low death rates were observed in the U.K. in both age groups.

Figure 5.1: Truncated age-standardised endometrial cancer incidence and mortality rates (Europe) for the period 1997-99, in age groups 25-49 and 50-74, sorted by country and age.









5.4.3.2 Temporal variations

Figure 5.2 describes the observed incidence and mortality rates by menopausal status for each country by European region, together with the corresponding linear slopes calculated between the joinpoints obtained from the regression analyses. Due to the coding system employed historically, data were unavailable in some countries for women aged under 50 either for the whole, or a selected period. Tables 5.1 and 5.2 present the EAPC and corresponding 95%CI for the most recent incidence and mortality trend obtained from the regression, where they provided a reasonable description of the observed data.

The majority of the trends required zero joinpoints, an indication of the slow rather linear changes in rates of endometrial cancer observed in European populations in the last few decades. Both incidence and mortality rates in premenopausal women have been uniformly decreasing throughout Europe. Incidence rates in this age group tended to decline by 2-4% per annum on average in most countries. Where sufficient numbers were available, corresponding falls in mortality were often more marked. The reduction in mortality in young women was most evident in several Western and Southern European countries, where decreases of 3-5% per year since the 1970s were observed.

Secular trends in postmenopausal women were rather heterogeneous between and within European areas (Figure 5.2). Trends in incidence in Northern Europe (e.g. the Nordic countries and the U.K.) were systematically increasing annually at around 1% to 2% on average, with the exception of Denmark, where a significant decline of 1% since 1978 was estimated (Table 5.1), and for which the decrease was particularly evident in the 1990s. Some increases were also seen; in Eastern Europe, particularly Slovakia, and in Spain and Slovenia in the South. In Italy, rates remained stable in recent years, and a non-significant decrease was indicated since the 1980s. Similar plateaus or modest declines in rates were seen in Western Europe (France, Germany, Switzerland and the Netherlands).

Despite the increases in incidence in women of menopausal age, in general, decreasing trends in mortality were seen in most countries. Although there was some variability in the extent of the decline, the mean reduction per annum in most European countries ranged from 1-2% per year (Table 5.2). In Bulgaria, Poland and Romania, the declines were observed somewhat later (from the mid-1980s onwards) than elsewhere, although in Hungary, there was a uniform annual mean decline of 1.6% since 1970. In contrast, rates in Belarus and Russia were relatively stable or increasing in recent years. The exception in Northern Europe was Sweden, where a non-significant increase in death rates was estimated among postmenopausal women diagnosed since around 1987.

Figure 5.2: Trends in age-adjusted rates (Europe) of endometrial cancer incidence (open symbols) and mortality (closed symbols) in ages 25-49 (triangles) and 50-74 (circles) by country within region. Solid and dashed lines are the fitted trends based on joinpoint regression of ages 25-49 and 50-74, respectively.

a) Northern European countries

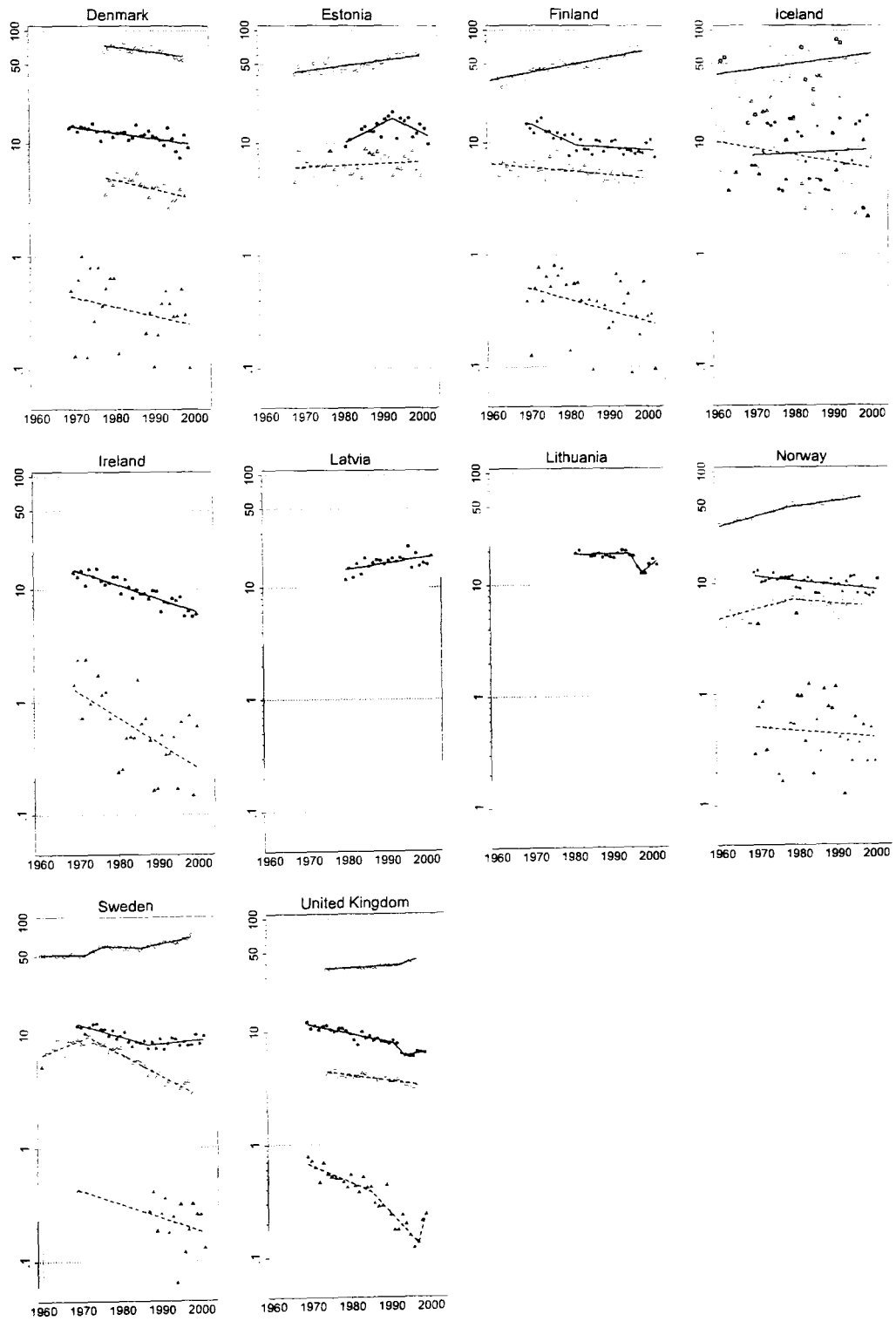


Figure 5.2 cont..

b) Eastern European countries

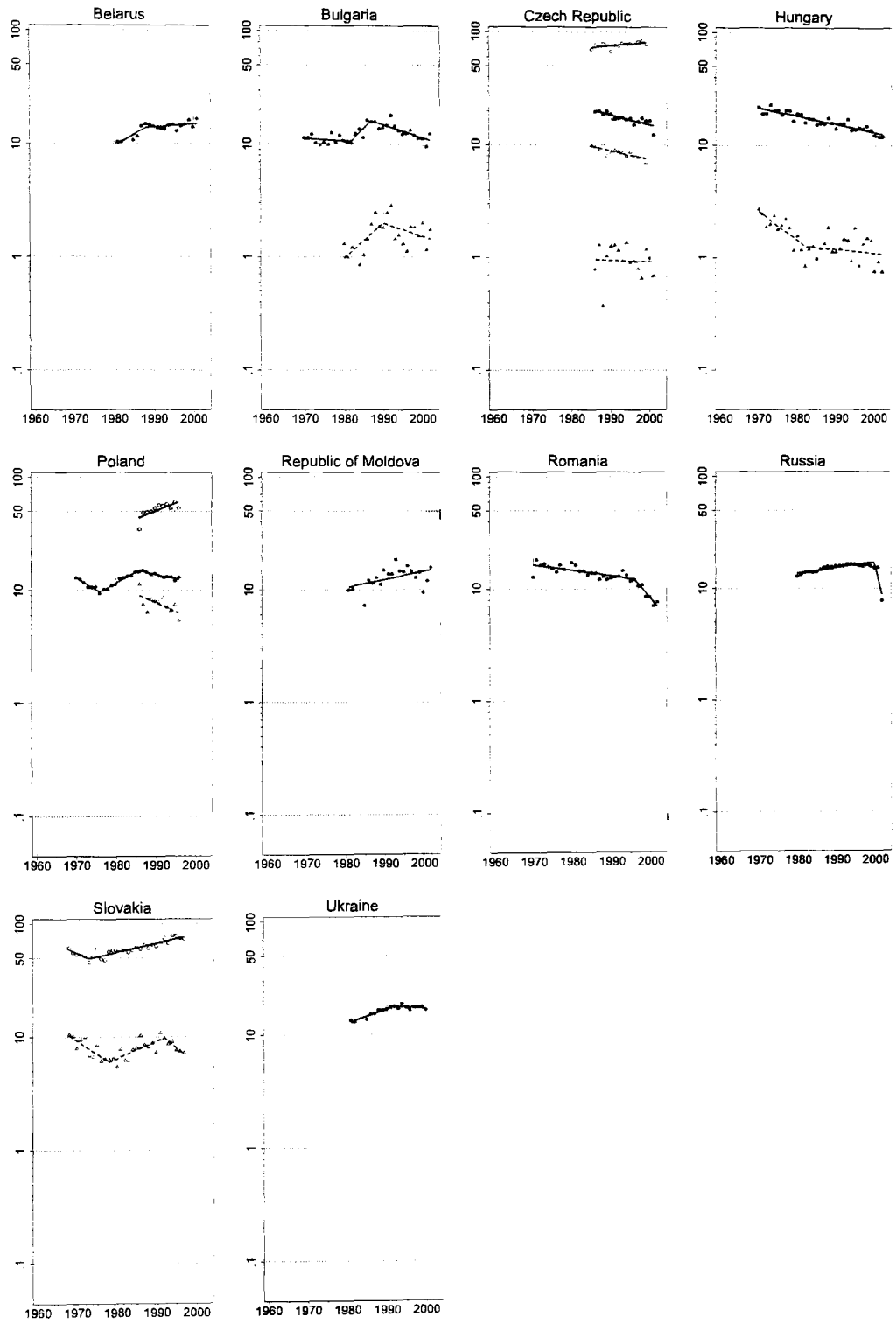


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Figure 5.2 cont...

c) Southern European countries

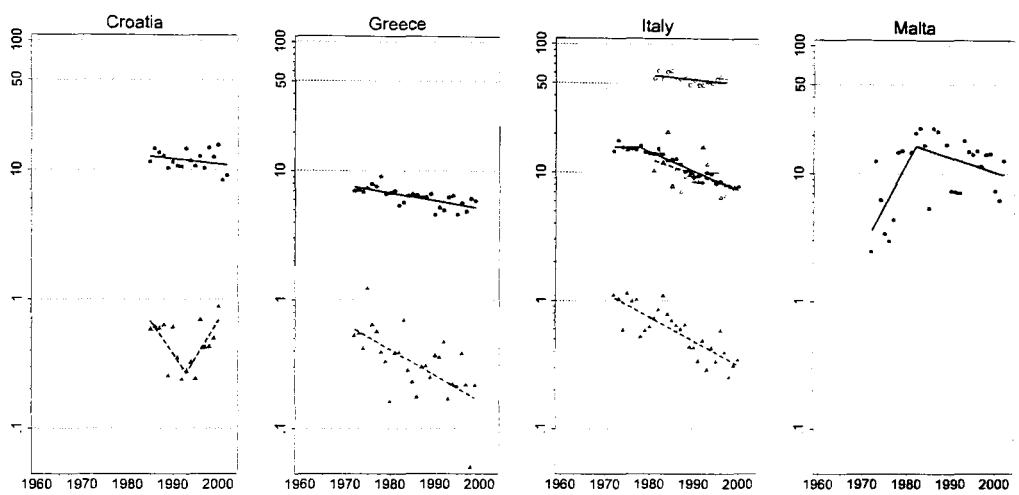
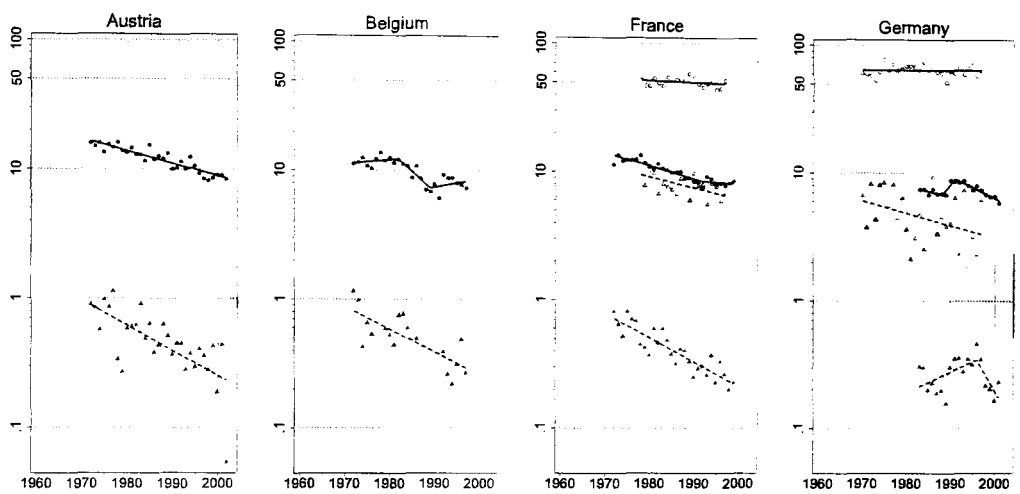


Figure 5.2 cont..

d) Western European countries



5.4.4 Discussion of main findings

This study has summarised endometrial cancer incidence and mortality rates in European populations by country, age group, and within country, over time. Incidence was 10 times higher, and mortality 10-30 times higher, amongst postmenopausal relative to premenopausal women. Incidence rates were relatively high across Europe, and levels corresponded to those seen in North America and Australia [17]. Mortality, while ranking much lower as a cause of cancer death than incidence, was higher in Eastern Europe, indicative of some disparity in early diagnosis and treatment of patients between regions, reflected in the lower survival estimates in some Eastern European populations relative to the European average [397].

The results presented here are in accordance with previous reports, and update and expand the analysis to countries where trends have not been reported. Further, the systematic approach utilised in this study, allowing a Europe-wide description of the contrasting variations in secular incidence and mortality trends, provided a useful tool to better understand the temporal variations in endometrial cancer, their relation to the underlying causes, and the development of more effective population-specific prevention strategies. The time trends of endometrial cancer in Europe are largely explained by our present understanding of the aetiology, for which several established risk factors are both highly prevalent in many European countries, and are most likely changing with time.

From the 1970s, corpus uteri cancer incidence has been declining in premenopausal women in almost all European countries where data was available, accompanied by uniformly decreasing mortality trends. The observation may be explained by the long-lasting protective effect of COC on endometrial cancer risk [391]. COC became increasingly available during their introduction in the 1960s, and their use has become widespread among women of reproductive age, particularly in higher-resource countries, where long-term use is common [417]. Previous studies examining trends in Europe have noted the decline in endometrial cancer occurrence among young women [152,406-409], several attributing the observations to oral contraceptive use.

Another possible contributor to the reduction in younger women may be the increasing number of women reproducing at later ages. Several studies have found an inverse association between older age at *last* birth and endometrial cancer risk [418-420], hypothesised to be due to mechanical shedding of cells that have undergone malignant transformation in women when they gave birth [421]. Further, the association appears stronger in women aged < 50 years than in older women, aged over 50 [419].

In postmenopausal women, incidence trends were observed to be either increasing (particularly in Northern Europe) or rather stable (particularly Western Europe). The use of exogenous hormones which increase endometrial cancer risk, and in particular the intake of postmenopausal oestrogens without progestins, considered particularly harmful, [394,400,422] may be responsible for the increasing rates where observed e.g. in Finland, Norway, Sweden and the U.K. – countries where the prevalence of HRT use has been high in postmenopausal women relative to other European areas.

The addition of progestins to HRT from the late-1970s onwards has been considered an explanation of the rather stable trends seen in the U.S. thereafter, [394] although some studies have found positive associations between the use of combined oestrogen and progestins in HRT and endometrial cancer risk [422]. Obesity and nulliparity may in combination be responsible for a large proportion of endometrial cancer in Europe: over one-third of all cases diagnosed in the European Union in 1995 have been estimated to be attributable to low fertility (36%) [19] and excess body weight (39%) [395]. Nulliparity is a well-established risk factor, giving a two- to three-fold increase in risk, with parity reductions dependant on number of children conceived [423]. Available census information from several European countries indicate that nulliparity levels are increasing in a number of European populations, while average completed family size is decreasing.

There is evidence that increasing energy supply is closely associated with the increases of overweight and obesity in many western countries [424], and these may have impacted on the European incidence trends amongst older women. Tretli and Magnus [425] estimated a potential 10% reduction in the incidence of uterine corpus cancer if obese women (women in the 5^{th} quintile of the body mass population distribution) could reduce their body weight to within the 4^{th} quintile. In a recent evaluation of the available evidence, IARC however considered that there was inadequate evidence of a reduction in risk, at least in humans, from intentional weight loss for any cancer site, including endometrial cancer [394]. In the same evaluation, physical activity was suggested as possibly preventing endometrial cancer, although the available evidence was considered limited. In a recent study in Sweden, it has been estimated that over 75% of the population attributable fraction (PAF) of endometrial cancer is due to the combined effect of low parity and age at first birth (PAF = 54.5%), family history (PAF=2.1%) and high socio-economic status (PAF = 5.9%) [426].

In Italy and in the Western European countries studied, relatively stable or decreasing trends were seen in women aged over 50. One might hypothesise as to the long-term protective effect of COC use in these populations, regardless of more recent or current HRT use, which is limited in these regions [417,427]. There are intriguing differences in the temporal

profile in certain countries relative to region as a whole. Endometrial cancer incidence trends in older women are increasing in Northern European countries with the exception of Denmark, where consistent decreases for at least a decade are noted. The effect of smoking, particularly current or recent and for high intensity or long duration exposures, has been consistently reported to decrease endometrial cancer risk, at least in postmenopausal women [396]. The mechanisms that drive the protective association remain unclear. There have been substantial increases in lung cancer mortality in Danish women since the 1970s, a clear marker for the historical effects of increasing tobacco consumption amongst women. Rates recently reached a plateau (in the 1990s), but only in women aged under 60 [307]. It may be conjectured that the factors that have driven the rates of endometrial cancer down in postmenopausal women include tobacco smoking.

The treatment of advanced breast cancer using Tamoxifen also confers an increased risk of endometrial cancer [428], although a Swedish study reported that the risk of endometrial cancer following breast cancer had not increased over time [429]. Swerdlow and colleagues have estimated that the use of Tamoxifen would be responsible for only about 2% of endometrial cancer cases in the U.K. [23]. Alternative anti-oestrogenic agents such as the aromatase inhibitor Anastrozole have emerged as a preferred first option for breast cancer treatment among premenopausal ER+ women, given the demonstration of less adverse effects on the endometrium five years after adjuvant therapy [430].

Mortality rates are decreasing in pre- and postmenopausal women in most countries. This is in line with previous reports on mortality rates reporting declining trends in most European populations [8,405]. Some exceptions are noted in this study. The decline in mortality rates in older women in certain Eastern European countries (and Estonia) was postponed to after the mid-1980s relative to elsewhere, whereas there was evidence of modest increases in Belarus and Russia, as well as in Sweden.

5.5 Study II: APC trends in endometrial cancer incidence in Europe

Study II narrows down the focus to incidence trends, with an aim to compare and contrast endometrial cancer trends in more depth using the longer data series available in 13 European countries, and an examination of age, period and cohort effects using the APC model. A version of the text in this section has been recently published in a peer-reviewed journal [367].

5.5.1 Data sources

The incidence data extracted as described in 5.4.1.1 was further restricted to countries for which registry data was available for 15 or more years. No restriction on the incidence data

going back in time was made, but a slightly different age range was used in this analysis (30-34, 35-39,..., 75-79). The final dataset incorporated 13 countries covering time spans from 15 to 45 years (Table 5.3).

Table 5.3: Endometrial cancer: populations included in the analysis, recent incidence rate and APC model fit statistics

European Area	Country	Period*	Incidence†	Person-years†	ASR††	APC model‡	Residual deviance§	d.f.§	p-value§
Northern	Denmark	1979-1998 (4)	535	1.5	31.8	APC	14.0	16	0.60
	Estonia	1971-2000 (6)	170	0.4	34.1	APC	43.7	32	0.08
	Finland	1955-1999 (9)	605	1.6	35.9	APC	116.8	56	<0.01
	Norway	1953-1997 (9)	416	1.2	33.1	APC	67.3	56	0.14
	Sweden	1964-1998 (7)	1087	2.6	37.3	APC	76.0	40	<0.01
	United Kingdom[a]	1978-1997 (4)	3765	15.5	22.8	APC	37.1	16	<0.01
Eastern	Czech Republic	1985-1999 (3)	1496	3.0	44.9	APC	11.7	8	0.16
	Slovakia	1968-1997 (6)	601	1.5	41.9	APC	56.5	32	<0.01
Southern	Italy[b]	1983-1997 (3)	520	1.3	30.3	AP	29.3	18	0.04
	Slovenia	1985-1999 (3)	246	0.6	38.2	AD	16.5	19	0.62
	Spain[c]	1983-1997 (3)	285	0.7	29.4	AC	5.0	9	0.83
Western	France[d]	1978-1997 (4)	311	0.8	27.8	A	34.5	30	0.26
	Switzerland[e]	1983-1997 (3)	291	0.7	32.7	AD	22.5	19	0.26

* data available according to period of diagnosis, figure in parentheses represent number of five-year periods available in the analysis
† average annual number of cases and person-years (per million) obtained from most recent five-year period
†† truncated age-standardised rates (Europe) for ages 35-79 obtained using most recent five-year period
‡ refers to the most parsimonious final model providing a good fit: A: Age; AD: Age+Drift; AC: Age+Drift+Cohort; AP: Age+Drift+Period; APC: Age+Drift+Period+Cohort
§ to determine the goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom (d.f.) determined by the model. $p<0.05$ indicates the full APC model does not yield an adequate fit
a aggregation of England, Scotland
b aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin
c aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza
d aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn
e aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich

5.5.2 Methods: characterising age, period and cohort effects

Period effects denote systematic changes that affect rates in all study age groups at a given point in time. They often represent a data artefact or artefacts related to changes in completeness of registration, diagnostic practices or disease classification [60]. They can occur through the introduction of specific environmental factors to which all population members are exposed regardless of age. The launch and subsequent uptake of HRT among peri- and postmenopausal women during the 1960s may be a candidate in this respect. Cohort effects reflect changes in exposure to risk factors in successive generations. For

endometrial cancer, these may include the changing prevalence of COC use among young women, decreasing parity, and the shift towards having children at a later age.

5.5.2.1 Fitting the APC model

The full APC model defined in 3.3.3 was fitted to the trends. The Holford approach [66] was utilised with age, period and cohort effects partitioned in terms of their linear and curvature elements (see 3.4.2). Overall goodness-of-fit and tests for the effects of net drift and period and cohort curvature were obtained using the hierarchical modelling approach of Clayton and Schifflers [63,68]. Two approaches to providing a unique set of age, period and cohort trends were used in this study and are described below.

5.5.2.2 Evidence of a steady state age curve

A fixed age structure was constructed via the longstanding consideration that endometrial cancer is a consequence of the physiological action of unopposed oestrogens that increase the cell proliferation, opposed by progestins which instigate differentiation to a secretory state [393,399]. A curve describing such characteristics would require that the risk of onset rises steeply from premenopausal through to perimenopausal age to a peak at menopause and a subsequent plateau thereafter. The relationship between the age curve of endometrial cancer and its aetiology was first commented on by Clemmesen [431] and Lilienfeld and Johnson [217] and developed by Moolgavkar [246] and Pike [220,223]. Moolgavkar suggested the possibility of a generalised age curve and a rather stable risk in women aged over 60 possibly due to their low levels of ancillary oestrogens [246].

To obtain a single set of parameter estimates, it was therefore assumed that the steady-state (period and cohort-adjusted) age-specific incidence curve for endometrial cancer in each population reflects the sensitivity of the target organ to unopposed oestrogens. Such an age curve was fixed for each country by choosing the age slopes α_L, for which for point estimates at ages 65-69, 70-74, and 75-79 were reasonably flat in each country, that is by selecting the estimates of α_L for which $\alpha_A - \alpha_{A-2} \approx 0$.

