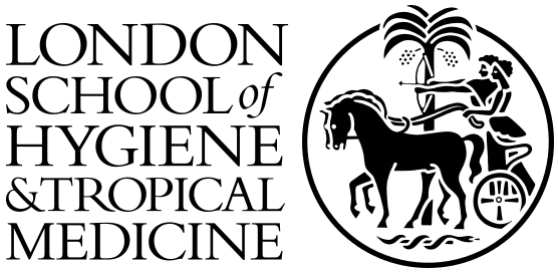

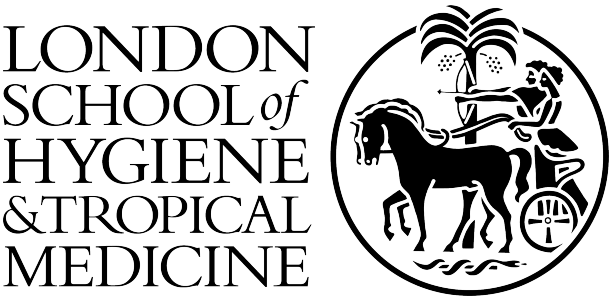

Inequalities in cancer care in England: from diagnosis to treatment

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Declaration of Authorship

I, Aimilia Exarchakou, declare that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Cancer is among the leading causes of death and morbidity worldwide. Although it is a disease that predominantly affects older people, cancer incidence is increasing among adolescents and young adults. In the UK, cancer outcomes have been historically lagging behind other comparable countries and wide geographical and socio-economic inequalities have been observed within the country.

The aim of this PhD is 1) to explore the increasing incidence of cancer among young adults and 2) to describe socio-economic inequalities in cancer outcomes in England. The second aim also entails the estimation of the societal and economic impact of those inequalities and identifying what may be some of the contributing health-system components.

The main data source for most analyses was the National Cancer Registration Dataset, enriched with information from Hospital Episode Statistics (HES) in some publications. Socio-economic deprivation of cancer patients was determined by the ecological English Index of Multiple Deprivation (IMD). A wide range of advanced statistical methods was used, including non-parametric approaches in the estimation of cancer survival and of alternative measures of cancer survival, the pseudo-observation approach in the estimation of crude probabilities of death due to cancer, hierarchical modelling and penalised regression.

For the first aim, I describe trends of colorectal cancer incidence rates in England, focusing on differences by anatomical sub-site and socio-demographic characteristics, particularly age (Research Paper 1). The findings pointed to a steep increase in colorectal cancer incidence among young adults aged 20-39 years in contrast to an overall stabilising trend in older adults. The reasons for these trends remain largely unknown, with most mechanisms pointing to a combination of genetic and lifestyle factors.

For the second aim, I set out to assess the effectiveness of the 2000 NHS Cancer Plan and of subsequent strategies in reducing the difference in cancer survival between the most and the least deprived cancer patients in England (Research Paper 2). Despite an overall improvement in cancer survival over time, survival in the most deprived remained consistently lower than in the least deprived.

I estimated the impact of these socio-economic inequalities on the Number of Life-Years Lost (NLYL) due to cancer (Research Paper 3). For the vast majority of cancers, the most deprived patients lost more life-time than the least deprived and the largest differences were seen mostly in young adults with poor prognosis cancers.

Finally, I explored the role of health care system factors on socio-economic inequalities in prompt diagnosis and receipt of treatment. More deprived colon cancer patients

used the emergency services more often, presenting with non-specific symptoms or conditions (Research Paper 4). Further, there was wide variation in resection rates and survival from pancreatic cancer between the 23 specialist centres in England where all pancreatic cancer resections are centralised (Research Paper 5). Resection rates for pancreatic cancer remained low at national level.

In summary, socio-economic inequalities in cancer outcomes have been persistent in England, costing in lives and resources. My PhD dissertation highlights that delays in diagnosis among more deprived cancer patients may be related to health-system barriers in accessing primary and secondary care. Substantial geographical variation in the resection rates for pancreatic cancer points to further barriers in access to treatment, potentially related to distance and travel time. Future cancer policies and interventions should prioritise inequalities and focus on building a health care system that removes barriers in access for all under-served populations.

Acknowledgements

This PhD is a summary of my research on cancer inequalities during the last 7 years. The work would not have been possible without the support of my mentors and colleagues at Cancer Survival Group (CSG) and Inequalities in Cancer Outcomes Network (ICON) research groups at LSHTM.

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Finally, I would like to thank my family for teaching me to persevere and follow my dreams. I am grateful to my husband Lefteris, who has been there for me through thick and thin.

Contents

Abbreviations

AIC	**A**kaike **I**nformation **C**riterion
AYAs	**A**dolescents and **Y**oung **A**dults
CAS	**C**ancer **A**nalysis **S**ystem
CCG	**C**linical **C**ommissioning **G**roup
CMO	**C**hief **M**edical **O**fficer
CPr	**C**rude **Pr**obability of Death
CPRD	**C**linical **P**ractice **R**esearch **D**atalink
CRC	**C**olo-**R**ectal **C**ancer
CSG	**C**ancer **S**urvival **G**roup
DAG	**D**irected **A**cyclic **G**raph
DALYs	**D**isability-**A**djusted **L**ife-**Y**ears
EP	**E**mergency **P**resentation
FDA	**F**ood **D**rug **A**dministration
FPM	**F**lexible **P**arametric **M**odelling
GDP	**G**ross **D**omestic **P**roduct
GP	**G**eneral **P**ractitioner
HEA	**H**ospital **E**mergency **A**dmissions
HES	**H**ospital **E**pisode **S**tatistics
HPB	**H**epato-**P**ancreato-**B**iliary
HRQoL	**H**ealth-**R**elated **Q**uality **o**f **L**ife
ICB	**I**ntegrated **C**are **B**oard
ICBP	**I**nternational **C**ancer **B**enchmarking **P**artnership
ICON	**I**nequalities in **C**ancer **O**utcomes **N**etwork
ISCB	**I**nternational **S**ociety for **C**linical **B**iostatistics
LRT	**L**ikelihood **R**atio **T**est
LSHTM	**L**ondon **S**chool of **H**ygiene & **T**ropical **M**edicine

LSOA	**L**ower Layer **S**uper **O**utput **A**rea
NHS	**N**ational **H**ealth **S**ervice
NICE	**N**ational **I**nstitute for Health and **C**are **E**xcellence
NLYL	**N**umber of **L**ife-**Y**ears **L**ost
OECD	**O**rganisation for **E**conomic and **C**o-operation **D**evelopment
ONS	**O**ffice for **N**ational **S**tatistics
PCT	**P**rimary **C**are **T**rust
PNET	**P**ancreatic **N**euroendocrine **T**umours
P-P	**P**ohar-**P**erme
PSA	**P**rostate **S**pecific **A**ntigen
PVS	**P**urposeful **V**ariable **S**selection
QALY	**Q**uality-**A**djusted **L**ife-**Y**ears
QoL	**Q**uality **O**f **L**ife
SEER	**S**urveillance, **E**pidemiology, and **E**nd **R**esults
SDGs	**S**ustainable **D**evelopment **G**oals
TWW	**T**wo-**W**eek **W**ait
UHC	**U**niversal