5.5.2.3 Evidence of a generation effect

The second assumption implied that cohort effects predominated the trends. Fixing the linear slope of the period effects to zero ($\beta_L = 0$) allowed the cohort slope to take up Holford's drift, the identifiable sum of the period and cohort slopes $\beta_L + \gamma_L$, while still allowing for non-linear period effects (see 3.4.2.1). The particular constraint implies that risk of endometrial cancer over time is mediated only by a changing distribution and prevalence of the known and putative risk factors in successive generations.

5.5.2.4 Obtaining identifiable period and cohort parameters

In addition to presenting the observed rates versus period and cohort by age, the effects of period and cohort are displayed on the basis of alternative parameterisations of the full APC model, as described in 5.5.2.2 and 5.5.2.3 above. APC models were also fitted in sub-strata according to menopausal status (ages 30-54 and 55-79). However, the models generated did not substantially alter the results obtained for the ages 30-79, in terms of the significance of individual effects, the overall fit of each of the hierarchal models and the interpretation of the parameters from these models. The results are thus presented solely on the basis of incidence data covering both pre- and postmenopausal age groups.

In presenting the model parameters, the period and cohort effects were once again reparameterised to rate ratios with reference points $P-1$ and $A+P-6$ respectively. The reference midpoints varied from 1990 to 1993 for period, and from 1938 to 1941 for birth cohort. On adding together the linear and curvature components, the resulting parameters thus described the risk of endometrial cancer in a given generation or period of diagnosis, relative to a reference category that was dependant on the particular time period analysed in each country.

5.5.3 Results: description of trends

Age-adjusted rates of endometrial cancer in the most recent period available varied less than twofold between the 13 countries, from over 40 per 100,000 in Slovakia and the Czech Republic to less then 30 per 100,000 in France, Spain and the U.K. (Table 5.3). Rates were lowest in the U.K. (23 per 100,000). The trends in age-specific rates by birth cohort and period of diagnosis are rather complex (see Figure 5.3). Figure 5.4 attempts to summarise these data using parameters obtained from the APC model using the two constraints specified above. Simpler models tended to yield adequate fits to the data where fewer periods (3 or 4) were available. The full APC model was required elsewhere, and for some countries, particularly those for which the incidence data spanned a longer time period, a significant lack-of-fit was observed (Table 5.3).

The interpretation of trends among the most recent cohorts is difficult given the rarity of events in women under the age of 45. Nevertheless, some general observations emerge from Figures 5.3 and 5.4, related mainly to a changing risk pattern according to menopausal status; both cohort and period effects were involved in risk changes in postmenopausal women, while in women of premenopausal age, diverse trends more orientated towards cohort emerged. These are described below by European region.

Figure 5.3: Incidence rates of endometrial cancer vs. period and cohort by age in 13 countries by European area, women aged 30-79. Age-specific rates on the cohort scale are identified by the mid-year of the quinqenniums

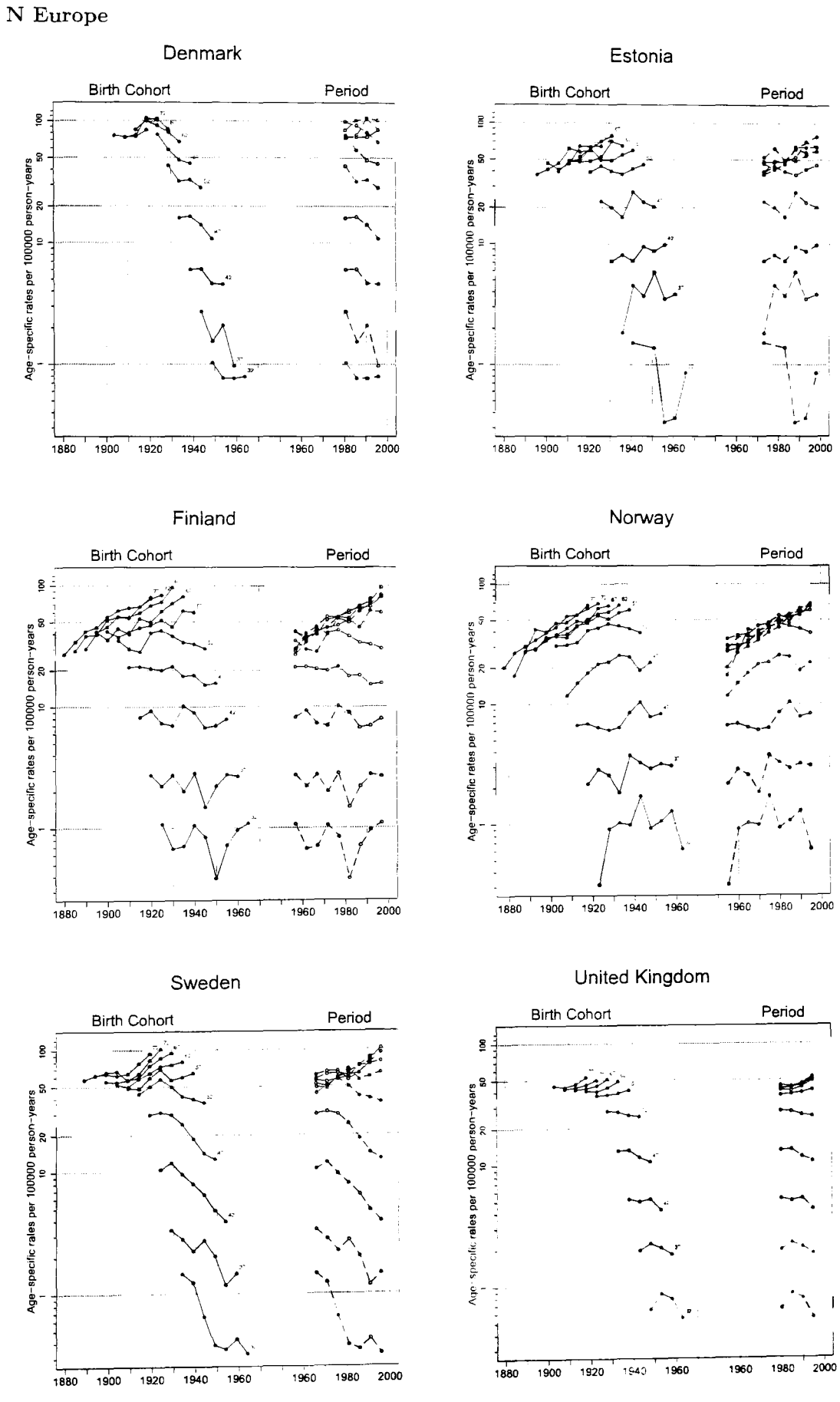
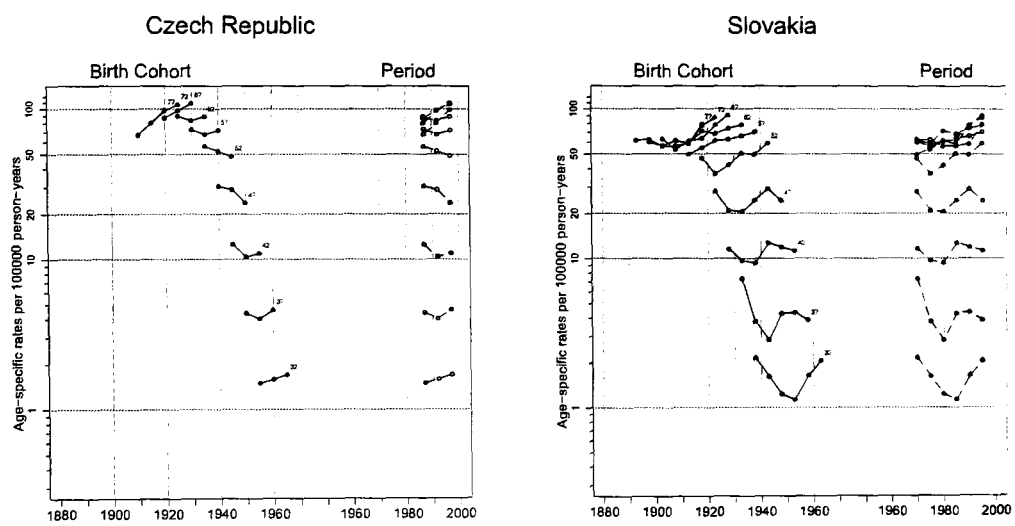


Figure 5.3 cont..

E Europe



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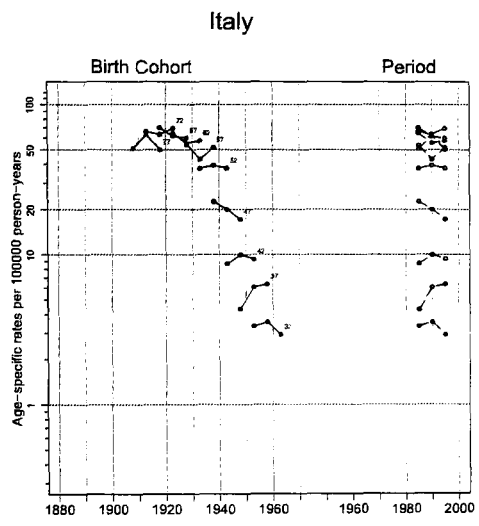
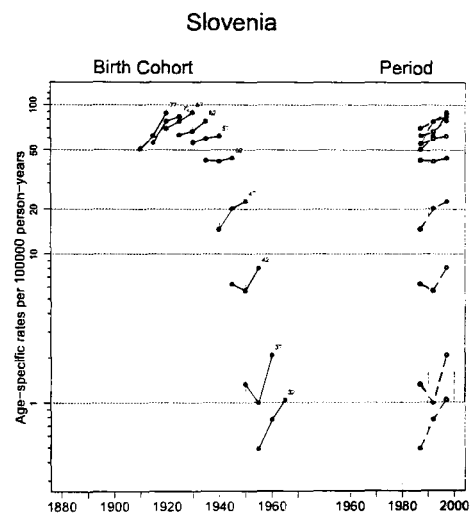
S Europe





Spain

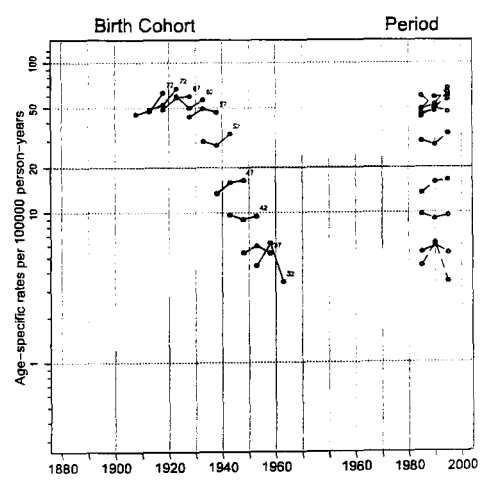


Figure 5.3 cont..

W Europe

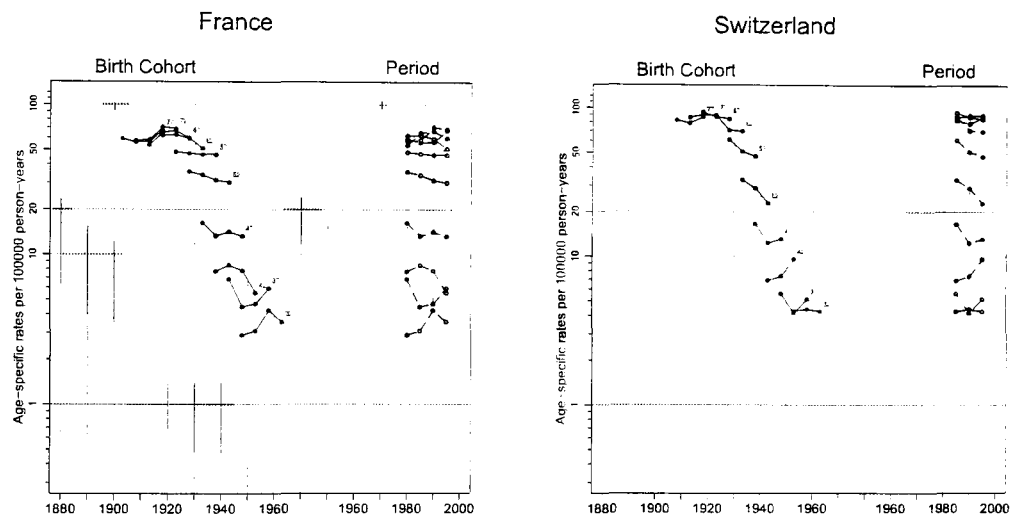


Figure 5.4: Incidence rate ratios of endometrial cancer for period and cohort by country within region for women aged 30-79. Estimates are from the APC model. Solid lines assume the age curve is fixed for which $\alpha_A - \alpha_{A-2} \approx 0$; dashed lines assume the linear slope of the period effects is zero ($\beta_L = 0$)

N Europe

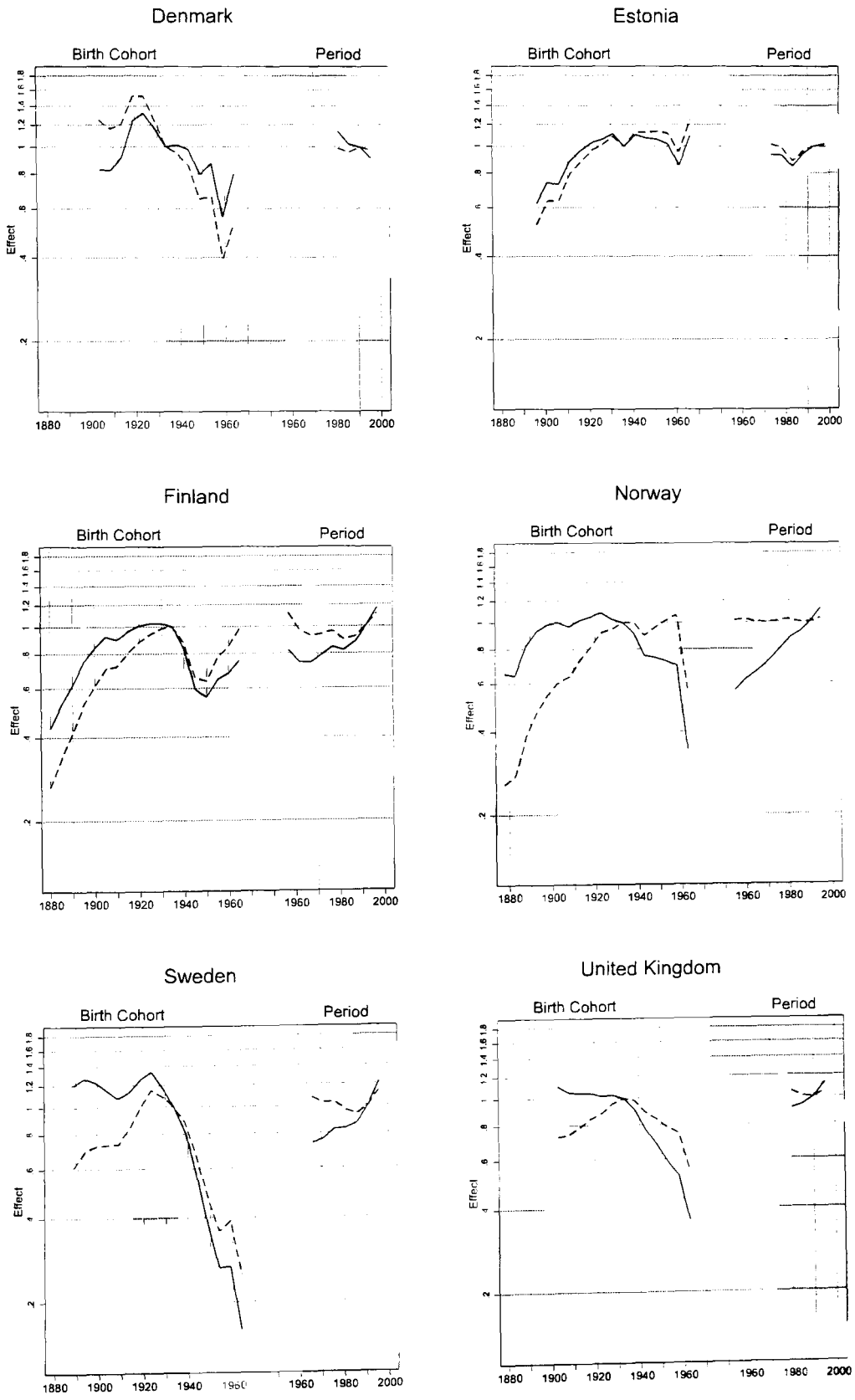


Figure 5.4 cont..

E Europe

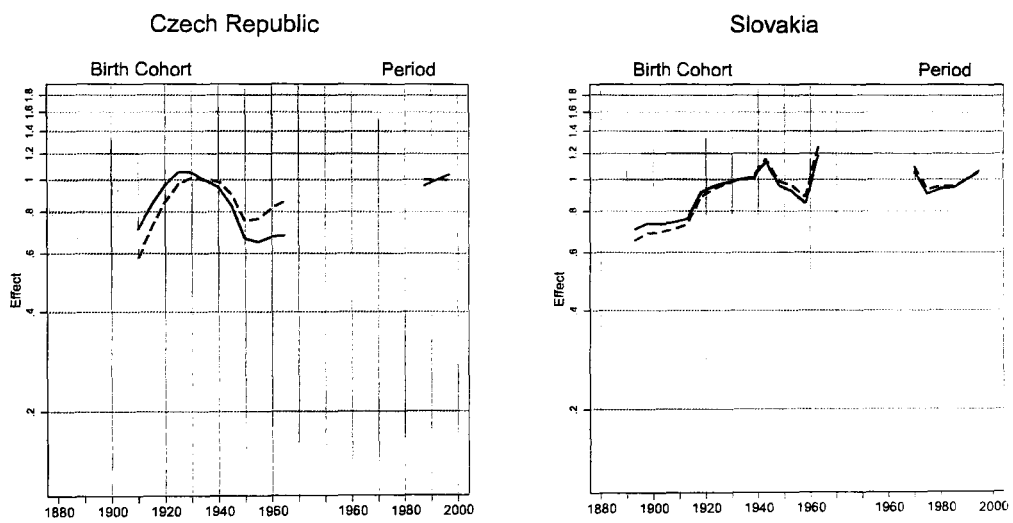
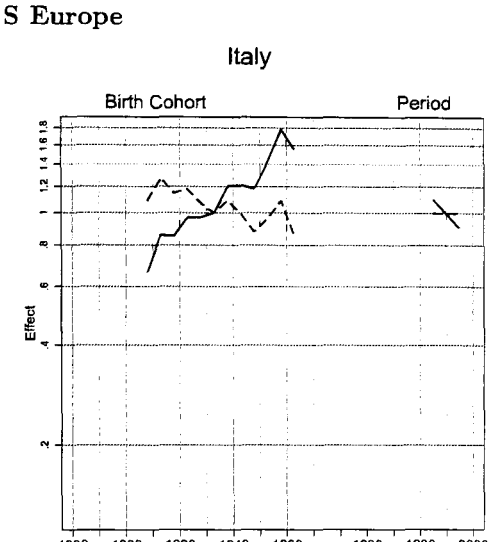
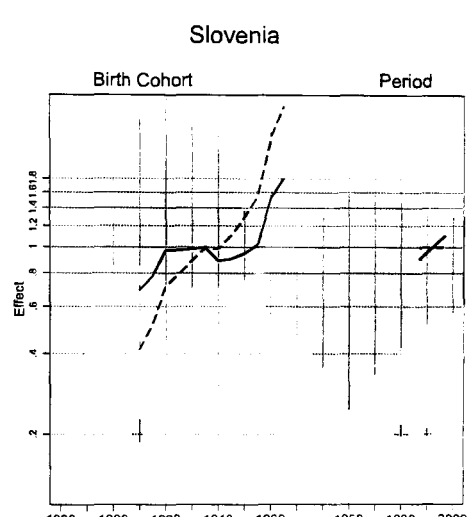


Figure 5.4 cont..

S Europe





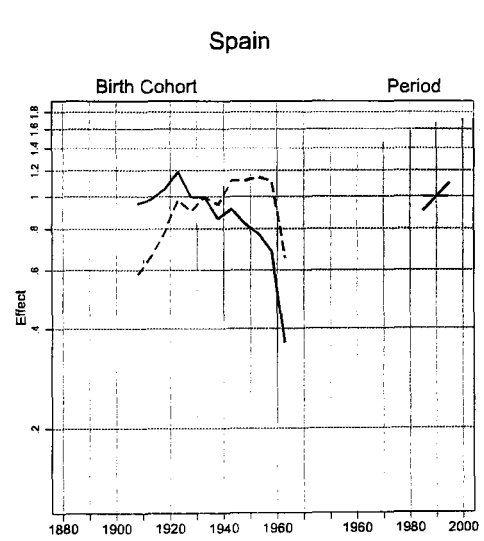
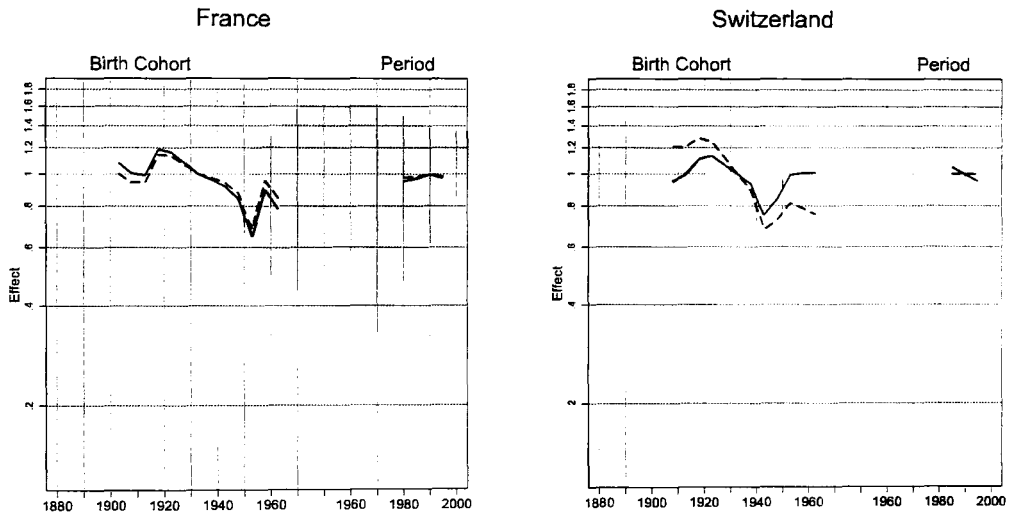


Figure 5.4 cont..

W Europe



5.5.3.1 Northern Europe

There were rather uniform increases in the incidence of endometrial cancer in women aged over 55 in Northern European countries except Denmark, and it is not clear from the observed data as to whether these upsurges may be apportioned more to generational or period influences (Figure 5.3). The full APC model was required in all six countries (Table 5.3). Steady increases in risk were most evident among women born successively from the late 19th century and diagnosed from the early-1960s onwards. An acceleration in risk among Swedish women over 55 was also observed, but later, namely in generations born after 1915. This phenomenon was also seen in the U.K, although the available cohort data do not go back further than 1910. Denmark is the exception in the region; decreasing rather than increasing trends were seen in women aged over 55 (Figure 5.4). Cohort effects seemingly dominated these trends, with successive declines in risk among generations of women born after 1925.

The upsurge in rates in older women contrasted with the more favourable trends seen in women aged under 55 in some of these countries, for which the consequence of generational changes were more evident (Figures 5.3 and 5.4). The modelled trends however implicate, depending on the assumptions specified, some importance of period effects, with increasing risk possibly more marked during the 1980s and 1990s in the long-term trends in Finland and Sweden (Figure 5.4). Downwards trends were discernible in younger women in Sweden, Finland and the U.K., with risk decreasing among successive cohorts born around 1925-35. In Norway, a cohort-led decline was suggested by the model effects, but not unequivocally; uniform period increases were strongly indicated in Figure 5.4, on assuming the proposed biological age curve. In Estonia, trends appeared relatively stable among recent cohorts.

When attention was restricted to women of perimenopausal age (45-54), continuously downward trends were observed in all Northern European countries except Estonia. The observation may relate specifically to a declining risk in consecutive generations of women born after 1920 (Figures 5.3 and 5.4). Finland is the exception; there was a suggestion that risk of endometrial cancer is increasing in women aged under 45 born after the Second World War (Figures 5.3 and 5.4).

5.5.3.2 Eastern Europe

Trends in the Czech Republic were difficult to interpret; there were increases in women aged 55 and over and declines in the 45-54 age groups, and these appear to follow a cohort pattern (Figures 5.3 and 5.4). Increasing risk is suggested among the youngest Czech women in the study, most notably among successive cohorts born since 1945 (Figure 5.4).

Uniformly increasing trends in incidence were observed in Slovakia, although it is not clear as to the specific importance of period or cohort-specific influences; non-linear effects of both types were significant (data not shown). One might consider period influences are more evident in view of the parallelism of the declining trends in women diagnosed during the 1970s followed by increases thereafter (Figure 5.3), an observation supported by the modelled trends (Figure 5.4).

5.5.3.3 Southern Europe

Trends in Slovenia were similar to those described in Slovakia with uniform increases in incidence rates of cancer of the corpus uteri in pre- and postmenopausal women by birth cohort and period of diagnosis (Figures 5.3 and 5.4). The trends in Spain and Italy were more difficult to interpret, although increases in endometrial cancer rates were evident in postmenopausal women in both countries, as well as in women aged 45-54 in Spain (Figure 5.4).

5.5.3.4 Western Europe

The trends in postmenopausal women in both France and Switzerland suggested the importance of cohort factors, with downward incidence trends seen in consecutive generations born after 1920 and before 1950 (Figure 5.3). These trends may be viewed as analogous to those observed in Denmark. The suggestion of increases in younger generations in France (Figure 5.4) cannot be confirmed or refuted, given the degree of randomness underlying these trends.

5.5.4 Discussion of main findings

This study has revealed the distinct patterns in the age-specific trends of cancer of the corpus uteri in Europe. A general profile emerged of increasing risk in postmenopausal women (aged over 55), and decreasing or stable trends in pre- and perimenopausal women (aged 30-54), particularly in Northern and Western countries. The most consistent declines in these regions were observed in women aged 45-54. In Southern and Eastern Europe, uniform increases in incidence were observed in several countries. In the majority of populations studied, both period and cohort effects seemed to influence the age-specific trends, particularly amongst women of menopausal age.

5.5.4.1 Methodological concerns

A number of methodological and data-related problems may have affected the results as reported in this analysis. Endometrial cancer is a rare event in younger women, and while recent trends may reveal short-term future patterns of risk, unfortunately these were

interpretable only in a few countries where sufficient numbers of cases were available. Additionally, the narrow span of period data for a number of countries (only three periods of incidence were available in five countries), made interpretation of the corresponding trends in these populations difficult.

The modelled component of the study involved an APC analysis, and two solutions were presented using simple constraints that were considered plausible given our understanding of the biology and epidemiology of the disease. The first set of age, period and cohort effects obtained attempted to preserve an element of biological plausibility. The identifiability problem was circumvented by fixing the underlying age structure assuming that endometrial cancer is a consequence of the physiological action of unopposed oestrogens that increase the cell proliferation, opposed by progestins which instigate differentiation to a secretory state [399,432].

An alternative solution involved the simple and commonly applied assumption that the overall period slope was zero [107], and the changing distribution and prevalence of the component causes were therefore presumed to show up mainly as generational influences in each country. Although the drift was attributable to birth cohort only, the formulation allowed non-linear period effects to be considered. The estimates presented in Figure 5.4 must however be interpreted with considerable caution, given an inherent inability to quantify the slopes for period and cohort. Nevertheless, the solutions obtained were based on two plausible assumptions: their joint examination together with the observed rates thus enabled an in-depth appraisal of the trends beyond the more arbitrary inferences available from an analysis restricted to the observed trends.

5.5.4.2 Determinants of trends by menopausal status

The trends provided clues as to the changing distribution of the primary risk factors, including use of exogenous oestrogens, reproductive factors, overweight and obesity, and smoking, and hence the potential for successful preventative strategies aimed at the population level in Europe. The text below builds on the discussion in the previous section, comparing the period and cohort trends with previous temporal studies and in light of the possible causes, according to menopausal status.

5.5.4.2.1 Trends in postmenopausal women

The rising trends in women aged 55 and over, as observed in many Northern and Western European countries, imply both period and birth cohort influences were in operation. Possible underlying mechanisms include temporal changes in reproductive behaviour and in the prevalence of overweight and obesity. Early age at menarche has been consistently

described as a risk factor for endometrial cancer [392]. During the last 150 years, age at menarche has declined at a rate of about 2-3 months per decade [433]. Completed family size has declined among female cohorts born during the twentieth century in most European countries [434]. The most substantial decreases occurred following the post-war "baby boom"; the peak in total fertility rates in the early to mid-1960s was followed by declines in successive generations born after the mid-1930s [435]. Nulliparity decreased in most European countries for cohorts born from 1930 to 1945 [435]. In England and Wales, where data are available for a longer period, the decline in nulliparity began for cohorts born since 1910 [152]. A recent study indicated that reproductive patterns may account for about half of the cases of endometrial cancer in Sweden in women diagnosed 1961-2002 [426], although the importance of reproductive behaviour on risk has been shown to decrease at older ages [419].

The use of HRT has been common in the Nordic countries and Western Europe, first during the 1960s containing oestrogens without the addition of progestins, and from the mid-1970s, as a succession of preparations combining oestrogens and progestins either sequentially, cyclically, or continuously [400]. Several studies confirmed a strong association between use of oestrogens without progestins and endometrial cancer risk [392], and a few studies also showed that the addition of progestins sequentially or cyclically to oestrogens increases risk too [436,437]. Risk increases with duration of HRT use and remains increased some years after cessation [400,438,439].

Part of the increase in risk of endometrial cancer among postmenopausal women may therefore be related to use of HRT in the European regions where use has been widespread [417]. This study reported uniform increases in endometrial cancer rates with time in Finland, Norway, Sweden and the U.K., and to a much lesser extent, in Estonia. In Finland and Norway, the cohort-specific increases began in women born towards the end of the nineteenth century. Exogenous oestrogens are an unlikely explanation for this trend as these women were aged over 65 when HRT was first introduced. Women born from 1910 onwards would have in theory the possibility of having being exposed to HRT. Indeed the main acceleration in risk among postmenopausal women in Sweden is seen after 1910 and coincides with the market introduction in the mid-1960s, and peak of sales in the mid-1970s [406]. The decline in sales of oestrogens without added progestins for treatment of menopausal symptoms thereafter [406] might imply a decline would be observed in more recent cohorts born thereafter. This has not been seen however, and in Sweden, as in Finland, Norway and the U.K, the postmenopausal increases suggest women born from at least 1920 up to 1945 were at consecutively increasing risk of endometrial cancer.

One possible explanation relates to the prevalence of overweight and obesity, which has been markedly increasing in some countries [440]. Obesity, in both in pre- and postmenopausal ages, is a strong risk factor for endometrial cancer [394]. Indeed, 34% of endometrial cancers have been attributed to obesity in the US during the period 1988-1994 and 40% in 1999-2000 [441]. Bergstrom and colleagues [395], from a meta analysis of papers published between 1966-97, also estimated that about 40% of cases were due to overweight and obesity in developed or industrialised countries. Endometrial cancer is also known to be more frequent among women suffering from diabetes mellitus [442-444], a condition closely associated with overweight, obesity and lack of physical exercise. The incidence of diabetes mellitus is increasing in Europe [445], as is the incidence of overweight and obesity [440]. Obesity-related factors probably explain at least part of the temporal pattern of endometrial cancer risk in postmenopausal women. This may be particularly the case in Southern and Eastern Europe, although fertility has also been declining in these countries [446]. Moreover, low levels of physical activity and high energy intake are increasingly commonly found in European populations and seem to increase risk for endometrial cancer independently of BMI [447,448].

Systematic declines of endometrial cancer incidence in Denmark were observed in women born since 1925, with no long-term increases in rates in postmenopausal women. This is at odds with other Northern European countries, and reverses the findings of a Danish study from the earlier period 1943-80 for which steady increases in all age groups was observed [404]. Comparisons of temporal data in Denmark with other Nordic countries regarding COC use and a late age at last birth reveal few dramatic differences, and therefore neither factor can be considered as providing a satisfactory explanation for the observation. The Danish trends do share some similarities however to those seen in France and Switzerland, for which endometrial cancer rates are also declining from around 1925. One conjecture is that smoking has impacted on the trends, given it is associated with a reduced risk of endometrial cancer, that is perhaps confined to postmenopausal women [396]. In both Denmark and France, trends in lung cancer mortality, a strong marker for previous tobacco consumption, have been uniformly increasing in successive cohorts born throughout the twentieth century up to 1950 [307]. Lung cancer mortality rates are highest in Denmark amongst the previous 15 Member State E.U., and shifted ranking from third in 1975 to first in 1995 [307].

5.5.4.2.2 Trends in premenopausal women

Systematic decreases in endometrial cancer incidence were observed in women aged 45-54 years resident in most Northern European countries, as well as in the Czech Republic,

France and Italy, with successively declining risk most evident in women born between 1930 and 1945. COC have a well-established protective effect [392,438], even after short durations of use of 1-3 years [399]. They have become increasingly available in Europe from the 1960s onwards, and women born after about 1925 have had the opportunity to use them. The trends in premenopausal women were however heterogeneous; in Denmark, Sweden and the U.K., for instance, there were rapid declines in risk in women aged under 45. These translate to a successively decreasing risk in women born around 1925, as has been reported in Sweden [406], through to the most recent cohorts born in the 1950s and 1960s.

A high exposure to COC was particularly common among cohorts born after 1950. In England and Wales, the proportion of "ever users" of hormonal contraceptives was about 40% for women born in the 1930s [449] compared with approximately 70% in birth cohorts of 1940s and 80-90% for those born in the 1950s [152]. In other European countries, the prevalence of use of COC has varied, tending to be relatively high in Northern and Western Europe, and low in much of Southern and Eastern Europe, at least before the 1980s [417].

The use of hormonal contraceptives may, at least in part, be responsible for the decreases in incidence in several countries. Steadily increasing incidence rates of endometrial cancer in the Czech Republic and Slovakia in Eastern Europe, as well as in Slovenia and Spain in Southern Europe, have been observed both in younger and older women. An explanation for the endometrial cancer trends in premenopausal ages may be that women in these regions have failed to benefit from the protective effects of COC due to their unavailability, or otherwise. Fertility has also been on the decline, although more slowly than seen elsewhere in Europe [446].

The declines seen in Sweden were not evident among premenopausal women in Finland and Norway. Further, there was some indication that there were increasing trends in young women in Finland, and possibly elsewhere (e.g. France). It is difficult to explain such a trend, should it be genuine. It is too early to conclude whether the observed incidence pattern might project itself into the future, given the underlying random variation arising from small numbers.

We are not aware of major changes in routine diagnostics for endometrial cancer in Europe that may have impacted on the results presented. New cases of uterine cancer with subsite unspecified represent a small proportion of all uterine cancers in each of the populations studied, and over time [18,160-162]. Other than the changing population prevalence of hysterectomy (discussed in 5.6.2.2), one artefact that may have impacted on trends is HRT use in countries where its consumption is common. Women who are users of menopausal

hormones are likely to be more intensively investigated, and early precancerous or cancerous lesions more readily detected and reported to the cancer registries as cancers.

5.6 General discussion

5.6.1 Brief summary of main findings

Study I showed that incidence and mortality rates of endometrial cancer in premenopausal women have been decreasing throughout Europe, with mortality declines more marked in Western and Southern European countries. Incidence rates among postmenopausal women were highest in the Czech Republic, Slovakia, Sweden and Slovenia, and lowest in France and the U.K. Increasing incidence trends in this age group were observed in the Nordic countries (except Denmark) and in the U.K. Some increases were also seen in Eastern (Slovakia) and Southern Europe (Spain and Slovenia), while relatively stable or modestly decreasing trends were observed in Italy and most Western European countries.

Postmenopausal mortality rates were systematically higher in Eastern Europe, with death rates in the Ukraine, Latvia, Czech Republic, Russia, and Belarus two to three times those seen in Western Europe. Declining mortality trends were seen in most populations, although in certain Eastern European countries, the declines began rather recently, during the 1980s. In Belarus and Russia, recent postmenopausal death rates were stable or increasing. An exception in Northern Europe was Sweden, where a non-significant increase was observed.

Study II involved an APC analysis of 13 countries, and reported that there were increasing trends among postmenopausal women in many Northern and Western countries. Denmark (and possibly France and Switzerland) were exceptions, with decreasing trends in postmenopausal women. In pre- and perimenopausal women, declines were observed in Northern and Western Europe, most evidently in Denmark, Sweden and the U.K., affecting consecutive generations born after 1925. These contrast with the increasing trends regardless of menopausal age in some Southern and Eastern European countries, particularly Slovakia and Slovenia.

These observations in combination provided evidence of changes in several established risk factors over time, which in turn have implications for possible primary prevention strategies. In postmenopausal women, changes in reproductive behaviour and prevalence of overweight and obesity may partially account for the observed increases, as well as HRT use in certain countries. Combined oral contraceptive use may be responsible for the declines observed among women aged under 55. While there are some prospects for chemoprevention in premenopausal women as oral contraceptive use becomes more widespread in Europe, increases in obesity, and decreases in fertility, imply that endometrial

cancer in postmenopausal women will become a more substantial public health problem in the future.

An interesting observation was the low rates of endometrial cancer incidence (and mortality) among both pre- and postmenopausal women diagnosed 1997-99 in the U.K. relative to other European countries studied. This in part may be due to artefact, in particular as a result of the failure to adjust for the relatively high rates of hysterectomy recorded in the population. If the mean hysterectomy prevalence percentages for 1996-2000 in England and Wales – estimated at approximately 20% in each of the 5-year categories the age group 50-74 [450] – were applied to the rates in Figure 5.1, the rates would be substantially larger, particularly among postmenopausal women. Hysterectomy-adjusted rates may have ranked higher in in the U.K. than in low-risk counties where the procedure has been less commonly practiced. One cannot exclude the possibility of underascertainment, although it seems unlikely that a shortfall related to diagnostic artefacts has sizably contributed to the low rates. One may speculate that a lower average number of routine visits to gynaecologists by U.K. residents, relative to other European countries, may have resulted in a lower detection of cases, and contributed consequently to a lower recorded rate.

Those established protective factors against endometrial cancer that reasonably correlate with the observed trends in the U.K. may have played a role. Foremost is the introduction and increasing use of oral contraceptives, possibly affecting rates of endometrial cancer in successive birth cohorts from the 1920s. COC have been shown to a long-lasting protective effect (at least 15 years) [391], and an 80% reduction in endometrial cancer has been observed following 10 years of use [399]. Their long-term consumption among U.K. women has likely had a beneficial impact on rates in both pre- and postmenopausal age groups.

5.6.2 Reconsideration of methods and further exploration

5.6.2.1 Limits to joinpoint regression

Owing to potential systematic errors in the data, excessive random variation, and particular nuances within the regression method, some of the EAPC may not be representative of the underlying endometrial cancer trends, and should be interpreted with suitable caution. An attempt was made to address this by reproducing in tabular form only those estimates that were considered to adequately represent the recent underlying trends.

5.6.2.2 Adjusting for hysterectomy rates

Recent evidence from Finland suggests that adjustment for hysterectomy affects the magnitude and direction of trends in endometrial cancer [130]. In this analysis, the effects of hysterectomy were not taken into account due to a lack of corresponding data in each

country for the requisite periods and ages. The varying prevalence of hysterectomies may have impacted on the trends however: the incidence of hysterectomy has been increasing in Finland [130], Denmark [369] and England and Wales [23], and the unadjusted trends presented in this chapter may have underestimated the overall time trend. As noted by Ewertz and Jensen [404], the assumption of a decline after the menopause used here to present one set of age, period and cohort trends may be artificially distorted by a declining number of "susceptibles" – women who have not had a hysterectomy. The trends may have been more accentuated in certain countries had the rising prevalence of hysterectomy in these populations (particularly in recent years) been taken into account.

5.6.2.3 Further studies

The more in-depth APC analysis of study II gave further insight into the nature of the trends obtained from a stratified description of the linear trends amongst two broad age groups in study I. In providing a unique solution, the constraint that fixed the age curve, although simplistic, did retain some degree of biological plausibility. Further work would establish better proposals for assuming a particular age curve, possibly along the lines of research by Pike that could also be applied to trends in cancer of the female breast and ovary, as well as to the endometrium [220]. The defining epidemiological characteristic of these cancers appears to be a rapid deceleration in the rate of increase with age around the time of menopause.

Both studies in this chapter are necessarily speculative with regards the factors that drive the trends, and other approaches may provide further insight. The difficulties addressing which of the main aetiological factors drive the trends in European populations, particularly in postmenopausal women, might be complemented by further study of concomitant trends in the population prevalence and distribution of obesity, HRT use, smoking and COC use.

5.6.3 Future prospects for prevention

Given the current aetiological and temporal profile of endometrial cancer, it is unlikely that rates of endometrial cancer will be decreasing among postmenopausal women in most European countries in the near future. The prevalence of obesity is increasing [424], while fertility rates are decreasing [446]. Trends in parity (or nulliparity) and age at last delivery, probably responsible for about half of the endometrial cancer cases in Europe, are not realistic targets for prevention. Avoiding use of postmenopausal hormones, or at least those drugs that clearly induce endometrial proliferation as oestrogens, would probably decrease endometrial cancer trends where use is widespread, such as in the Nordic countries and a

few Western European countries (e.g. the U.K. and Germany). The use of exogenous oestrogens has been rather limited in most Southern and Eastern European countries.

The evidence for an elevated risk of endometrial cancer due to obesity is beyond doubt [394], and the obesity epidemic observed in Europe in the recent decades [394,424] may have contributed to increases in endometrial cancer incidence among postmenopausal women [392]. Thus, preventing obesity through weight control would probably have a substantial impact on endometrial cancer incidence trends over time, besides having other positive health impacts, such as prevention of other conditions also associated with endometrial cancer such as diabetes mellitus, hypertension, gallbladder disease, and most importantly cardio-vascular diseases.

Reducing mortality rates, other than via a reduction in incidence, is not a simple task, particularly in countries where health systems face a shortage of resources, as in some Eastern European countries, where endometrial cancer mortality rates are systematically higher than in other regions. Improvements in the quality of, and access to, diagnostic and therapeutic services, as well as the implementation of strategies aimed at alerting women that vaginal bleeding after menopause is abnormal, may reduce such disparities in the mortality rates.

Uniform increases were observed in rates of endometrial cancer incidence amongst the main risk group, postmenopausal women in most European countries studied, with Denmark being an important exception. Both calendar period and birth cohort effects appear to be in operation. The reasons for the increases in countries as diverse as Sweden and Slovakia may include a Europe-wide shift towards declining fertility rates and marked increases in overweight and obesity, although only in Sweden and several other affluent countries can the effects of HRT be responsible for the rising trends. In pre- and perimenopausal women, rates are declining in Sweden, Denmark and the U.K., mostly evidently in successive cohorts born since 1930.

The downward trends in young women are presumably the result of increasing use of COC in these countries, since they became available mainly to cohorts born in the mid-1920s and thereafter. In a number of Southern and Eastern countries (notably Slovakia), trends are increasing regardless of menopausal age, countries for which the lack of availability of COC has offered little protection in these younger women. Prevention of endometrial cancer will possibly be realised in these areas as COC use becomes increasingly widespread. The continuing increases in obesity and decreases in fertility however forewarns that endometrial cancer, as a postmenopausal disease, will become a more important public health problem in Europe in future years.

6 Analyses of temporal trends in testicular cancer in Europe

6.1 Introduction to the chapter

This chapter has two main objectives. The first involves a broad description of the time trends of testicular germ cell cancer incidence and testicular cancer mortality in European countries. From previous research on testicular cancer, generational and period-related influences are expected to play a major role in the respective trends of incidence and mortality. Of particular interest is the variability in cohort-specific patterns between countries, and whether there is evidence that trends in any of the study populations have reached a peak, or are in decline.

The second aim is to compare the heterogeneity of generation-specific trends in the two major subtypes of testicular germ cell cancer, seminoma and non-seminoma, hypothesising that similar temporal patterns in the cohort dimension suggests a relative consistency in their respective aetiologies. As in the previous chapters, analyses involving the APC model and Holford's method of 3.4.2 are used to accomplish the objectives.

6.1.1 Why analyse trends in testicular germ cell cancer incidence?

Attention was first drawn to increases in testicular cancer incidence in England and Wales [451] and Denmark [452] half a century ago; yet the aetiology of the disease remains largely unexplained, in spite of having a very distinct epidemiology. Incidence trends in almost all European populations are characterised by rapid increases in rates of between 3% and 6% per annum in the last few decades [8,229,453-455], particularly in adolescent men and young adults [456]. The large variation in testicular cancer incidence across and within European countries in each population over time could point to one or several ubiquitous and highly prevalent environmental agents being responsible. Moreover, the factor(s) involved must vary in prevalence between populations, and within populations, over time.

6.1.2 Why analyse trends in testicular cancer mortality?

Irrespective of the increasing incidence, declining rates of mortality of the same order of magnitude have been observed in many of the more affluent countries of Europe, largely as a result of the introduction of Cisplatin therapy for advanced germ cell tumours in the 1970s, and the substantial progress in prognosis in younger patients [457]. The relative decline in death rates of testicular cancer is expected to reflect the extent of their introduction, and the evolution of cancer care practices within each country.

6.1.3 Why analyse trends in testicular seminoma and non-seminoma?

The division of testicular germ cell cancer to seminoma and non-seminoma emerged mainly from the clinically distinct treatment options available for treatment of the respective subtypes. Pike *et al* on reviewing testicular cancer incidence and mortality noted the value of the potential subdivision of germ cell cancer into the "epidemiologically interesting" entities of seminoma and non-seminoma (teratoma), provided the age range was restricted to between 15 and 50 [186]. Both subtypes are preceded by testicular carcinoma in situ [458], and comparisons of their epidemiological profile would indicate that they share largely the same underlying causes. Despite well-documented differences in the peak age of incidence – non-seminoma occurs approximately a decade earlier in life than seminoma [186] – most studies have revealed little variation in risk factors between the two sub-types. In line with overall testicular germ cell cancer incidence rates, trends in pure seminoma and non-seminoma are increasing with calendar time in many European countries.

6.1.4 Review of testicular cancer epidemiology

6.1.4.1 Descriptive epidemiology

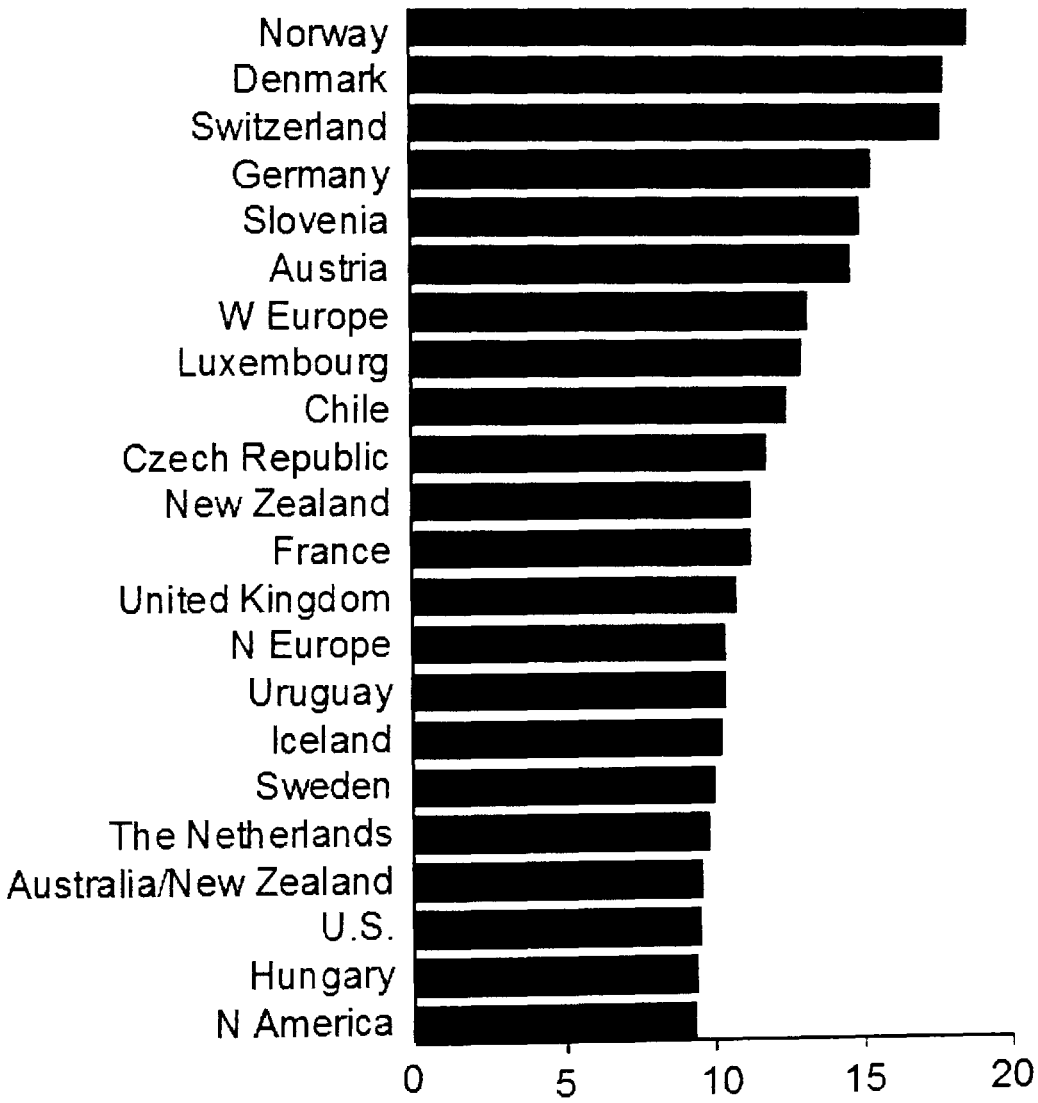
Descriptive epidemiology has revealed considerable geographical, ethnic and temporal variations in incidence: at least a 30-fold variation in risk worldwide, rates ranging from 0.3 in Beijing, China to 12.5 in Zurich, Switzerland [18], with men of European origin in the U.S. having rates five times higher than their African origin counterparts [459]. Nearly 50,000 new cases of testicular cancer were diagnosed worldwide in 2002 [263]. The disease affects mainly Western populations, with rates about six times higher in developed areas relative to developing areas. Figure 6.1 indicates that among the highest incidence rates worldwide are those recorded in countries in Northern (Denmark, Norway) and Western Europe (Germany, Switzerland). Testicular cancer accounts for 1% to 3% of all male cancers in Europe, but is the most common malignancy among young adult men aged 15-34 in most countries in the region [18].

6.1.4.2 Aetiology

It has been hypothesised that the risk of testicular cancer is to a large extent determined very early in life, perhaps in-utero [460]. Several perinatal factors, including low birth weight [461-464], older maternal age [461,465], prematurity [462,463,465,466], low birth order [229,461,463-465,467] have been associated with an increased risk of testicular cancer, although the evidence is not entirely consistent across studies. Testicular cancer is however consistently associated with cryptorchidism, the most common congenital malformation of the male genital organs [468]. Results for perinatal risk factors have been often interpreted

in the light of the so-called oestrogen hypothesis which postulates a carcinogenic effect due to an excess of sex hormones at the time of testicular differentiation [469]. Maternal life-styles during pregnancy could also affect testicular cancer risk. Ecologic studies have identified maternal smoking as a possible risk factor [466], although this hypothesis has not found support from analytical studies [470,471].

Figure 6.1: Truncated (15-54) age-standardised testicular cancer incidence rates (World) in countries/regions with the highest rates globally, rates presented in descending order of magnitude.



6.1.4.2.1 Differences in main histological subtypes

Several risk factors associated with prenatal and perinatal exposures have been suggested for testicular cancer [461,463-466,472-475], although asides from cryptorchidism, few risk determinants are well-established. These in combination with other putative causal factors, such as low birth weight and low maternal parity, can only account for a small fraction of the total incidence. Numerous studies have examined aetiological differences in the two main clinical sub-entities of testicular germ cell cancer [186,229,461,463,476-479], most have

however revealed little variation in risk factors between the two sub-types and, where particular associations have been found, they have been inconsistent across studies.

6.2 Review of temporal studies of testicular cancer in Europe

6.2.1 Testicular germ cell cancer incidence

As the aetiology of testicular cancer is not well understood, the underlying reasons for the consistent increase in incidence of between 3% to 5% per annum throughout Europe remain largely unknown. Improving ascertainment and better diagnostic procedures cannot account for the extent of the increase given the course of the disease is rapidly fatal if left untreated. In addition, the evidence derives mainly from a number of well-established European cancer registries with standardised procedures [454].

6.2.2 Testicular germ cell seminoma vs. non-seminoma

The rising incidence of both seminoma and non-seminoma is unlikely to be explained by changes in disease classification or diagnostic activities [291,480]. The majority of temporal studies have reported rapid increases but similar trends between subtypes when examined by birth cohort [229,251,291,292,460,481]. Exceptions are a recent Canadian study that reported some heterogeneity in patterns of cohort-specific risk [292], while a U.S. study based on SEER data suggested some important temporal differences by subtype and within subtype by race [291].

6.2.3 Testicular cancer mortality

In contrast to incidence, testicular cancer mortality has been markedly declining in a number of European countries since the mid-1970s, due to the introduction of platinum-based chemotherapy schemes [457] and best-practice tumour management [482]. Echoing these improvements, the pooled five-year relative survival estimate among European patients diagnosed in the early-1990s was over 90%, although striking differences across Europe were observed, with five-year survival as low as 71% in Estonia [138,483]. The reductions in mortality have thus not been uniform between countries, with slower and later declines seen in lower resource settings [484], in accordance with the high cost of appropriate treatments, and possibly inadequate patient referral systems [485].

6.3 Study I: APC trends in testicular cancer incidence and mortality

6.3.1 Data sources and data quality

6.3.1.1 Incidence

Incident cases of testicular germ cell cancer (ICD-O-2 9060-9102) were extracted from EUROCIM [160] for men aged 15-54 (see 2.8 for details and standard inclusion criteria).

Due to computation difficulties in dealing with small numbers, Estonia was not included in these analyses. Table 6.1 provides details of the cancer registries included in the analysis of incidence trends. The testicle is a visible and palpable organ, and so the origin of the tumour is usually evident, notably among young and middle-aged men. Hence, misclassification or underascertainment of registration should be minor issues relative to many other malignancies. A version of this section is *in press* in a peer-reviewed journal [486].

6.3.1.2 Mortality

Testicular cancer mortality data (ICD-9 186) was extracted from the WHO mortality databank for men aged 15-54 (see 2.7.2 for details and standard inclusion criteria). Datasets spanned at least 15 years and trends in mortality prior to 1968 were excluded in order to focus on how the effects of improving treatment, starting 5-10 years later, subsequently impacted on the observed trends (see 6.3.2.1.2). Table 6.2 provides information on the national data from 22 countries that met the criteria: the time-span varied from three to seven five-year periods. Due to small numbers, Luxembourg, Malta and Slovenia were not included in the subsequent analyses.

6.3.2 Methods: fitting the APC model

Birth cohorts were obtained on subtracting the midpoints of five-year age groups (15-19, 20-24,..., 50-54) from the corresponding five-year periods. The effects of time period and birth cohort were examined using the full APC model of {3.6} as described in 3.3.3. Tests for goodness-of-fit of the APC models, as well as the overall slope and non-linear effects of period and cohort were obtained using the approach of Clayton and Schifflers [63,68] (see 3.4.1.1.3). The net drift was used to quantify the overall direction and magnitude of the time trend in each country.

6.3.2.1 Obtaining identifiable period and cohort parameters

As in the previous chapters, the non-identifiability problem was highlighted by partitioning the age, period and cohort effects in terms of their linear and curvature component parts, according to the method of Holford [66,110]. To identify plausible period and cohort effects, different specifications of the range of the period and cohort slopes were postulated, as described in general terms in 3.4.2, and outlined below for the specific study of testicular incidence and mortality trends, respectively.

6.3.2.1.1 Assumptions on incidence slopes

For incidence, the possibility of period-specific increases was respected, thus an allowance was made for gradual increases that would result from improving diagnostic procedures or

ascertainment with time. The substantial contribution of cohort influences in explaining testicular cancer incidence trends in Europe has been consistently demonstrated in previous reports [8,455,487,488], likely due to the changing prevalence and distribution of (largely unknown) factors that impact on the rates in successive generations. Thus it was assumed *a priori* that the overall linear slopes of period and birth cohort were positive, and specified scenarios for which the cohort component accounted for i) all of the regular trend; ii) half of the regular trend. The possible values of the cohort slopes γ_L were thus bounded so that $\frac{\beta_L + \gamma_L}{2} \leq \gamma_L \leq \beta_L + \gamma_L$, leaving the period slopes β_L to range from zero and half of Holford's drift defining the corresponding linear slopes as $0 \leq \beta_L \leq \frac{\beta_L + \gamma_L}{2}$. Age parameters were similarly bound between two estimable functions.

6.3.2.1.2 Assumptions on slopes for mortality

For mortality, two specifications of the period slope were postulated that mirror those for incidence. The first scenario attempted to capture the period-related decline in testicular cancer mortality due to the introduction of effective therapy and care starting, in some populations, in the early to mid-1970s, initially in high-resource European countries. The second specification took into account that the regular mortality trend related to the underlying incidence (and its generational influences), as well as to case-fatality. On the basis of these requirements, two sets of parameter estimates were presented that constrained the period component β_L to take either i) all of the regular trend, or ii) half of the regular trend. The boundary values of the period slopes were $\frac{\beta_L + \gamma_L}{2} \leq \beta_L \leq \beta_L + \gamma_L$, and accordingly, the range of linear slopes for cohort γ_L were $0 \leq \gamma_L \leq \frac{\beta_L + \gamma_L}{2}$. Each postulation of the period slope provided an identifiable range of the age and cohort slopes.

In 6.3.1.1 and 6.3.1.2, the effects for the individual categories of each effect were generated by adding together the linear and curvature components. For example, the effect for age group a can be expressed as $\alpha_a = (a-(A+1)/2)\times\alpha_L + \varphi_a$, with φ_a representing the departures from the linear trend, and β_L and γ_L, the period and cohort slopes, defined as before [110].

6.3.3 Results: description of trends

6.3.3.1 Incidence

There was a five-fold variation in incidence in the 12 European countries in this study (Table 6.1), with rates ranging from around 5 per 100,000 in Spain, Finland and Italy to more than 15 per 100,000 in Denmark and Switzerland. Increases in incidence during the period 1983-97 were observed in all countries studied. The extent of the increase varied considerably, although no clear relation between the level of incidence and the magnitude of the recent trend was apparent (Figure 6.2). The average increases per annum varied at least six-fold (Table 6.1), with the most rapid inclines in Spain and Slovenia, estimated to be almost 6% per year on average, compared to overall increases of 1 to 2% per annum in Norway, Switzerland, Italy, France and Denmark. There was a suggestion of a recent peak in several countries, most evidently in Switzerland and Norway, during the 1990s (Figure 6.2).

The full APC model or a submodel explained a sufficient amount of variation in each population (Table 6.1). Cohort effects dominated in the majority, with cohort curvature significantly improving the fit in 10 of the 12 countries studied, with Italy and Slovenia being the exceptions (Table 6.3). The age-cohort model adequately explained the variation in seven countries. Only in three countries (Finland, Norway and Slovakia) did non-linear period effects significantly improve the fit.

Figure 6.3 shows the corresponding period and cohort risk parameters. It is evident that even when half of the regular trend is attributed to period of diagnosis, successive generational increases in risk can be seen in almost all European countries. The rises were fairly uniform and rapid with successive generations in Finland and the U.K, and in the Czech Republic and Slovakia.

There was some evidence of a short-term dip in cohort-specific risk (regardless of the attribution of drift) in most European countries, affecting men born around 1940-45 in Denmark, Norway and possibly Sweden, and also in France, Italy, Slovenia and Spain, although the data are based on fewer years of observation for these countries. Rapid acceleration in risk followed thereafter (Figure 6.3). There was also a suggestion that successive generations of Swiss men, born after the early to mid-1960s, had experienced a steadily declining risk of testicular germ cell cancer.

Table 6.1: Testicular germ cell cancer incidence: populations included in the trends analysis, regular trend, and goodness-of-fit statistics for best-fitting APC model by European area

European Area	Country	Period available (# of five-year periods)	Incident cases*	Person-years†	ASR‡	Rank§	Overall trend¶	95% CI	APC model**	Residual deviance††	d.f.††	p-value††
Northern	Denmark	1979-1998 (4)	262	7.7	16.6	1	+1.7	(1.2 to 2.3)	AC	10.1	14	0.76
	Finland	1955-1999 (9)	72	7.4	5.0	11	+4.4	(3.9 to 4.9)	APC	30.7	42	0.90
	Norway	1953-1997 (9)	155	6.3	11.9	3	+2.3	(2.0 to 2.6)	APC	41.7	42	0.48
	Sweden	1964-1998 (7)	206	12.1	8.4	9	+2.9	(2.6 to 3.2)	AC	33.7	35	0.53
	United Kingdom[a]	1978-1997 (4)	1359	75.4	8.6	7	+2.8	(2.5 to 3.0)	AC	15.0	14	0.38
Eastern	Czech Republic	1985-1999 (3)	327	15.4	10.8	5	+4.0	(3.1 to 4.9)	AC	7.3	7	0.40
	Slovakia	1968-1997 (6)	138	7.8	8.6	8	+6.8	(6.1 to 7.6)	APC	28.0	24	0.26
Southern	Italy[b]	1983-1997 (3)	77	6.4	5.8	10	+1.2	(-0.5 to 3.0)	A	16.1	16	0.45
	Slovenia	1985-1999 (3)	68	2.9	11.3	4	+7.3	(5.0 to 9.8)	AD	15.4	15	0.42
	Spain[c]	1983-1997 (3)	31	4.6	3.1	12	+7.7	(4.2 to 11.7)	AC	11.1	7	0.13
Western	France[d]	1978-1997 (4)	103	5.8	8.6	6	+2.6	(1.6 to 3.6)	AC	6.4	14	0.96
	Switzerland[e]	1983-1997 (3)	140	4.2	15.9	2	+1.2	(0.1 to 2.4)	AC	3.1	7	0.88

* mean annual number of incidence cases in most recent five-year period in age group 15-54
† mean annual male population in most recent five-year period in age group 15-54, expressed in million person-years at risk
‡ truncated (ages 15-54) age standardised rate in most recent five-year period (using European standard)
§ ranked in descending order of ASR
¶ EAPC e.g. the net drift parameter from the Age+Drift model
** refers to the most parsimonious final model providing a good fit: A: Age; AD: Age+Drift; AC: Age+Drift+Cohort; AP: Age+Drift+Period; APC: Age+Drift+Period+Cohort
†† to determine the goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom (d.f.) determined by the model. A p-value of <0.05 denotes the full APC model does not yield an adequate fit
a aggregation of England, Scotland
b aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin
c aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza
d aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn
e aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich

Table 6.2: Testicular cancer mortality: populations included in the trends analysis, regular trend and goodness-of-fit statistics for best-fitting APC model by European area

European Area	Country	Period available (# of five-year periods)	Deaths*	Person-years†	ASR‡	Rank§	Overall trend¶	95% CI	APC model**	Residual deviance††	d.f.††	p-value††
Northern	Denmark	1969-1998 (6)	13	7.7	0.8	5	-4.5	(-5.0 to -4.0)	APC	31.4	30	0.40
	Finland	1970-1999 (6)	5	7.4	0.8	12	-2.2	(-3.3 to -1.0)	AP	39.2	42	0.59
	Ireland	1969-1998 (6)	4	5.2	0.8	22	-2.6	(-3.7 to -1.4)	AP	31.1	42	0.89
	Norway	1969-1998 (6)	6	6.3	0.6	20	-5.4	(-6.1 to -4.7)	AP	47.8	42	0.25
	Sweden	1969-1998 (6)	7	12.1	0.5	17	-4.7	(-5.4 to -4.0)	AP	40.1	42	0.55
	United Kingdom	1970-1999 (6)	68	82.5	0.5	19	-5.0	(-5.3 to -4.8)	APC	29.7	24	0.19
Eastern	Bulgaria	1970-1999 (6)	34	11.6	1.4	1	+1.0	(0.3 to 1.8)	AP	35.5	35	0.45
	Czech Republic	1986-2000 (3)	39	15.4	1.3	2	-3.0	(-4.5 to -1.4)	AC	8.7	7	0.27
	Hungary	1971-2000 (6)	34	14.5	1.2	3	-1.0	(-1.5 to -0.4)	AC	18.2	28	0.92
	Poland	1980-1994 (3)	114	53.4	1.0	4	-1.5	(-2.5 to -0.4)	AD	24.4	15	0.06
	Romania	1981-2000 (4)	48	32.5	0.9	6	-0.1	(-1.2 to 1.0)	A	29.7	24	0.19
Southern	Croatia	1986-2000 (3)	11	6.3	0.5	21	4.4	(-0.3 to 10.0)	A	13.0	16	0.68
	Greece	1969-1998 (6)	9	14.7	0.4	7	-2.5	(-3.6 to -1.4)	AC	33.2	28	0.23
	Italy	1969-1998 (6)	46	81.2	0.4	8	-4.0	(-4.3 to -3.7)	AP	55.2	42	0.08
	Portugal	1980-1999 (4)	11	14.0	0.4	9	+2.0	(-0.7 to 5.1)	AC	22.7	14	0.06
	Spain	1974-1998 (5)	29	57.2	0.4	11	-1.7	(-2.6 to -0.7)	AD	42.0	31	0.09
Western	Austria	1971-2000 (6)	12	11.6	0.4	15	-4.0	(-4.6 to -3.5)	APC	29.8	30	0.48
	Belgium	1971-1995 (5)	7	14.1	0.3	10	-3.3	(-4.3 to -2.2)	AD	43.5	39	0.28
	France	1969-1998 (6)	78	82.0	0.3	13	-2.7	(-2.9 to -2.4)	AP	45.1	42	0.34
	Germany	1985-1999 (3)	148	115.8	0.3	14	-6.2	(-6.8 to -5.6)	APC	108.3	6	<0.01
	The Netherlands	1970-1999 (6)	22	23.3	0.3	18	-5.1	(-5.5 to -4.6)	APC	32.1	30	0.36
	Switzerland	1970-1994 (5)	17	10.0	0.2	16	-3.3	(-4.0 to -2.7)	AP	43.0	35	0.17

* mean annual number of deaths in most recent five-year period in age group 15-54
† mean annual male population in most recent five-year period in age group 15-54, expressed in million person-years at risk
‡ truncated (ages 15-54) age standardised rate in most recent five-year period (using European standard)
§ ranked in descending order of ASR
¶ EAPC e.g. the net drift parameter from the Age+Drift model
** refers to the most parsimonious final model providing a good fit: A: Age; AD: Age+Drift; AC: Age+Drift+Cohort; AP: Age+Drift+Period; APC: Age+Drift+Period+Cohort
†† to determine the goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom (d.f.) determined by the model. A p-value of <0.05 denotes the full APC model does not yield an adequate fi

Figure 6.2: Trends in truncated (15-54) age-standardised incidence and mortality rates (Europe) for selected countries. Rates are based on five-year aggregates and correspond to the period available

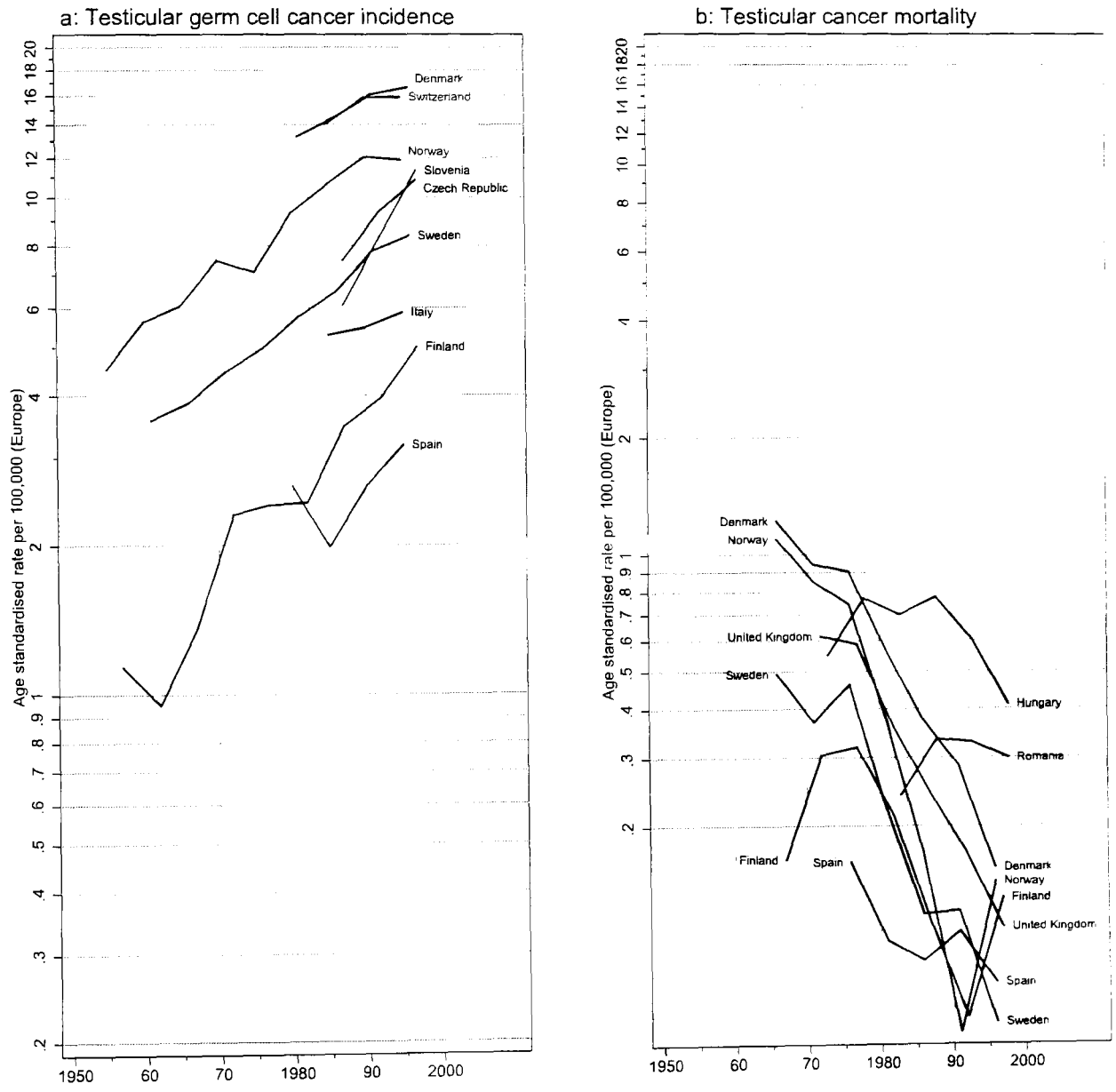


Figure 6.3: Age period cohort parameters based on assumptions on period and cohort slopes: incidence trends by country within European area (Panels 1-2: E Europe; 2-7: N Europe; 8-10: S Europe; 11-12: W Europe). Solid line: assumption of zero period slope (drift taken up entirely by cohort); dashed line: assumption of positive equal slopes for period and cohort (drift attributed equally to period and cohort)

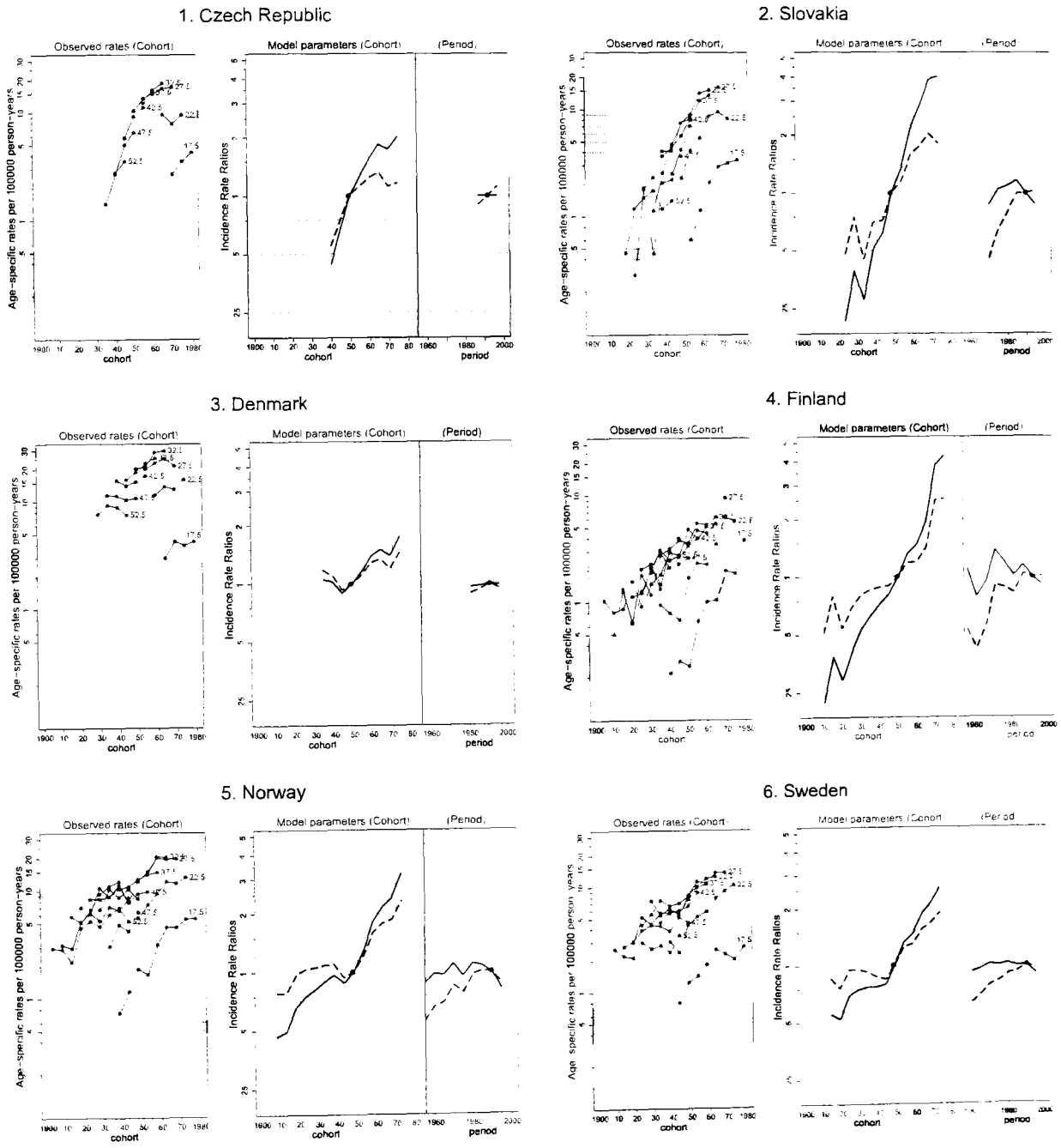
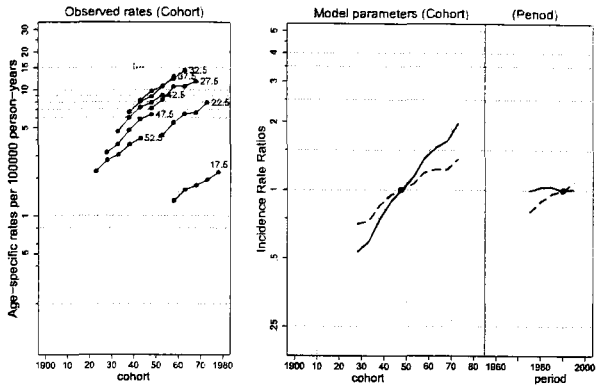
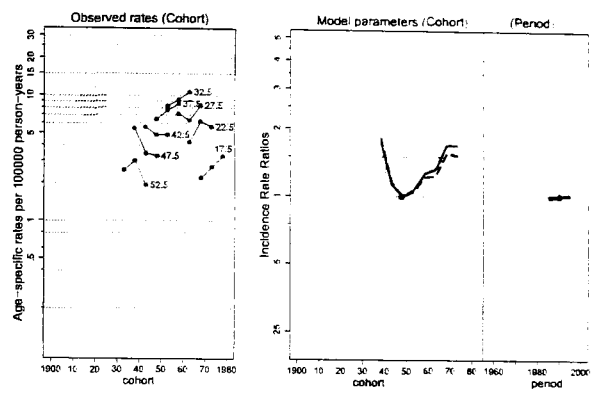


Figure 6.3 cont..

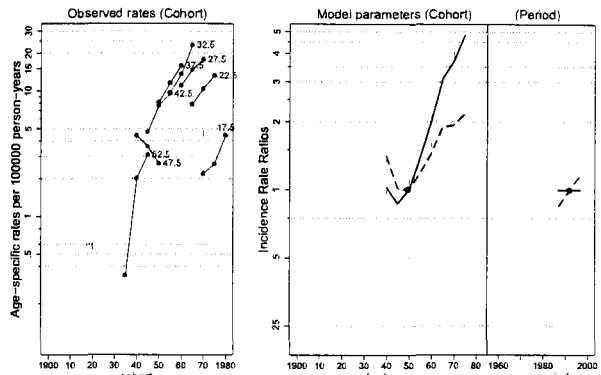
7. United Kingdom



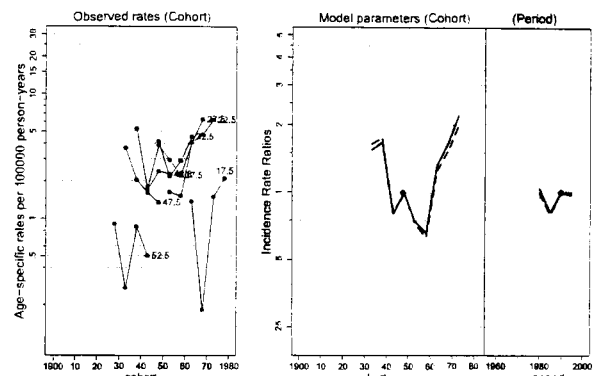
8. Italy



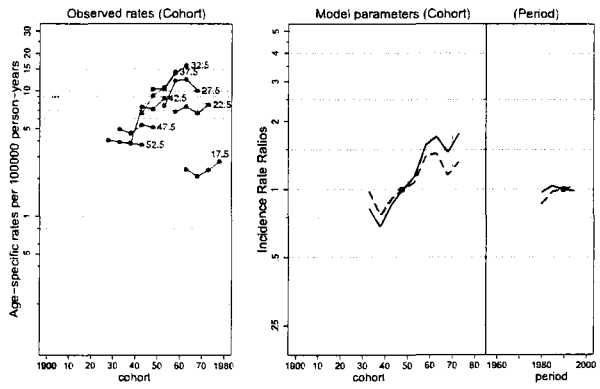
9. Slovenia



10. Spain



11. France



12. Switzerland

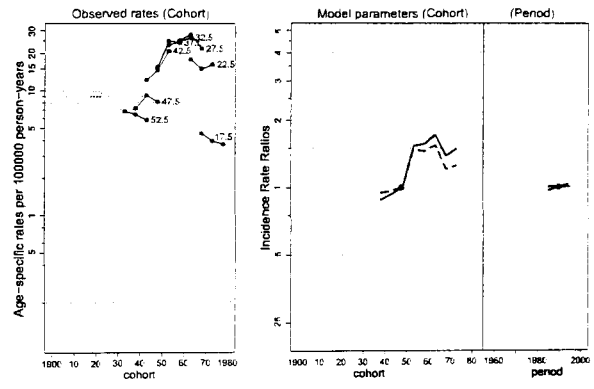


Table 6.3: Period and Cohort curvature over and above net drift (incidence)

		Period curvature			Cohort curvature		
European Area	**Country**	**Δ Deviance[b]**	**Δ d.f.[c]**	**p-value[d]**	**Δ Deviance[b]**	**Δ d.f.[c]**	**p-value[d]**
Northern	Denmark	1.7	2	0.43	30.0	9	<0.01
	Finland	16.8	7	0.02	33.1	14	<0.01
	Norway	18.4	7	0.01	57.8	14	<0.01
	Sweden	2.8	5	0.72	52.1	12	<0.01
	United Kingdom	2.4	2	0.30	22.2	9	0.01
Eastern	Czech Republic	1.3	1	0.25	39.4	8	<0.01
	Slovakia	27.5	4	<0.01	35.7	11	<0.01
Southern	Italy	0.2	1	0.69	12.2	8	0.14
	Slovenia	0.01	1	0.94	9.9	8	0.27
	Spain	1.7	1	0.20	16.1	8	0.04
Western	France	0.4	2	0.83	19.9	9	0.02
	Switzerland	1.8	1	0.18	29.5	8	<0.01

6.3.3.2 Mortality

The ratio of testicular cancer incidence to mortality ranged from 8:1 in the Czech Republic to over 30:1 in Switzerland, with a clustering of rates within region more apparent than was noted for incidence (Table 6.2). Death rates were generally highest in Eastern and Southern Europe, with Bulgaria, the Czech Republic, Hungary and Poland holding the first four positions, and Denmark in fifth place. In further contrast to incidence, decreases in testicular cancer mortality were observed in 19 of the 22 populations in the most recent two decades, with declines of 3% to 6% seen throughout Northern and Western Europe, as well as in Italy, the Czech Republic and Hungary. Elsewhere in Eastern Europe (e.g. in Romania and Bulgaria), the magnitude of the declines were negligible (Table 6.2), while in the South, increases in the overall mortality trend of 2% and over 4% were observed in Portugal and Croatia, respectively.

The declines in mortality rates started first in Denmark, Norway and the U.K. in the 1970s, followed a few years later in Sweden, Finland and France. The lower level of recent mortality declines in Eastern Europe partially reflects a tendency for the respective downturns to have occurred mainly in the last decade of observation, from the late 1980s.

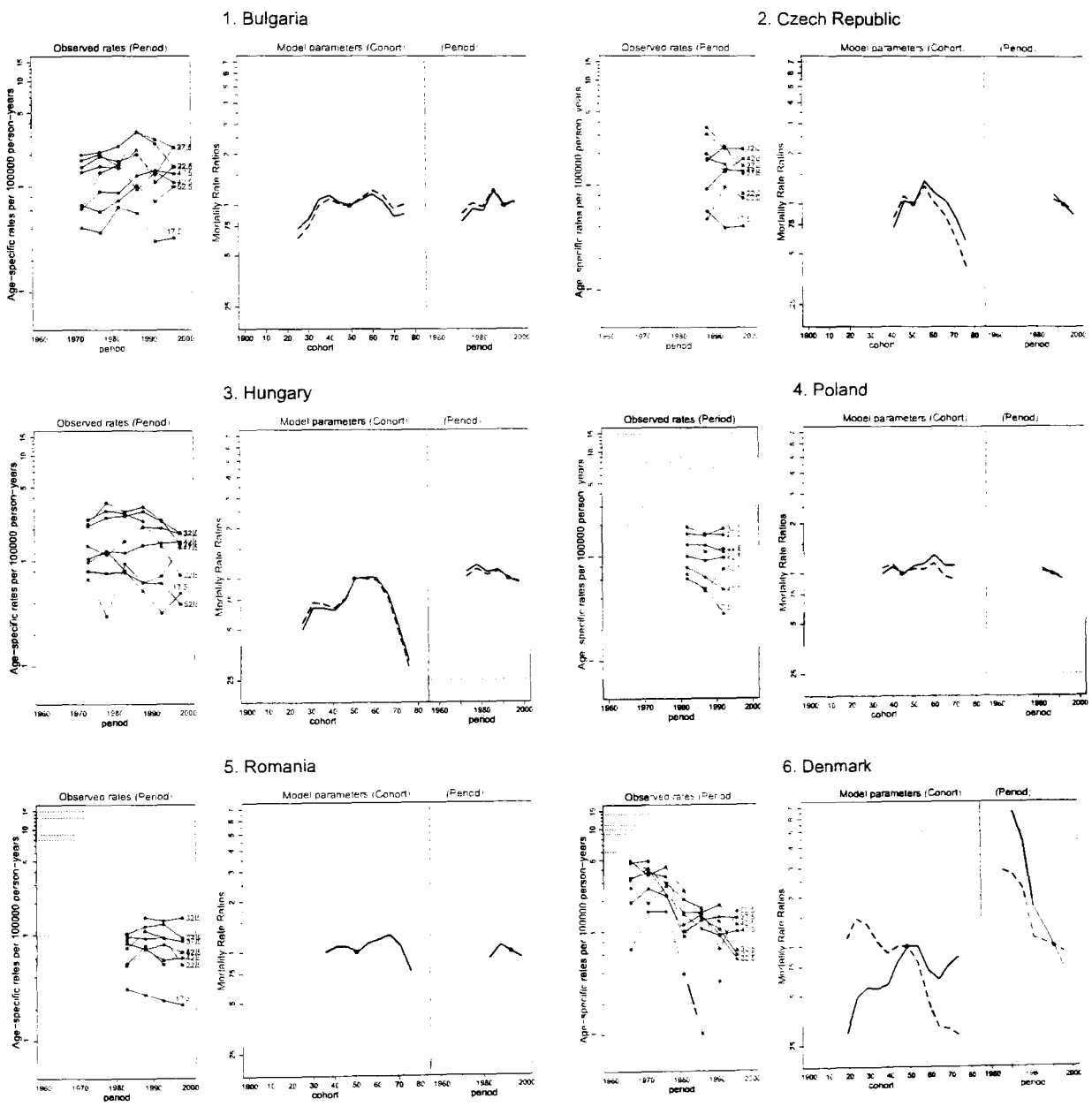
A deviance analysis of the mortality trends (Table 6.2) indicated that sub-models or the full APC model provided an adequate fit in every country, excepting Germany. Period and cohort curvature significantly improved the fit in 14 and 13 populations, respectively (Table 6.4). Downwards trends in mortality rates were seen in most Northern and Western European countries (and Italy) from the mid-1970s onwards, translating (in spite of the rapid increases in incidence observed) to generation-specific decreases in risk of death for men born after 1940 (Figure 6.4).

The period-specific trends elsewhere in Southern Europe were difficult to interpret. The reduction in risk by calendar period in Greece and Spain since the 1970s led to a discontinuation in the increases in risk of death amongst affected birth cohorts. In contrast, the risk of death appeared to increase in Portugal and Croatia in consecutive cohorts born after 1950. In Eastern Europe, period-specific declines were most evident in Hungary (where a sufficient span of data was available) and the Czech Republic. The declines in Bulgaria and Romania were seen at least a decade later than in Northern Europe, with cohort-specific declines suggested only in Romania, and only among generations born recently.

Table 6.4: Period and Cohort curvature over and above net drift (mortality)

		Period curvature			Cohort curvature		
European Area	**Country**	**Δ Deviance[b]**	**Δ d.f.[c]**	**p-value[d]**	**Δ Deviance[b]**	**Δ d.f.[c]**	**p-value[d]**
Northern	Denmark	21.9	5	<0.01	34.6	12	<0.01
	Finland	18.5	5	<0.01	13.9	12	0.31
	Ireland	23.0	5	<0.01	11.6	12	0.48
	Norway	26.1	5	<0.01	21.5	12	0.04
	Sweden	35.2	5	<0.01	23.5	12	0.02
	United Kingdom	35.3	4	<0.01	81.3	11	<0.01
Eastern	Bulgaria	15.5	4	<0.01	15.3	11	0.17
	Czech Republic	0.4	1	0.55	19.1	8	0.01
	Hungary	18.0	4	<0.01	88.7	11	<0.01
	Poland	2.9	1	0.09	11.4	8	0.18
	Romania	8.8	2	0.01	12.9	9	0.17
Southern	Croatia	0.4	1	0.54	4.7	8	0.79
	Greece	1.3	4	0.86	21.5	11	0.03
	Italy	48.5	5	<0.01	17.9	12	0.12
	Portugal	1.2	2	0.56	18.9	9	0.03
	Spain	7.5	3	0.06	10.1	10	0.43
Western	Austria	44.4	5	<0.01	34.3	12	<0.01
	Belgium	5.6	4	0.23	5.7	11	0.89
	France	85.5	5	<0.01	32.2	12	<0.01
	Germany	1.3	1	0.25	48.6	8	<0.01
	The Netherlands	20.5	5	<0.01	28.4	12	<0.01
	Switzerland	40.2	4	<0.01	29.3	11	<0.01

Figure 6.4: Age period cohort parameters based on assumptions on period slope: mortality trends by country within European area (Panels 1-5: E Europe; 6-11: N Europe; 12-16: S Europe; 17-22: W Europe). Solid line: assumption of zero cohort slope (drift taken up entirely by period); dashed line: assumption of positive equal slopes for period and cohort (drift attributed equally to period and cohort)



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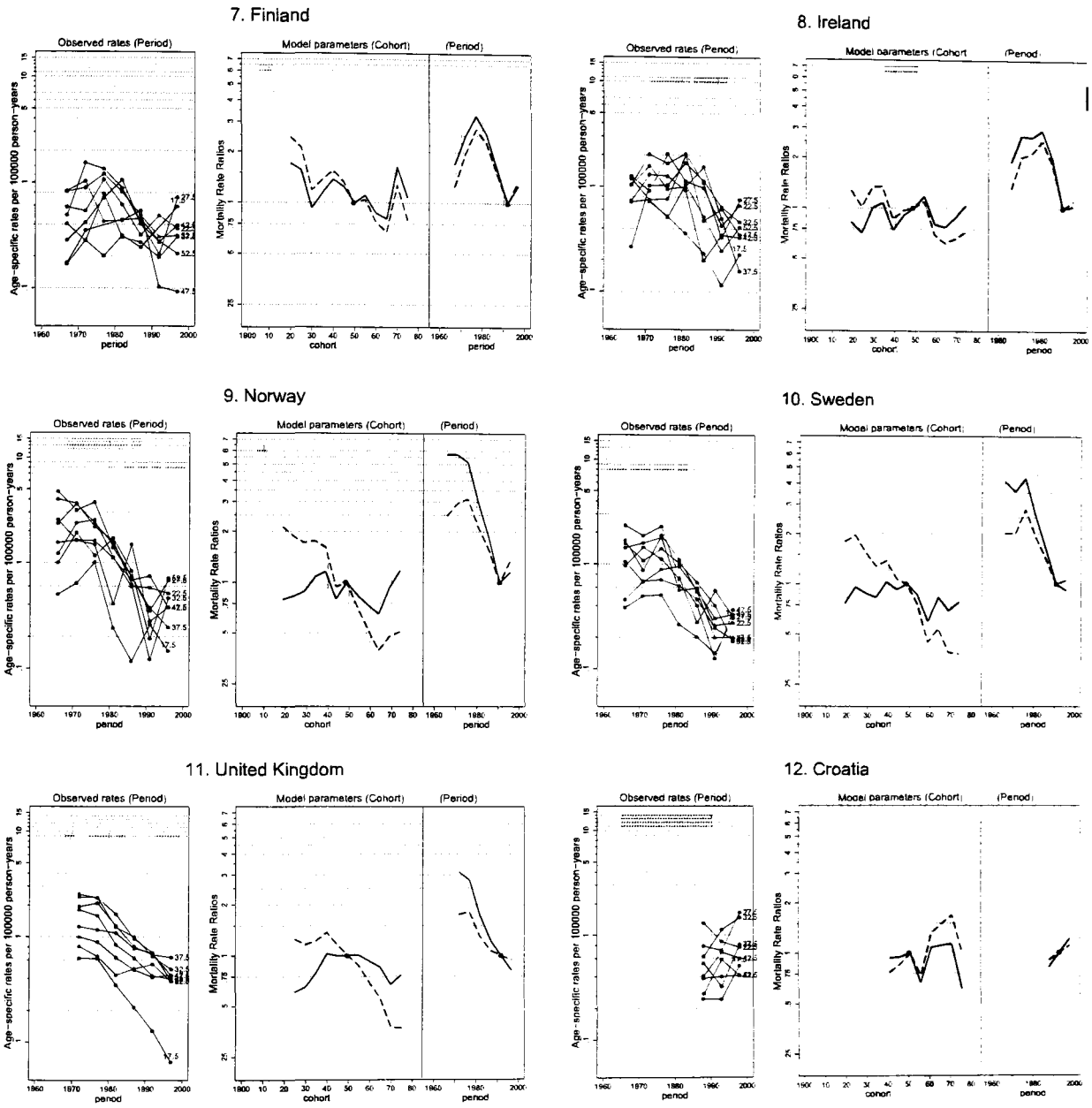
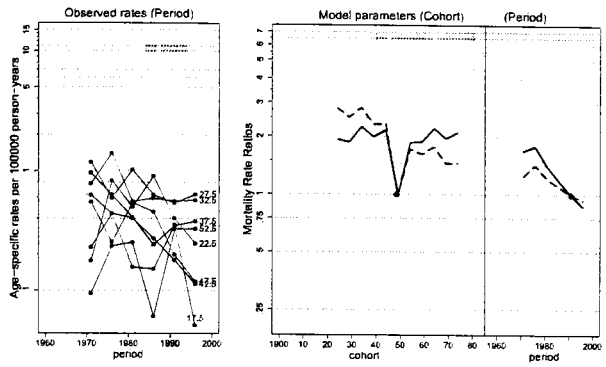
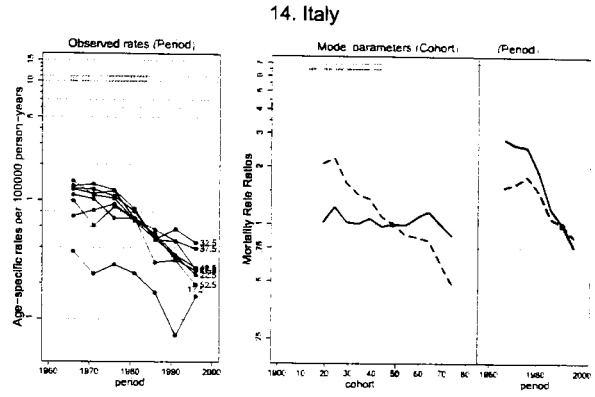


Figure 6.4 cont..

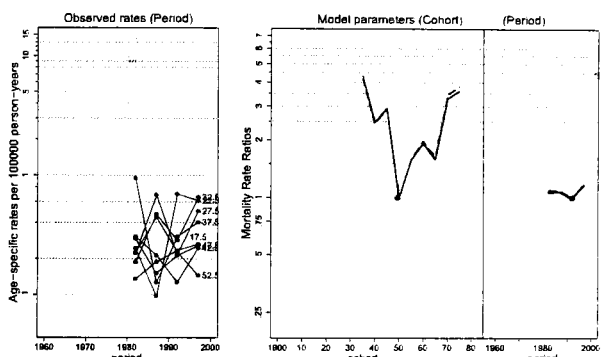
13. Greece



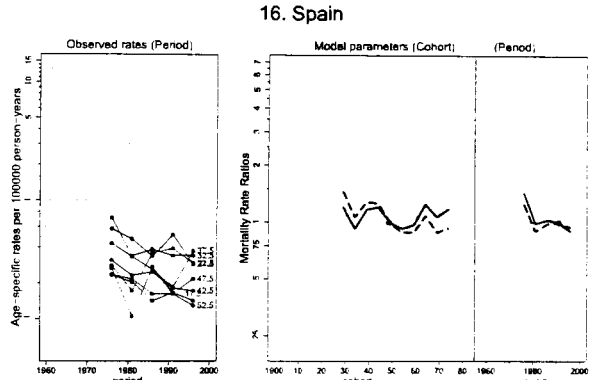
14. Italy



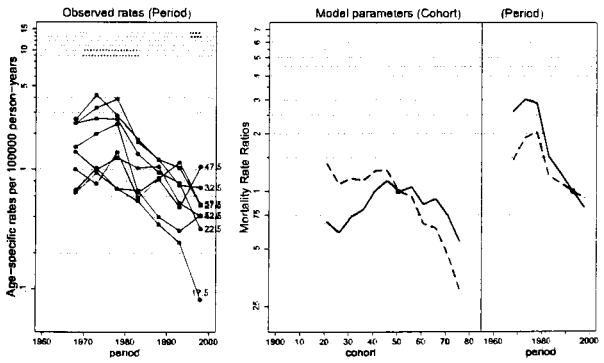
15. Portugal



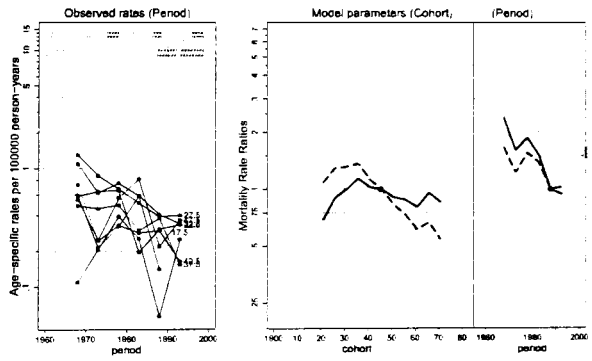
16. Spain



17. Austria



18. Belgium



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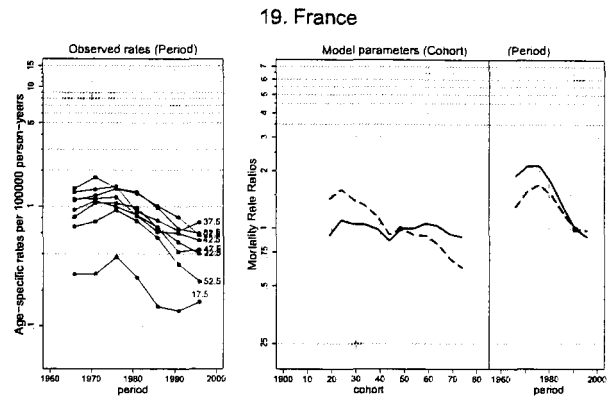
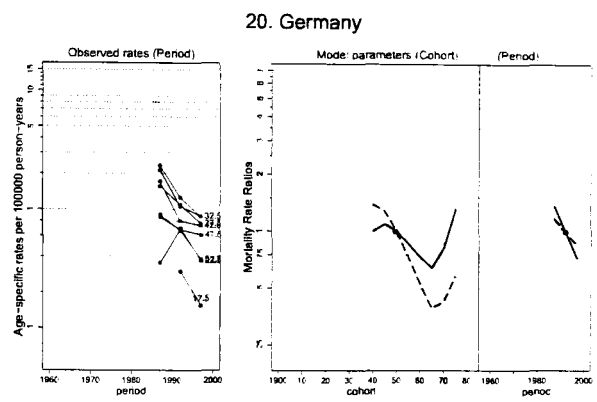
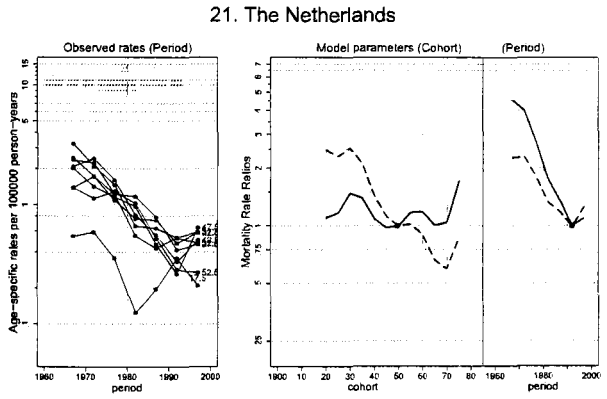
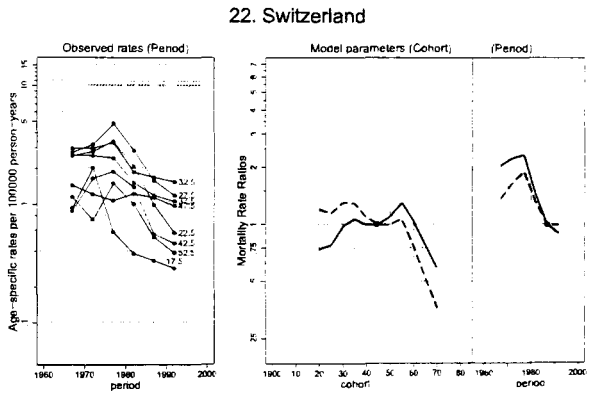








6.3.4 Discussion of main findings

This study described the temporal patterns of testicular germ cell cancer incidence and testicular cancer mortality in European countries, with particular reference to the importance of cohort effects (on incidence trends) and period effects (on mortality trends). Similar multi-country analyses of incidence in Europe have been compiled previously [453,455], although this report extended the analysis to 12 countries, including several in Southern and Eastern Europe. The variability in the geographical and temporal patterns within Europe was extensive: a five-fold variation in incidence rates was observed as well as a steady rise in incidence across populations that varied from 1% to 6% per annum. Rates rose most rapidly in low- to intermediate-risk countries, particularly in Spain and Slovenia. Switzerland was the exception to the increasing profile; rates have been extremely high but stable over several decades [489].

A feature of this study was the suggestion of recent declines in testicular cancer among recent cohorts in certain high-risk populations. It can be speculated that a levelling off of incidence in such countries may represent a mature phase in the epidemic, relative to lower-risk countries for which the testicular cancer phenomenon might be considered to be at an early phase, with further increases anticipated in forthcoming years.

Regardless of temporal and geographical disparities, the age-incidence curves of testicular cancer are well-known to be largely invariate, implying that the age window of susceptibility to strong determinants of testicular cancer is likely equivalent in different populations [460]. One of the strongest lines of evidence relates to the importance of factors acting prenatally or early in life that may initiate the process of testicular carcinogenesis. The strong causes involved in the development of carcinoma *in situ*, the precursor lesion of all germ cell tumours [490], appear identical to the strong causes of testicular cancer [460].

Carcinoma *in situ* most probably occurs during the first trimester of pregnancy, and the associations between testicular cancer, genital malformations and prenatal factors suggest that the strong causes of carcinoma *in situ* and, subsequently, of testicular cancer, act prenatally. Increased oestrogen exposure *in utero* has been related to increasing abnormities in the development and functioning of the testis [491], and a number of prenatal and peri-natal exposure-related factors have been implicated for testicular cancer in analytical studies.

Asides from congenital malformations, of which cryptorchidism is the strongest and most consistent determinant [468,492,493], certain prenatal factors have been reported in epidemiological studies with some consistency. These include premature birth

[462,463,465,466], low birthweight [461-465], high birthweight [463,464], neonatal jaundice [464], exogenous oestrogen use [462,466], older maternal age [461,465] and first born [461,463-465,467]. Other factors have been suggested: smoking during pregnancy [470,494], subfertility [229,495], exposure to viral infections [496] and a sedentary lifestyle [497].

As has been consistently demonstrated [8,229,455,488], generational influences appeared largely responsible for the increasing incidence trends in Europe. Cohort curvature significantly improved the fit in all countries, except Italy and Slovenia, where age and age-drift models already provided a reasonable fit, respectively, possibly because of a lack of power to reject these simpler models [381]. Trends in Finland, Norway and Slovenia required the full APC model, indicative of some period curvature being in operation in addition to the cohort effects. Birth cohort effects can be viewed as a consequence of the changing prevalence of the risk determinants of the disease in successive generations, and generational increases of testicular germ cell tumour are in accordance with the known biology of the disease, with possibly a role for external environmental factors mediated through exposure of the developing male embryo [498]. The sharp rise in incidence observed around the onset of puberty implies a role of male sex hormones in the progression of germ cell tumours.

A reduced incidence amongst a specific cohort born during World War II was observed in a number of countries, particularly in Denmark and Norway, as has been reported previously [229,251,455,460,488]. It has been hypothesised that an altered supply of provisions in Denmark [460,488] may have impacted on consumption of a variety of foodstuffs and other commodities during the German military occupation. Interestingly, the pattern was also seen around the same time in Sweden, as previously reported [455], and in Italy, Slovenia, France and Switzerland. In Spain, a cohort with minimum risk was also identified, but at least a decade later, in the late-1950s. In the remaining countries (Finland, the U.K., Slovakia and the Czech Republic), no such break in the generational increases was evident.

That the observation arises in many European countries suggests that modifications in lifestyle, possibly brought about by a war-related supply restriction at this time, were strong determinants of the disease, and that they acted very early in life, given the transitory nature of the phenomenon [460,488]. If a dietary factor is involved, this would probably concern an alteration in maternal diet affecting offspring prenatally or postnatally. A recent study hypothesised that the mycotoxin Ochratoxin A, a contaminator of stored foods such as cereals and coffee, may be a causal factor [499].

Despite the increases in incidence, decreasing mortality trends of between 3% and 6% per annum were observed throughout Northern and Western Europe, and in Italy, the Czech Republic and Hungary. The starting point and the rate of decrease in each country appears closely related to the dramatic improvements in survival of young and middle-aged patients, following the introduction of Cisplatin as a therapeutic agent for advanced germ cell tumours [457]. Notable declines were first observed in Denmark, Norway and the U.K in the early-1970s, followed soon after by Sweden, Finland and France. Further developments of Cisplatin-based regimens, improvements in tumour imaging and surgical interventions of residual disease, together with a multidisciplinary approach to cancer care, have all contributed to the declining mortality trends in the 1970s and 1980s [500]. Thus, in spite of a generation-specific increase in incidence, the risk of death has been on the decline in generations of men born after 1940 in higher resource countries.

In several Eastern European countries, where death rates are currently among the highest in Europe, the rate of decrease was of a relatively low order of magnitude, in part due to a later decline around the mid- to late-1980s, at least a decade after Northern and Western Europe. The notable success of chemotherapy in terms of a reduction in mortality were thus not uniformly seen across Europe, and slower and later declines in some lower resource countries appear to be primarily due to the high cost of appropriate treatment as well as inadequate patient management. Of particular and immediate concern were the increases in testicular cancer mortality in Portugal and Croatia of 2% and over 4% per annum respectively. The cohort analysis clearly shows that the risk of death from testicular cancer has increased among men born in these countries since 1950.

Regarding the presentation of APC effects, the setting of a slope to a particular value should be ideally founded on biological or epidemiological evidence, as has been a major theme in this thesis in recommending and practising particular methods of APC analysis. Although an erroneous choice will induce a bias in all of the effects [107], selecting a range of slopes leaves some margin for error, allowing the researcher to contrast the age, period and cohort effects, based on their particular preference(s) for the fixed slope, with other less plausible specifications [107].

The approach used here in presenting APC estimates was predisposed *a priori* towards a cohort-based approach in analysing trends in testicular germ cell cancer incidence, given that knowledge of the epidemiology and the biological mechanisms point to the importance of generational influences on disease occurrence. Unique estimates of the period and cohort effects were presented in two ways, firstly on assuming a period slope of zero, implying birth cohort influences were entirely responsible for the time trend. Secondly, by acknowledging

the possibility of some increases in rates across all age groups over a period of time, and attributing the regular trend equally to period and cohort slopes. The underlying risk factors responsible remain elusive for testicular cancer, though the extent of variation in the increases perhaps lends some support to the idea of an epidemic in different phases in different countries.

For mortality, *a priori* evidence suggested that the presentation of trends should incorporate the well-known benefits from treatment, which should show up as period-related effects. Mirroring the approach to incidence, it was assumed firstly that the regular trend was a result of period influences, setting the cohort slope to zero. A second set of presented estimates accounted for the possibility of generational influences related to disease occurrence; the regular trend was then apportioned evenly to the slopes of period and cohort, as it was for incidence. Advances in therapy and the management of testicular cancer since the mid 1970s have led to large declines in mortality in some European countries, despite the unabated increases in incidence. More disturbing in lower resource countries has been the apparently slower progress towards delivery of optimal care reflected in the time trends of mortality. In countries like Bulgaria and Romania, the first beneficiaries of therapy appear to be men born – rather than diagnosed – in the era of this major breakthrough in oncology.

6.4 Study II: comparison of incidence trends in the main subtypes by cohort

The main objective of this study was to test the hypothesis that testicular seminoma and non-seminoma trends in successive generations largely conform to the same temporal patterns, implying that they share the same prevalence and distribution of the main risk factors in operation. A version of this section has been submitted to a peer-reviewed journal (see Appendix 1).

6.4.1 Data sources

Data were obtained from the EUROCIM [160] (see 2.8 for details and standard inclusion criteria). The main histological grouping, germ cell tumours (ICD-O codes 9060-9102), generally comprising 95% to 99% of all testicular cancers in men under age 60, was abstracted for analysis, as were the subtypes seminoma (9060-9064) and non-seminoma (including embryonal carcinoma (9070-9073), malignant teratoma (9080-9085, 9102), choriocarcinoma (9100-9101), and mixed tumours). The dataset was restricted to the age group 15-54, to provide a well-defined grouping for the study of trends of histological subtypes of germ cell cancers [186].

Given the relative paucity of incident cases after stratifying germ cell cancers into seminoma and non-seminoma, countries with less than an average of five cases per period in any age

stratum were excluded. Eight countries were included in the final analyses (Table 6.5). Palpable availability of the testicle together with standardised therapeutic approaches and primary inguinal orchiectomy provides the basis for the high proportion of histologically verified tumours in most European countries [131].

6.4.2 Methods: fitting the APC model

To allow a systematic evaluation of the histological trends across countries, the results are presented using the full APC model, and the non-identifiability problem highlighted as previously using assumptions based on the method of Holford [66].

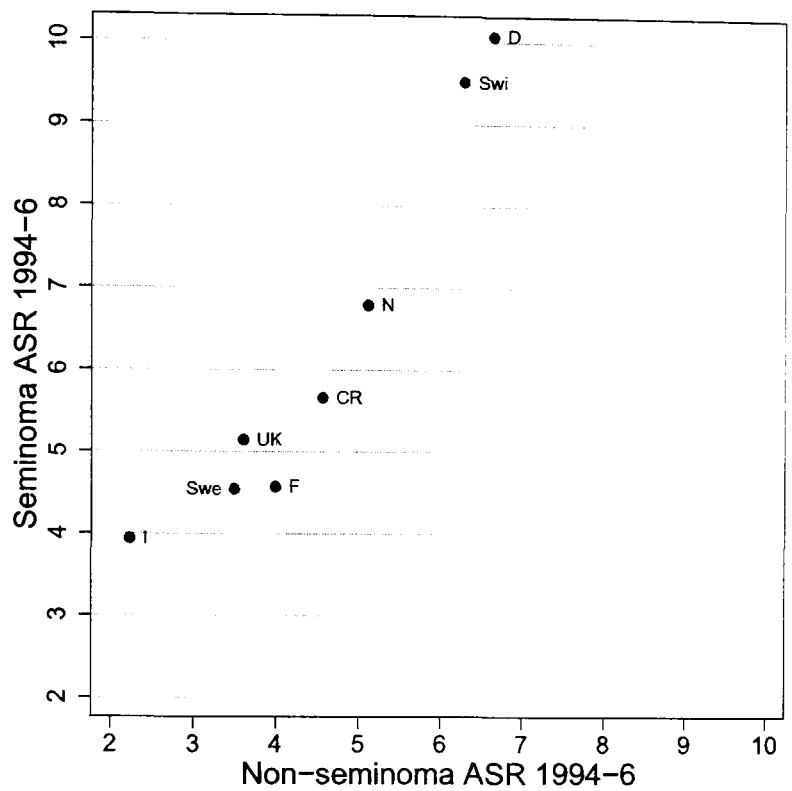
6.4.2.1 Characterising the cohort effects

As underlined in study I of this section, the major contribution of cohort effects has been consistently demonstrated in previous reports describing the increasing incidence of testicular cancer with time in Europe [8,229,455,488]. Birth cohort effects may be considered the consequence of a changing prevalence of known and/or putative risk factors for both subtypes in successive generations. It was therefore assumed *a priori* that cohort effects predominated and the period slopes of both seminoma and non-seminoma were on average of zero magnitude. The cohort effects were presented as incidence rate ratios with country-specific reference cohort $c = A + P - 7$. Due to small numbers in the cells comprising the youngest and oldest cohorts, the corresponding birth cohort effects were not displayed in the accompanying figure.

6.4.3 Results: description of trends

Figure 6.5 compares, using a scatter plot, the age-truncated (ages 15-54) standardised rates (European standard) of seminoma and non-seminoma in eight countries for diagnoses 1994-96. Rates of seminoma tended to be about a third higher than non-seminoma, but there is a clear relationship between the absolute magnitude of the two, with rates of seminoma increasing proportionally with rates of non-seminoma in low risk (e.g. Italy, France) through to intermediate risk (Czech Republic, Norway) to high-risk countries (Denmark and Switzerland).

Figure 6.5: Truncated age-standardised rates (Europe) of seminoma versus non-seminoma in men aged 15-54 and diagnosed 1994-96 in eight European countries (CR: Czech Republic; D: Denmark; F: France; I: Italy; N: Norway; Swe: Sweden; Swi: Switzerland; UK: United Kingdom)



There were clear increases in the incidence of both histologies with calendar period in each European country, with the magnitude of the slopes of seminoma and non-seminoma comparable across populations (Figure 6.6). The overall ranking of rates between countries was also retained over time. A notable feature of the trends was the observed decline in non-seminoma rates in some but not all countries in the last five-year period, concerning diagnoses in the 1990s. This pattern was seen in highest-risk countries, Switzerland and Denmark as well as in Norway, Italy and Sweden, but not in the Czech Republic and the U.K. In France, non-seminoma trends appear to have reached a plateau during the latest period.

No such declines were observed in the seminoma trends (Figure 6.6). The relative proportions of seminoma and non-seminoma were largely similar between countries, despite the three-fold variation in risk. Seminoma comprised the larger share with 55% to 60% of germ cell cancers, leaving 40 to 45% non-seminomas (Table 6.5). The proportions of seminoma were slightly higher in low-risk Italy and high-risk Switzerland.

For the seminoma trends, a sufficient amount of variation in each country was explained either by a model representing the linear trend adjusted for age (in France, Italy and the United Kingdom) or with additional cohort curvature (the Czech Republic, Denmark, Norway,

Sweden and Switzerland) (data not shown). The non-linear effects of cohort over and above the net drift provided a statistically significant contribution to the seminoma trends in four of the eight countries (Norway, Sweden, Denmark and the Czech Republic), and were of borderline significance in two (Italy and Switzerland) (Table 6.6). In contrast, period curvature was not required in describing the seminoma trends in any of the study populations.

Figure 6.6: Truncated age-standardised rates (Europe) vs. five-year period of diagnosis of pure seminoma (left) and non-seminoma (right) in men aged 15-54 in eight European countries (CR: Czech Republic; D: Denmark; F: France; I: Italy; N: Norway; Swe: Sweden; Swi: Switzerland; UK: United Kingdom)

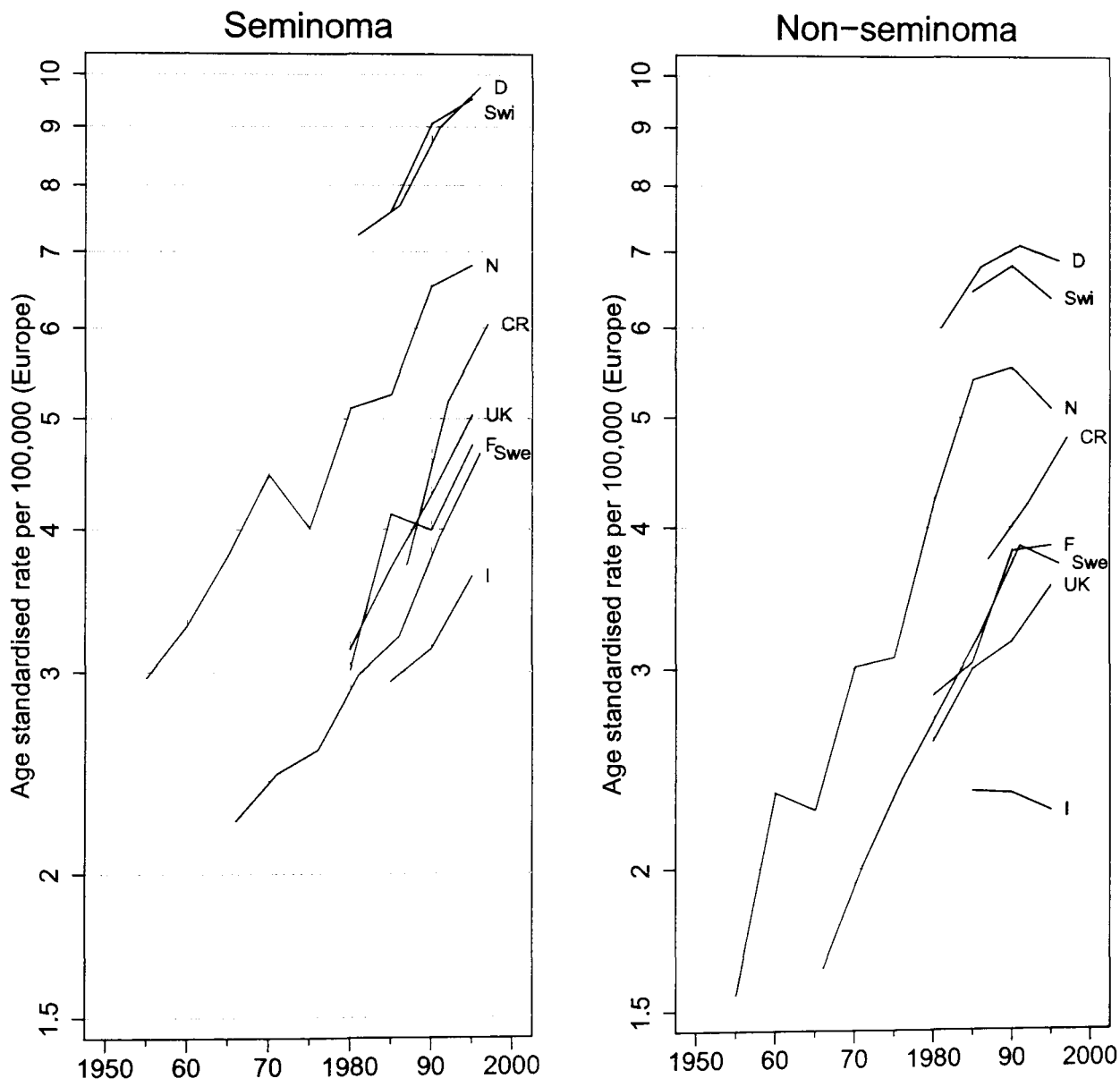


Table 6.5: testicular germ cell incidence: populations included in the trends analysis by histological subtype

European Area	Country	Calendar Period*	Person-years†	Incidence (seminoma) ††	% of germ cell‖	Incidence (non-seminoma) ††	% of germ cell‖	Person-years†
Eastern	Czech Republic	1985-1999 (3)	3.1	179	54.8%	148	45.2%	3,071,444
Northern	Denmark	1979-1998 (4)	1.5	154	58.9%	108	41.1%	1,530,603
	Norway	1953-1997 (9)	1.3	88	57.2%	66	42.8%	1,251,442
	Sweden	1964-1998 (7)	2.4	116	56.4%	90	43.6%	2,426,688
	United Kingdom[a]	1978-1997 (4)	15.1	792	58.3%	567	41.7%	15,089,155
Southern	Italy[b]	1983-1997 (3)	1.3	48	61.7%	30	38.3%	1,238,491
Western	France[c]	1978-1997 (4)	1.2	56	54.4%	47	45.6%	1,162,916
	Switzerland[d]	1983-1997 (3)	0.8	85	60.9%	55	39.1%	834,828

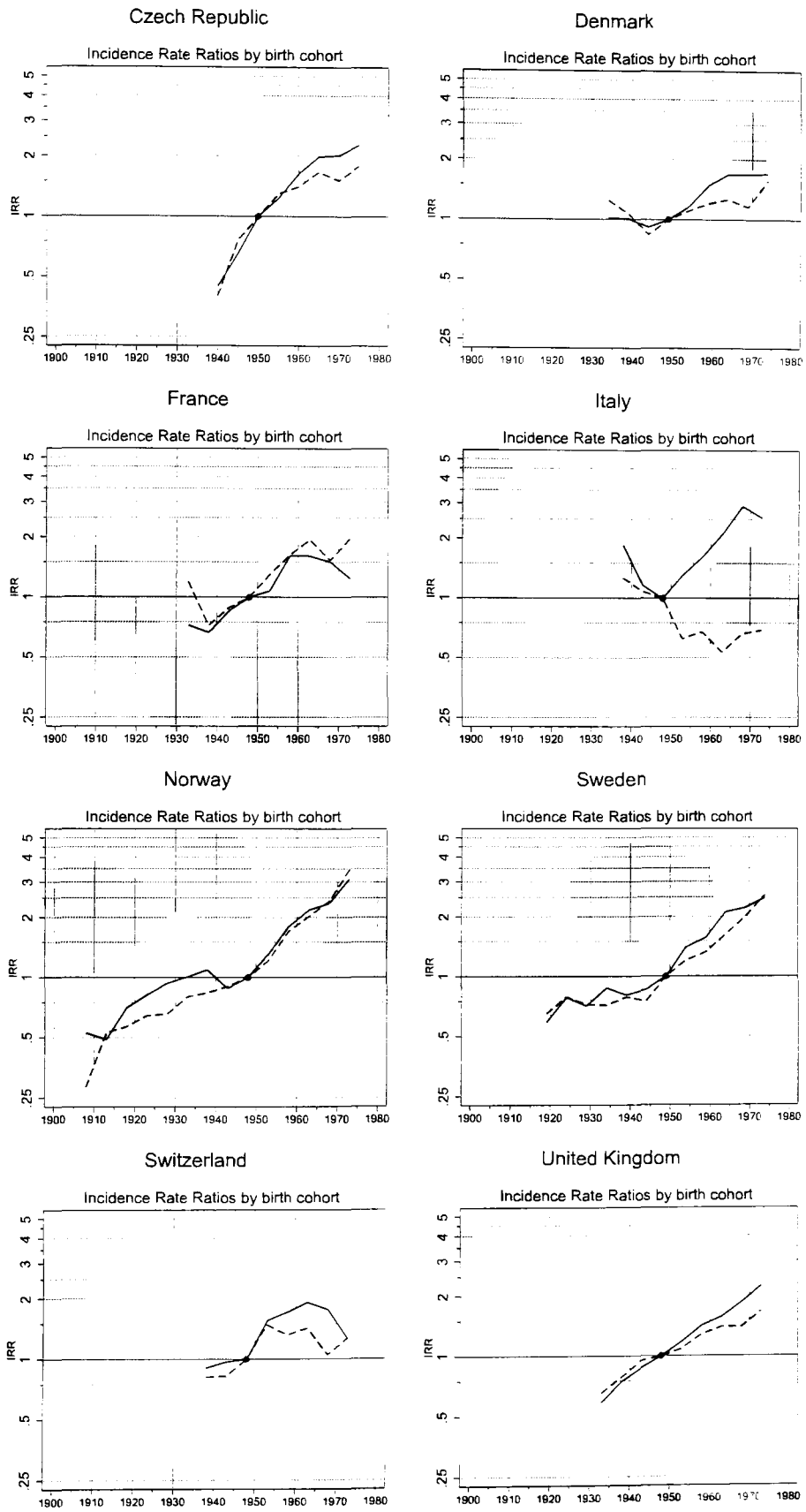
* data available according to period of diagnosis, figure in parentheses represent number of five-year periods available in the analysis
† average annual male population expressed in million person-years at risk obtained from most recent 5-year period
†† annual number of incident cases obtained from most recent 5-year period
‖ proportion based on cases in most recent 5-year period
a aggregation of England (1978-1997), Scotland (1978-1997)
b aggregation of Florence (1985-1997), Varese Province (1983-1997), Parma Province (1983-1997), Ragusa Province (1983-1997), Turin (1985-1997)
c aggregation of Bas-Rhin (1978-1997), Calvados (1978-1997), Doubs (1978-1997), Isere (1979-1997), Somme (1982-1997), Tarn (1982-1997)
d aggregation of Basel (1983-1997), Geneva (1983-1997), Neuchatel (1983-1996), St.Gall-Appenzell (1983-1997), Vaud (1988-1996), Zurich (1983-1996)

Table 6.6: Period and Cohort curvature over and above net drift: seminoma trends

		Period curvature			Cohort curvature		
European Area	Incidence Population	Δ Deviance*	Δ d.f.†	p-value§	Δ Deviance**	Δ d.f.††	p-value[d]
Eastern	Czech Republic	3.1	1	0.08	17.5	8	0.02
Northern	Denmark	1.3	2	0.52	22.6	9	0.01
	Norway	6.2	7	0.52	60.9	14	<0.01
	Sweden	5.8	5	0.32	43.7	12	<0.01
	United Kingdom[a]	0.2	2	0.88	7.0	9	0.63
Southern	Italy[b]	0.2	1	0.64	15.5	8	0.05
Western	France[c]	3.5	2	0.17	11.8	9	0.22
	Switzerland[d]	1.2	1	0.28	15.6	8	0.05

* Represents the difference in the deviance of the Age+Drift model and the Age+Drift+Period model
† Represents the difference in the degrees of freedom of the Age+Drift model and the Age+Drift+Period model
§ to determine the goodness-of-fit, the change in deviance was compared with the chi-squared distribution on the change in degrees of freedom between the models
** Represents the difference in the deviance of the Age+Drift model and the Age+Drift+Cohort model
†† Represents the difference in the degrees of freedom of the Age+Drift model and the Age+Drift+Cohort model
a aggregation of England (1978-1997), Scotland (1978-1997)
b aggregation of Florence (1985-1997), Varese Province (1983-1997), Parma Province (1983-1997), Ragusa Province (1983-1997), Turin (1985-1997)
c aggregation of Bas-Rhin (1978-1997), Calvados (1978-1997), Doubs (1978-1997), Isere (1979-1997), Somme (1982-1997), Tarn (1982-1997)
d aggregation of Basel (1983-1997), Geneva (1983-1997), Neuchatel (1983-1996), St.Gall-Appenzell (1983-1997), Vaud (1988-1996), Zurich (1983-1996)

Figure 6.7: Incidence rate ratios of testicular germ cell seminoma (solid line) and non-seminoma (dashed line) by birth cohort in eight European countries, assuming an overall period slope of zero. The reference category (IRR=1) is marked as a closed circle, corresponding to birth cohort A+P-7



None of the population-based trends for non-seminoma suffered from a significant lack-of-fit, although the required complexity of the model varied by population (data not shown). In Italy and Switzerland, only age effects were required, while both age and period were necessary in Denmark and France. Cohort curvature was necessary in explaining the non-seminoma incidence trends in three countries (the Czech Republic, the U.K. and Denmark) and were of borderline significance in Switzerland (Table 6.7). Period curvature significantly improved the fit of the non-seminoma trends in Norway.

Table 6.7: Period and cohort curvature over and above net drift: non-seminoma trends

Non-seminoma		Period curvature			Cohort curvature		
European Area	**Incidence Population**	**Δ Deviance***	**Δ d.f.†**	**p-value§**	**Δ Deviance****	**Δ d.f.††**	**p-value§**
Eastern	Czech Republic	0.0	1	0.88	21.2	8	0.01
Northern	Denmark	3.6	2	0.16	16.6	9	0.05
	Norway	30.3	7	<0.01	11.8	14	0.62
	Sweden	11.0	5	0.05	15.4	12	0.22
	United Kingdom[a]	3.3	2	0.19	17.4	9	0.04
Southern	Italy[b]	0.0	1	0.85	6.5	8	0.60
Western	France[c]	1.6	2	0.45	13.0	9	0.16
	Switzerland[d]	0.8	1	0.38	15.6	8	0.05

* Represents the difference in the deviance of the Age+Drift model and the Age+Drift+Period model
† Represents the difference in the degrees of freedom of the Age+Drift model and the Age+Drift+Period model
§ to determine the goodness-of-fit, the change in deviance was compared with the chi-squared distribution on the change in degrees of freedom between the models
** Represents the difference in the deviance of the Age+Drift model and the Age+Drift+Cohort model
†† Represents the difference in the degrees of freedom of the Age+Drift model and the Age+Drift+Cohort model
a aggregation of England (1978-1997), Scotland (1978-1997)
b aggregation of Florence (1985-1997), Varese Province (1983-1997), Parma Province (1983-1997), Ragusa Province (1983-1997), Turin (1985-1997)
c aggregation of Bas-Rhin (1978-1997), Calvados (1978-1997), Doubs (1978-1997), Isere (1979-1997), Somme (1982-1997), Tarn (1982-1997)
d aggregation of Basel (1983-1997), Geneva (1983-1997), Neuchatel (1983-1996), St.Gall-Appenzell (1983-1997), Vaud (1988-1996), Zurich (1983-1996)

Figure 6.7 displays the incidence rate ratios from the APC model according to birth cohort. The incidence trends of seminoma and non-seminoma in successive generations were similar, although the trends tended to be more heterogeneous in the more recently-born cohorts, where data was more sparse and most of the cases were non-seminomas. The exception was Italy, where the trends in histology diverged in generations born after 1945. In Switzerland, there was a strong indication of cohort-specific declines in both seminoma and non-seminoma rates in consecutive cohorts born since the 1960s. Finally, there was also some indication of a plateau in rates of both subtypes in recent generations born in France and Denmark, but the observation was more apparent for seminoma.

6.4.4 Discussion of main findings

This study provided broad support for the hypothesis that generation-specific trends in testicular seminoma and non-seminoma conform to largely the same temporal patterns,

implying that they also share important aetiological factors. Trends in pure seminoma and non-seminoma were increasing with calendar time in most of the countries studied, although there were recent plateaus or minor declines in cross-sectional age-adjusted rates of non-seminoma in Denmark and Switzerland. Declines in incidence rates of both subtypes were also evident among recent birth cohorts in the latter country.

The importance of birth cohort effects in this study was in accordance with many prior reports of combined or subtype-stratified testicular cancer trends in Europe [8,229,455,488], the U.S. [459] and Canada [292,481]. Non-linear cohort effects significantly improved the fit of the APC model in six countries for both subtypes, indicating the importance of generational influences, while period curvature was not required in the majority. Further (as was seen in study I for testicular germ cell cancer trends overall), short-term attenuations of increasing risk in men born around 1940-45 were evident in Denmark (for both histologies) and Norway (seminoma only), and less unequivocally, in Sweden and France, but for both subtypes. Such observations have been reported previously for incidence trends in the Scandinavian countries, not only for testicular cancer trends in general but also for both subtypes [251,455,460,488,501]. In Denmark, the temporary irregularity has been hypothesised to be at least partially a result of specific events (e.g. dietary changes or tobacco consumption) at the time of German occupation during the Second World War [460]. The similarity of the subtype trends implies such a wartime effect would act in an identical manner on seminoma and non-seminoma.

The observed lag of approximately 10 years in the age at peak incidence of subtypes has been consistently reported in Western populations, with non-seminoma peaking earlier, in men aged in their late twenties [186]. The differential age profile may perhaps reflect that non-seminoma is more aggressive and rapidly-growing than seminoma at diagnosis; the proportion of metastatic to localised tumours is often higher for non-seminoma than seminoma [460]. Any departure from the steady increases in testicular cancer over time is therefore likely to occur for non-seminomas some years ahead of seminoma. This appears as an artefact of analysis on the period scale that is absent on the birth cohort scale. With a narrow time window of susceptibility to exposures earlier in life, and a biologically constant time to diagnosis, all temporal changes in rate-limiting exposures should appear as cohort effects.

Some evidence of a plateau in the cohort-specific risk of both types was observed amongst recent cohorts in some populations (Czech Republic, Denmark and France), although it is unknown whether there will be declines subsequently. With the exception of Italy, the subtype trends followed a rather similar generational course, and the homogeneity parallels

several previous observations reported for temporal variations in testicular germ cell incidence. The period-specific decline in non-seminoma (but not seminoma) seen in Switzerland in the 1990s, is in agreement with reports describing trends in the Vaud region [502]. However, the observation in this study of a diminution in risk, evident since the mid-1960s, in both histologies in consecutive Swiss cohorts, adds weight to the hypothesis that only a delay of around a decade in the clinical manifestation of cancer distinguishes seminoma from non-seminoma.

In the unavoidable presence of non-identifiability of the three effects – the linear interdependency arising from cohort being entirely defined in terms of period and age - analysing and interpreting parameter estimates via the APC model is inherently problematic. In circumventing the problem using Holford's method [66], and setting the period component of Holford's drift to zero in each country, it has been assumed that the rising regular trend is exclusively the result of a birth cohort phenomenon, and that there are no diagnostic or coding artefacts that would lead to increases or decreases in rates with calendar time. The prominence paid to the operation of cohort effects would seem a reasonable assumption given that carcinogenic development of both seminoma and non-seminoma is likely mediated through early-in-life or *in utero* exposures [458,460]. If left untreated, testicular cancer is highly fatal, and diagnostic or coding artefacts seem unlikely to be responsible for much of the rapid rises in the regular trend [186].

Diagnostic changes in one or both subtypes cannot be entirely excluded however. In Italy, the cohort effects, in discordance with other countries, diverge after the late 1940s. The recent seminoma:non-seminoma incidence ratio is unusually high in Italy, while the trends in non-seminoma are rather flat. Non-linear period effects, a potential indicator of sudden temporal changes related to artefact, were non-significant for either subtype, although a lack of power to reject simpler models [381] cannot be discounted.

It is worth considering the possibility that artefactual changes were in operation but these influences were gradual, occurring throughout the study period. Such linear changes in period cannot be tested or quantified and would go undetected in the APC analysis. If such a linear component was present, and if the magnitude of the period slopes differed between subtypes, adjustment, were it possible, may have provided more consistency between cohort effects for seminoma and non-seminoma in Italy, in line with the APC trends seen elsewhere.

The observations in study II are in broad agreement with a number of previous studies examining cohort trends in the two main subtypes. Using a varying level of analytic sophistication, a general consensus has emerged of increasing trends of similar magnitude

by subtype, based on European reports in Denmark [460], Norway [251], England and Wales [503] and more recently in a number of Northern European countries [229], as well as from reports in Canada (Ontario) [481] and the U.S. (Connecticut) [459].

One study found increasing trends between 1963 and 1984 in Scotland for both histologies, with non-seminoma increasing more rapidly than seminoma. [504] Some differences in trends in the subtypes have been found by two recent studies analysing testicular cancer data up to 1998 in the U.S. [291], and up to 1995 in Canada [292]. In the U.S. study (based on SEER data), non-seminoma reached a plateau in white men, with seminoma:non-seminoma ratios of 50:50 in the mid-1970s comparing with 60:40, some 20 years later [291]. The Canadian study reported that subtype trends differed by age and by birth cohort. Using a method analogous to the present study, the authors suggested that there were distinct cohort patterns in aggregated data from Ontario, Saskatchewan, and British Columbia [292]. The subtype trends they plotted from the APC model were however not dissimilar in successive cohorts born after 1920, and could in fact be interpreted as indicators of homogeneity in the seminoma and non-seminoma trends.

Further evidence that the subtypes share the same aetiological factors comes from several analytical studies examining pre- and perinatal exposures and the risk of testicular cancer. A Danish study [461] argued that seminoma and non-seminoma have similar causes, finding that while cryptorchidism, birth weight and maternal age were all independent risk factors for testicular cancer, only the latter differed by subtype, with higher maternal age being more strongly associated with seminoma. Recent studies in Canada [466], the U.S. [467] and Sweden [475] have generally upheld the hypothesis of a similar aetiology; despite markers of high oestrogen levels consistently increasing the risk of germ cell cancer, little evidence of heterogeneity on stratification by histological group have emerged.

Some studies have reported statistically significant differences in risk factors for seminoma and non-seminoma, but these have not been found consistently across studies. Thus, Sabroe and Olsen [465] found elevated risks of seminoma in Danish men of a lower birth order, while a Swedish study [463] reported that markers of oestrogen during pregnancy, higher maternal age, higher placental weight and lower parity affected seminomas, and factors related to neonatal growth retardation, specifically lower maternal age and lower placental weight, increased the risk of non-seminoma. In a U.K study, a history of sexually-transmitted disease and participation in certain sports was linked to a higher risk of non-seminoma cancer [479]. The impact of socio-economic status on testicular cancer is not conclusive, although men belonging to higher socio-economic groups are often reported to

be at higher risk of testicular cancer relative to less privileged groups [505,506]. As with other variables, the risk estimates tend not however to be consistent by subtype [506].

Difficulties in achieving sufficient statistical power to detect truly significant effects in analytical studies make such investigations problematic, while the multiple testing of candidate risk factors increases the likelihood of finding statistically significant effects by chance. In parallel, statements as to the degree of homogeneity of seminoma and non-seminoma trends must be equivocal, given that the identifiability problem precludes the possibility to present and compare unique estimates of the cohort trends. Nevertheless, on assuming that only generational influences operate, the incidence trends are rather similar in this time dimension for most European countries studied, indicating that the subtypes shared largely the same distribution of causal factors within a number of diverse populations. Where the subtype trends substantially diverged (in Italy), it may be worth investigating whether they may be explained by the presence of linear period effects, implicating reasonably steady changes in diagnostic or coding artefacts with calendar time.

This study provides further evidence of the aetiological similarity of testicular seminoma and non-seminoma. The importance of birth cohort coincided with the view that, given a short time interval of susceptibility to exposures earlier in life and a biologically constant time to diagnosis, all temporal changes in rate-limiting exposures should appear as generational effects. Trends in seminoma and non-seminoma conform to largely the same temporal patterns on this scale, implying that they share important aetiological factors.

6.5 General discussion

6.5.1 Brief summary of main findings

Study I profiled testicular cancer incidence and mortality across Europe, and the effects of age, period and generational influences using APC modelling. A five-fold variation in incidence rates was observed and with average increases in incidence ranging from around 6% per annum (Spain and Slovenia) to 1% to 2% (Norway).

In contrast, declines in testicular cancer mortality of 3-6% per annum were observed in the 1980s and 1990s for the majority of 22 countries studied, particularly within Northern and Western Europe. The mortality trends in several European countries were however rather stable (Romania and Bulgaria) or increasing (Portugal and Croatia). Short-term attenuations in increasing cohort-specific risk of incidence were indicated among men born between 1940-45 in seven European countries. In Switzerland, successive generations born from the mid 1960s may have experienced a steadily declining risk of disease occurrence.

Study II compared generation-specific trends in eight European countries, hypothesising that similar temporal patterns by birth cohort implied seminoma and non-seminoma had a largely comparable aetiology. Using the APC model, the focus was on cohort effects assuming zero period slope. Despite uniform overall increases by calendar period, declining rates of non-seminoma, but not pure seminoma, were observed in the majority of countries during the 1990s. The subtype trends were however largely analogous on a birth cohort scale. Notable observations were a decline in rates of both subtypes among recent birth cohorts in Switzerland, and a short-term wartime effect in several countries, involving an attenuation of increasing risk of both subtypes in men born 1940-5. Departures from the steady increases in testicular cancer over time were likely to occur for non-seminoma some years ahead of seminoma on a period scale.

6.5.2 Reconsideration of methods and further exploration

Presentation of the APC effects in this chapter relied on the assumption that the regular increase in incidence of testicular cancer and its subtypes was entirely a birth cohort phenomenon, reasonable perhaps, given the aforementioned biological and epidemiological evidence supporting its role. Another approach would have been to restrict the age slope to a value that provided a suitable age structure, analogous to the methods used to describe cervical squamous cell carcinoma trends in Chapter 4.

Testicular germ cell cancer occurs most commonly among men aged 20-34, incidence rates increasing after the onset of puberty and declining after the age of 35 years. Rather homogenous age curves are seen in different populations in cancer diagnosed under the age of 60, irrespective of the ethnicity of the population or the magnitude of its incidence rates [453,454]. This characteristic may provide a platform to obtain a unique solution to the APC model on assuming – instead of a period slope of zero – a particular age slope that provides an age curve that closely resembles that what might be considered a reference curve for testicular cancer. If the uniformity of age curves in different European populations can be demonstrated, the results could be pooled (analogous to Gustafsson's scaled incidence ratios for cervical cancer [221], and a ratio of two age points that are reasonably constant across populations measured. One potential problem is the prospect of a wide range of age slopes seemingly providing biologically plausible age distributions for testis cancer, leading to a correspondingly wide selection of possible period and cohort parameters.

In parallel to the possibilities for modelling trends in the main histological subtypes of cervical cancer as outlined in 4.6.3.1, trends in seminoma and non-seminoma could also be examined within a single framework. Seminoma and non-seminoma have distinct age-

distributions, with seminoma typically occurring 10 years later in life than the faster-growing and more aggressive non-seminoma [186]. Other than the different age at peak incidence however, the age curves are similar and potentially one may assume that seminoma and non-seminoma have the same age profile. An alternative approach to presenting the cohort effects would be to estimate a single age slope that reasonably characterises the age structure of *both* subtypes, thereby allowing a comparison of birth cohort trends that is independent of assumptions on the linear trends in period of diagnosis.

6.5.3 Future prospects for testicular cancer prevention

Epidemiological studies of testicular cancer will continue to be fundamental in gaining insight into a disease with few known causal determinants, and at present, little scope for primary prevention. While the underlying risk factors remain elusive, the temporal and geographical variability in testicular cancer occurrence may point to an epidemic in different phases in different countries – the result of country-specific differences in the prevalence of one or several ubiquitous and highly prevalent environmental determinants of the disease. Advances in treatment have led to major declines in testicular cancer mortality in many European countries from the mid-1970s, which has translated to cohorts of men at successively lower risk of death from the disease. Slower progress in the delivery of optimal care is however evident from the mortality trends in several lower-resource countries in Southern and Eastern Europe. In these countries, it appears that men born – rather than diagnosed – in the mid-1970s will be among the first recipients of appropriate therapy for the disease.

7 Conclusions

This thesis has critically reviewed graphical and analytical approaches to temporal analyses of cancer rates and provided a broad set of recommendations to inform a detailed analysis of cancer trends across Europe. The introductory chapter made the case for the utility of the study of temporal analyses, and in particular, the role of birth cohort analyses. This emphasis on the established benefits of such investigations was appropriate given that subsequent chapters were devoted to outlining the complexities that threaten to obscure interpretation.

One has to contend with the numerous grey areas that constitute research in this area. An obvious concern is the possible distortion of cancer trends by data artefact, and the difficulties getting a handle on the extent of its impact. In terms of methodology, this thesis paid particular prominence to a critical assessment of the numerous graphical and statistical approaches at hand; some broad guidelines were provided, with particular reference to fitting and presenting effects from the APC model.

The methodological review focussed on the role of the model in the analysis of trends and the specific methods available to deal with the identifiability problem. In recent years, APC analyses have become standard in studying cancer trends. That a diverse range of techniques are applied in practice reflects the numerous proposals purporting to circumvent the problem. This heterogeneity in methods may in part be hypothesis-driven, but it also exposes the difficulties achieving consensus where there is an intrinsic inexactness in any given solution.

The wide range of available methods and an absence of a unique solution may facilitate ambiguity in the analysis and presentation. The observations and recommendations put an emphasis on clear and consistent graphical approaches and APC analyses that borrowed some form of biological or epidemiological support in providing one or more solutions. For this and other reasons, Holford's approach was particularly recommended, and employed in relation to several lines of external support to describe trends of cervical, endometrial and testicular cancer in Europe.

The final remarks revisit the main objectives of this thesis. The methods of analysis using APC models are considered once more in 7.1; the utility of the model, with respect to the studies assembled in later chapters are reviewed in 7.2. Finally, the question of what constitutes a systematic analysis of cancer trends is addressed in 7.3.

7.1 The guiding principle in APC modelling

In their 1997 investigation of the utility of three APC approaches to NHL incidence trends, McNally *et al* comment that "several methods of analysing age, period and cohort effects are available [although there is] no general agreement as to which is most appropriate" [227]. Both Clayton and Schifflers [68] and Holford have however unanimously identified methods that they consider inappropriate. Rephrasing the concluding comments by Clayton and Schifflers in their second APC paper, "[the] relationship between age, period and cohort implies the search for methods that bypass identifiability problem is both futile and pointless" [68]. In a similar vein, Holford states that "some current methods are completely arbitrary and only serve to obscure the real limitations in summarising time trends for disease" [107]. Clearly then, the purely mathematical solutions outlined in 3.4.4 provide only arbitrary interpretations; they are informed by algebraic rather than biological properties.

On the opposite end of the spectrum of solutions, non-identifiability may be resolved by the explicit introduction of detailed information regarding the biological basis of the disease. Multistage models have important applications in this area, particularly for cancers where, through advances in the understanding of molecular biology, the processes of carcinogenesis is more established, as they are for cancers of the lung [507] and large bowel [248]. Understanding of the disease process is however limited for many cancer forms, and ascertaining reasonable description of period and cohort trends, weak proxies as they are for their respective underlying determinants, need be achieved via other approaches.

Analyses should highlight rather than hide the identifiability problem. Estimable functions represent an honest and informative way to better understand temporal influences. Clayton and Schifflers advocate regular trend estimation and the search for identifiable functions. These ideas complement Holford's proposal that partitions the non-identifiable linear components and their identifiable curvature. This approach is flexible in that one can readily place the drift component with cohort or period explicitly and rather precisely. By specifying plausible assumptions regarding the linear trends of one time component, or by specifying a range of credible values, the nature of the identifiability problem is emphasised; presenting a range of solutions effectively steers the description, and the search for explanation, away from over-interpretation.

Selecting one set of effects would necessarily be arbitrary were it that specific information on the possible artefactual, biological and epidemiological factors involved were lacking. If however external knowledge from these sources can be brought to bear in support of a

particular choice of just one slope, all slopes are determined and, on adding curvature terms, provides a unique description of the age, period and cohort effects.

7.2 The utility of APC models in practice

Six Europe-wide studies of age, period and cohort trends in three cancers formed a major part of this thesis. The techniques used were informed by the recommendations in 3.5 (Table 7.1). Graphical descriptions of the observed trends involved C by A and P by A descriptions, and joinpoint regression was used to convey the recent trends in endometrial cancer incidence and mortality. Five of the studies focussed on APC modelling as an aid to graphical approaches in providing clues as to the underlying determinants. Recent and past estimates of the net drift were presented as per the recommendations.

Table 7.1: Specific methods applied to site-specific studies and relevant section where topic is discussed

Main recommendations for temporal analyses	Cervix Study I	Cervix Study II	Endometrium Study I	Endometrium Study II	Testis Study I	Testis Study II
Observed rates vs. period and cohort by age. Apply rules for presentation (0)	☑ (4.4.3.2)	☑ (4.5.3.6)	☑ (5.4.3.2)	☑ (5.5.3)	☑ (6.3.3)	
Joinpoint regression (3.2.3.2)			☑ (5.4.2 and 5.4.3.2)			
APC modelling to aid graphical approaches (3.3)	☑ (4.4.2 and 4.4.3)	☑ (4.5.2 and 4.5.3)		☑ (5.5.2 and 5.5.3)	☑ (6.3.2 and 6.3.3)	☑ (6.4.2 and 6.4.3)
Recent and past estimates of net drift (3.4.1.1.3)	☑ (4.4.3)	☑ (4.5.3)		☑ (5.5.3)	☑ (6.3.2)	
Use of Holford's approach and external biological information to provide unique solution (3.4.2)	☑ (4.4.2)	☑ (4.5.2.2)		☑ (5.5.2)	☑ (6.3.2)	☑ (6.4.2)
Second differences (3.4.3.1)	☑ (4.4.2.5)					
Spline regression (3.4.5.5)		☑ (4.5.2.2.2)				

Holford's approach required speculation with regards the slope of one effect. Where possible, the age slope was fixed; reasonable assumptions were introduced regarding the characteristics of the underlying age curves that were in keeping with the possible underlying biological mechanisms for the cancer under study. Such an approach was a prerequisite in investigating the trends of cervical squamous cell carcinoma incidence. By fixing the age slope to a value that produced well-documented unique age curves – assumed to follow the natural history of HPV infection – it was hypothesised that the period

and cohort parameters from the determined APC models would reflect the impact of screening and changing sexual behaviour, respectively.

Increasing risk in successive generations born after 1930 emerged in most European countries (possible exceptions being the Czech Republic, France, Sweden, and Switzerland), but well-organised screening programmes have been highly effective in reducing the overall incidence of cervical squamous cell carcinoma. Disconcertingly, cervical screening programmes have still not been implemented in certain European countries where rapid increases in risk in successive generations of women have been observed.

In providing a broad description of the trends and the separate impact of screening vs. HPV infection, the analytic approach worked reasonably well in providing an informative and realistic solution, but remains an arbitrary one, by definition. Two age curves with ages at peak incidence five years apart could provide rather different interpretations of the resulting period and cohort effects. There were difficulties in obtaining plausible age curves in some countries, related both to random variation associated with the underlying rates, and the short span of data available and the subsequent trends were less informative.

For cervical adenocarcinoma, there was less evidence for a steady stage age curve; instead the observation that screening had historically failed to detect pre-invasive disease of the adenocarcinoma subtype was considered, and an assumption of a period slope of zero was specified in the APC model. While increasing specificity over time of cervical cancer subtypes may have been responsible for some of the increases, the trends implicated both a changing prevalence of persistent infection with high-risk HPV types as well as the inability to detect cervical adenocarcinoma within screening programmes. Screening may have had a recent impact in reducing cervical adenocarcinoma incidence in the U.K., Denmark and Sweden during the 1990s.

Trends in endometrial cancer incidence also involved APC analyses and attempt to preserve an element of biological plausibility. In the presentation of one set of trends, the age slope was fixed to an age curve that was reasonably flat for the ages 65-69, 70-74, and 75-79 under the hypothesis that endometrial cancer increases with age were a consequence of unopposed oestrogens; and when opposed by progestins, at around the menopausal age, a large reduction and stability in risk of endometrial cancer follows. Although the assumption was plausible, the method was rather simplistic, and it was considered appropriate to compare the method with a solution assuming the changes in risk involved cohort influences, obtained on assuming a period slope of zero.

Trends in the observed rates – in combination with the two solutions from the APC model – provided evidence of changes in several established risk factors over time. In postmenopausal women, changes in HRT use (where prevalent), reproductive behaviour and prevalence of overweight and obesity may have partially accounted for the observed increases. COC use may have been responsible for declines observed among premenopausal women in more affluent European countries, but increases in obesity and decreases in fertility in Europe implies endometrial cancer will become a more common neoplasm among women of postmenopausal age in the future.

Age, period and cohort effects of testicular germ cell cancer incidence were presented using Holford's method on assuming the regular trend was taken up birth cohort, in line with biological and empirical evidence pointing to generational *in utero* or *early in life* influences as the major causes of cancer of the testes. It was still considered necessary however to simultaneously provide solutions that attributed half of the drift to period. For testicular cancer mortality, the introduction of effective treatment from the 1970s would have likely impacted on the increasing incidence in consecutive generations as a period effect. An approach to providing a solution or solutions was not easy to configure, but one intuitive solution was to take the converse of the approach to incidence –a period trend was first assumed, but a second solution allocated Holford's drift equally to period and cohort.

Geographical and temporal variations were apparent in testicular cancer incidence, but the average increases in rates of between 2% and 5% per year were in contrast with the corresponding declines in mortality, particularly in richer European countries. Short-term attenuations in increasing cohort-specific risk of incidence were indicated among men born between 1940-45 in seven European countries, with successive generations born from the mid-1960s possibly at a steadily declining risk of testicular germ cell cancer occurrence in Switzerland.

A more focussed study compared generation-specific trends of the main histological subtypes of testicular germ-cell cancer, hypothesising that analogous trends by birth cohort implied seminoma and non-seminoma had a largely similar aetiology. Cohort effects were again assumed to dominate, and a zero period slope fixed in the APC model. The subtype trends were indeed rather comparable on a cohort scale. It was speculated that on a period scale, departures from the uniform increases in testis cancer overall would occur for the more aggressive non-seminomas some years ahead of seminoma.

Each of these chapters closed with a discussion of approaches that might be considered in future studies, and this thesis does not pretend to provide a definitive analysis of trends by age, period and cohort for these sites. This work may be seen as analytic in terms of the

modelling strategies, but it remains necessarily descriptive in its interpretation. Each of the studies hopefully will act as a template for further developments that tailor APC analyses towards the inclusion of pertinent biological and epidemiological information, where available. More systematic and quantifiable approaches to APC modelling are certainly warranted. These may have particular application in the study of subtypes of both cervical and testicular cancer, for which a shared aetiology seems likely, as was outlined in Chapters 5 and 6 respectively. The final section deals with the possibilities of achieving a truly systematic approach to time trend analyses of cancer rates.

7.3 The utility of systematic approaches in practice

An integrated approach to data collection, analysis and presentation facilitates comparison and objective interpretation; insights into cancer may be derived from the variability in trends between and within subgroups. In this thesis, the need for a systematic approach to data collection, analysis and presentation was considered from the outset, and the intention was to systematically analyse trends both in terms of the populations and cancers under investigation. In reality however, only the analyses across countries could be considered as systematic: there was consistency in aspects of the collection of data (inclusion criteria), analysis (single methodology) and presentation (uniform graphical and tabular descriptions). Controlling these analyses across populations for a given disease is necessary if one is to critically compare temporal variations in different populations and interpret these differences in terms of the factors that may have produced the observations. The temporal analyses did not however impose such a limitation on analyses across the three cancer sites. In part, this reflected a requirement to adapt methods to answer research hypotheses that were specific to the cancer under investigation. More fundamentally, a customised approach to these analyses reflected the importance of bringing to bear external information on the biology or epidemiology specific to the cancer under study. Given the heterogeneous nature of the disease entities that comprise the cancer types under study, it would have been inappropriate to do otherwise.

It is worth considering previous large studies examining broad groups of cancers in one or more populations and assessing the degree to which a systematic approach can be applied in practice. Two compilations of time trends of incidence and mortality of multiple sites published 1993-94 varied substantially in this respect [8,113]. Coleman and colleagues published a strictly systematic attempt at the analysis of worldwide trends of the major cancers in four continents [8], with a consistent APC modelling approach and presentation undertaken by five authors. The results, although comprehensive and comparable, were highly processed, and may have suffered from a lack of basic description of the observed

data, and the absence of tailored analyses specific to particular cancer types and/or populations. Dealing as it did with over 2000 sub-analyses however, the study demonstrates a very understandable motive for a strictly systematic approach: the need to efficiently process large amounts of information.

The editorial process in the monograph by Doll *et al* allowed considerably more flexibility; each chapter was left to a designated cancer-specific expert or experts to decide on the selection of data, the presentation format and interpretation [113]. The result of which was a rather disparate set of studies on cancer-specific trends: very different approaches to the graphical and statistical display of trends were provided in each chapter, yet this often enabled a much more detailed exposition of the trends of specific cancers, centred around the authors' hypotheses and interests.

Several publications have examined cancer incidence and mortality trends in one country using relatively systematic but more descriptive approaches [23,208]. One interesting initiative by Rouch *et al* was to provide sets of parameter estimates for each subgroup analysis as an Appendix, thus enabling the interested reader to reconstruct the trends according to a different set of model constraints [208]. Others have published brief descriptive reviews of mortality trends in Europe [508] using a specific APC modelling technique [120].

Some of the inconsistencies in the Doll *et al* monograph are perhaps also embedded in the work in this thesis; the analytic components of the six studies that comprise Chapters 4 to 6 are neither consistent between cancer sites, subtype or the measure investigated (incidence, mortality), as seen in Table 7.1. The underlying importance attached to addressing biological and epidemiological evidence on a site-by-site basis may explain some of the disparity. In the sprit of the Doll *et* al book, the work in this thesis also involved numerous collaborators in three cancer-specific working groups (see Appendix 2). Although the aims and methods were set out *a priori* (by the first author), collaboration naturally allowed constructive comments, opinions and ideas that may have altered certain aspects of the analysis and presentation of the data.

This work has then raised the question of whether a single methodological approach can be applied to multiple cancer sites. It is clearly problematic to make a systematic approach given that a temporal analysis of two cancer sites may differ in a number of respects. The analyses in this thesis incorporated (where informative) trends in the major histological subtypes. For cervical cancer, differences in screen detection and (possibly) aetiology drive the need for stratification. For testicular germ cell cancer the main subtypes appear to be similar; confirmation was sought on the basis of cohort trends in different countries.

Hypotheses based on existing knowledge will drive the type of temporal analyses necessary to answer them, and these must reflect the possible artefacts, major risk factors, interventions and prospects for prevention; these clearly differ considerably between cancer sites, anatomical subsites and histological subtypes, and so forth.

The utility of temporal analyses and their application to the study of cancer is evident from the hundreds of pivotal time trends studies published over the last 50 years, and such investigations will continue to be of fundamental value in the next half century. This thesis provides a small contribution to maintaining this outlook. It has reviewed and recommended graphical and statistical approaches to the analysis of cancer trends, and applied these in practice. One may hope, if not anticipate, that these will be given due consideration in future studies of time trends. In particular, optimal returns from the APC model will require a shift of emphasis from ambiguous choices of presentation, to those that consider what is known regarding the cancer in question. Our ever-expanding understanding of the biology and epidemiology of the disease should certainly provide for this necessary change from arbitrariness to enlightenment.

Appendix 1: Peer-reviewed articles published as a result of this research

Chapter 4: Cervical cancer

Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Møller H, Hakama M, Parkin DM. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev 2005;14(3):677-86.

Bray F, Carstensen B, Møller H, Zappa M, Primic Žakelj M, Lawrence G, Hakama M, Weiderpass E. Incidence trends in adenocarcinoma of the cervix in 13 European countries, Cancer Epidemiol Biomarkers Prev, 2005;14(9).

Chapter 5: Endometrial cancer

Bray F, Loos A, Oostindier M, Weiderpass E. Geographical and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and post-menopausal women in Europe, Int J Cancer;117(1):123-31.

Bray F, Møller H, dos Santos Silva I, Weiderpass E. Endometrial cancer incidence trends in Europe: underlying determinants and prospects for prevention. Cancer Epidemiol Biomarkers Prev, 2005;14(5):1132-42.

Chapter 6: Testicular cancer

Bray F, Richiardi L, Ekbom A, Pukkala E, Cuninkova M, Møller H. Trends in testicular cancer incidence and mortality in Europe: continuing increases in incidence but further declines in mortality. Int J Cancer, *in press*.

Bray F, Richiardi L, Ekbom A, Forman D, Pukkala E, Cuninkova M, Møller H. Do testicular seminoma and non-seminoma share the same aetiology? Evidence from age-period-cohort analysis of incidence trends in eight European countries. Cancer Epidemiol Biomarkers Prev, *in press*.

Appendix 2: Declaration and acknowledgement of co-investigators

The research was undertaken whilst F Bray embarked on a collaborative time trends project at the International Agency for Research on Cancer (IARC), Lyon, France. The research was part of the objectives of Comprehensive Cancer Monitoring Project (CaMon) project funded by the European Commission, Agreement No. SI2.327599 (2001CVG3 – 512), involving analysis of time trends of incidence of, and mortality from specific cancers in Europe.

The research undertaken in the Chapters 1 through 3 was constructive in establishing the methodology in the time trends project. The analysis and interpretation of time trends in Chapter 4 through 6 are the consequence of F Bray applying the main outcomes and conclusions of these chapters to provide original analyses of European incidence and mortality data for the three cancers specified. These three chapters formed the basis of six papers disseminated in peer-reviewed journals by a collaborative writing groups that consisted of an IARC secretariat, enlisted cancer registry personnel, and a senior epidemiologist who acted as coordinator of the activity. F Bray was substantially involved in the planning, analysis and interpretation stages of each paper, and wrote the first and subsequent drafts leading to submission and the publications cited in Appendix 1.

The three chapters and the articles are a product of a successful collaboration with numerous researchers in each of the Working Groups and the European cancer registries whom contributed not only their incidence data, but also expert commentary on the final draft of the manuscript:

Cervical Cancer Working Group

Marc Arbyn
Bendix Carstensen
Anja Loos
Gill Lawrence
Peter McCarron
Henrik Møller
Maja Primic Žakelj
Elisabete Weiderpass Vainio
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Endometrial Cancer Working Group

Isabel dos Santos Silva
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Testicular Cancer Working Group

Lorenzo Richiardi
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David Forman
Martina Cuninkova
Henrik Møller

The European Network of Cancer Registries (Director in parentheses)

Czech Republic – Czech National Cancer Registry, Prague (Dr Marie Jechová)

Denmark – Danish Cancer Registry, Copenhagen (Dr Hans H. Storm)

Estonia – Estonian Cancer Registry, Tallinn (Dr Tiiu Aareleid)

Finland – Finnish Cancer Registry, Helsinki (Dr Timo Hakulinen)

France – Registre Bas Rhinois des Cancers, Strasbourg (Dr Michel Velten), Registre Général des Tumeurs du Calvados, Caen (Dr J. Macé-Lesech), Registre des Tumeurs du Doubs, Besançon (Dr Arlette Danzon), Registre du Cancer de l'Isère, Meylan (Dr François Ménégoz), Registre du Cancer de la Somme, Amiens (Mme Nicole Raverdy), Registre des Cancers du Tarn, Albi (Dr Martine Sauvage)

Germany – Saarland Cancer Registry Saarbrücken (Mr Hartwig Ziegler)

Iceland – Icelandic Cancer Registry, Reykjavik (Dr Laufey Tryggvadottir)

Italy – Registro Tumori Toscano, Florence (Dr Eugenio Paci), Registro Tumori Lombardia (Provincia di Varese), Milan (Dr Paolo Crosignani), Registro Tumori della Provincia di Parma (Dr Vincenzo De Lisi), Registro Tumori della Provincia di Ragusa, Ragusa (Dr Rosario Tumino), Piedmont Cancer Registry, Turin (Dr Roberto Zanetti)

The Netherlands – Eindhoven Cancer Registry, Eindhoven (Dr Jan Willem Coebergh), Maastricht Cancer Registry, Maastricht (Dr Miranda Dirx)

Norway – Cancer Registry of Norway, Oslo (Dr Frøydis Langmark)

Poland – Cracow Cancer Registry, Cracow (Dr Jadwiga Rachtan), Lower Silesian Cancer Registry, Wroclaw (Mr Jerzy Blaszczyk), Warsaw Cancer Registry, Warsaw (Dr Maria Zwierko)

Slovakia – National Cancer Registry of Slovak Republic, Bratislava (Dr Ivan Plesko)

Slovenia – Cancer Registry of Slovenia, Ljubljana (Dr Maja Primic-Zakelj)
Spain – Tarragona Cancer Registry, Reus (Dr Jaume Galceran), Registro de Cáncer de Granada, Granada (Dr Carmen Martínez Garcia), Registro de Cáncer de Murcia, Murcia (Dr Carmen Navarro Sánchez), Registro de Cáncer de Navarra, Pamplona (Dr E. Ardanaz Aicua), Zaragoza Cancer Registry, Zaragoza (Dr Carmen Martos Jimenez)
Sweden – Swedish Cancer Registry, Stockholm (Dr Lotti Barlow)
Switzerland – Krebsregister Basel-Stadt und Basel-Land, Basle (Dr Gernot Jundt), Registre Genevois des Tumeurs, Geneva (Dr Christine Bouchardy), Registre Neuchâtelois des Tumeurs, Neuchâtel (Dr Fabio Levi), Krebsregister St Gallen Appenzell, St Gallen (Dr Thomas Fisch), Registre Vaudois des Tumeurs, Lausanne (Dr Fabio Levi), Kantonalzürcherisches Krebsregister, Zürich (Dr Nicole Probst)
United Kingdom – National Cancer Intelligence Centre, London (Dr Mike Quinn), Scottish Cancer Intelligence Unit, Edinburgh (Dr David Brewster)

Appendix 3: R Program and graphical output: Holford's zero period slope

#set directory and bring in data and R functions

```
setwd("c:/ttdata/bladder.it")
library(Epi)
source("C:/ttprogs/tt.R")
bladder<-read.table("bladder.txt",header=T)
```

calculate cohort, and specify age, period and cohorts as factors

```
bladder<-transform(bladder,cohort = period - age)
bladder<-transform(bladder, A=factor(age), P=factor(period), C=factor(cohort))
attach(bladder)
```

index age, period and cohort such that sum of effects is zero

```
sumzero_a<-((age-min(age))/5+1) - mean((age-min(age))/5+1)
sumzero_p<-((period-min(period))/5+1) - mean((period-min(period))/5+1)
sumzero_c<-((cohort-min(cohort))/5+1) - mean((cohort-min(cohort))/5+1)
```

calculate number of levels for age, period and cohort

```
max_a<-max((age-min(age))/5+1)
max_p<-max((period-min(period))/5+1)
max_c<-max((cohort-min(cohort))/5+1)
```

fit APC models using orthogonal contrasts with period and cohort slopes both included

```
pc_APC<- glm(D/Y~sumzero_p+sumzero_c+C(A,contr.orth,how.many=max_a-
2)+C(P,contr.orth,how.many=max_p-2)+C(C,contr.orth,how.many=max_c-2),
family=poisson,weights=Y)
rep1<-report.coef(pc_APC,round=2,exp=FALSE)
```

#get "true" slopes from relationship between biased ones

#biased_slope_a=true_slope_a+v

#biased_slope_p=true_slope_p-v

#biased_slope_c=true_slope_c+v

#extract biased period and cohort slopes from the model

```
biased_slope_p<-(report.coef(pc_APC,subset="sumzero_p",exp=FALSE))[1]
biased_slope_c<-(report.coef(pc_APC,subset="sumzero_c",exp=FALSE))[1]
```

#assume "true" period slope is equal to..zero

```
true_slope_p <- 0
```

#so v now determined..

```
v <-  true_slope_p - biased_slope_p
```

#..and can be used to obtain "true" cohort slope

```
true_slope_c <- biased_slope_c - v
```

still need to obtain "true" age slope, same procedure but with age and cohort slopes estimated in APC model

```
ap_APC<-glm(D/Y~sumzero_a+sumzero_p+C(A,contr.orth,how.many=max_a-
2)+C(P,contr.orth,how.many=max_p-2)+C(C,contr.orth,how.many=max_c-2),
family=poisson,weights=Y)
rep2<-report.coef(ap_APC,round=2,exp=FALSE)
biased_slope_a<-(report.coef(ap_APC,subset="sumzero_a",exp=FALSE))[1]
true_slope_a <- biased_slope_a - v
```

#overall curvature obtained by applying, for each effect, the design matrix, orthogonal to Holford drift, to the regression parameters

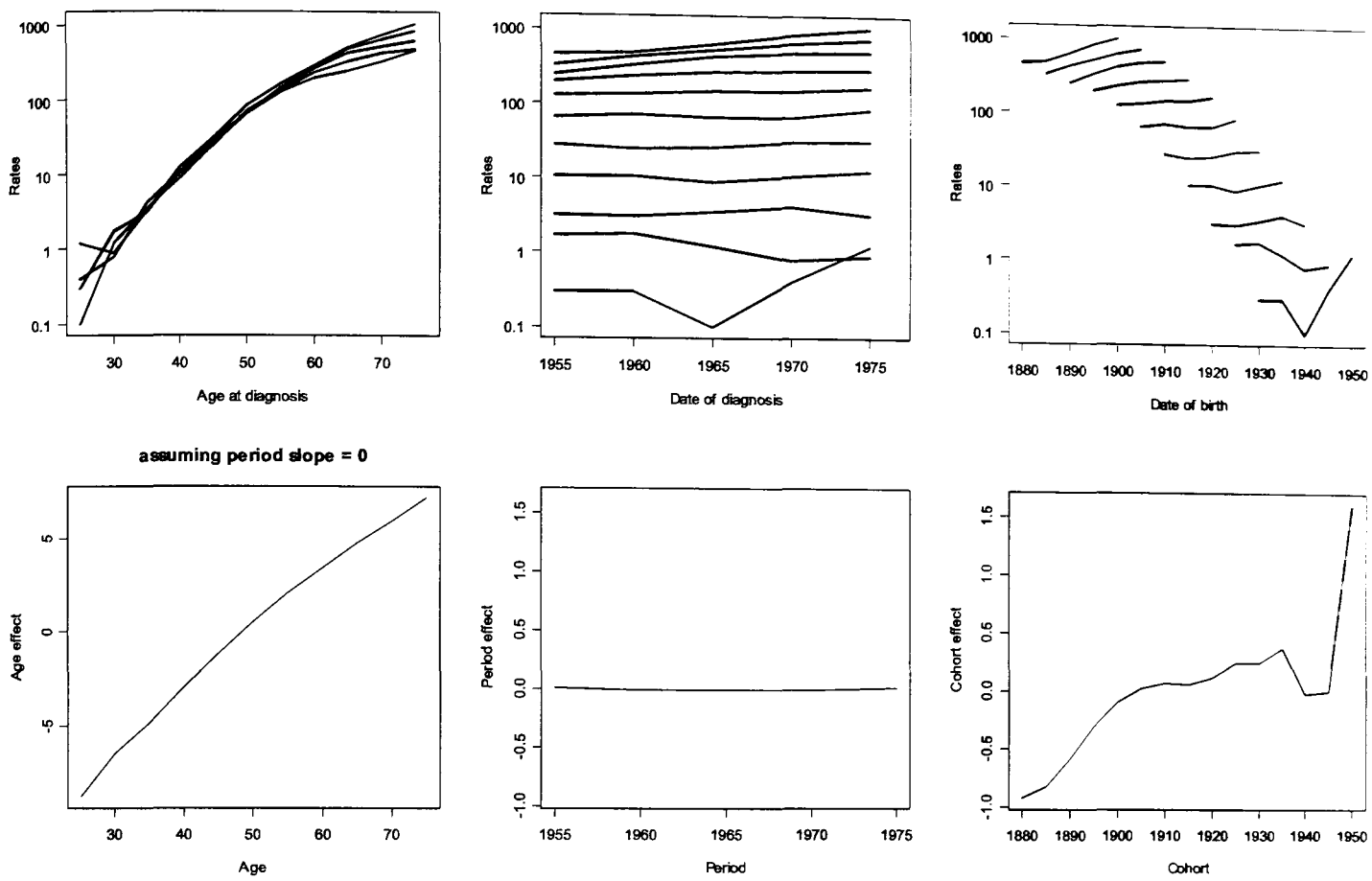
```
ACURV<-contr.orth(max_a)%*%as.matrix(report.coef(pc_APC,subset="A,",exp=FALSE)[,1])
PCURV<-contr.orth(max_p)%*%as.matrix(report.coef(pc_APC,subset="P,",exp=FALSE)[,1])
CCURV<-contr.orth(max_c)%*%as.matrix(report.coef(pc_APC,subset="C,",exp=FALSE)[,1])
```

#individual categories of each effect found by adding together corresponding linear and curvature components

```
effect_a=true_slope_a*sort(unique(sumzero_a))+ACURV
effect_p=true_slope_p*sort(unique(sumzero_p))+PCURV
effect_c=true_slope_c*sort(unique(sumzero_c))+CCURV
```

#table of 3 x 2 graphs, top is observed, bottom is effects based on assumed slope of one effect

```
bl.rate <- tapply( D, list(age,period), sum ) / tapply( Y, list(age,period), sum )
par( mfrow=c(2,3) )
rateplot( bl.rate*10^6, at=10^(-1:3), labels=c(0.1,1,10,100,1000),which="AP" )
rateplot( bl.rate*10^6, at=10^(-1:3), labels=c(0.1,1,10,100,1000),which="PA" )
rateplot( bl.rate*10^6, at=10^(-1:3), labels=c(0.1,1,10,100,1000),which="CA" )
xa<-sort(unique(age))
plot(xa,effect_a,"l",ylab="Age effect", xlab="Age")
xp<-sort(unique(period))
plot(xp,effect_p,"l",ylab="Period effect", xlab="Period",ylim = range(effect_c),
title("assuming period slope = 0"))
xc<-sort(unique(cohort))
plot(xc,effect_c,"l",ylab="Cohort effect", xlab="Cohort", ylim = range(effect_c))
```



Graphical output from R on running above program. Bladder cancer incidence data in men in Italy 1955-79 (source: Clayton and Schiffflers, 1987). Top: observed rates vs. age by period (left), vs. period by age (middle) vs. cohort by age (right). Bottom: on assuming a period slope of zero, APC model effects for age (left), period (middle), cohort (right) NB *contr.orth* was written in **R** by Dr Bjørn Møller [205] after Holford [66].

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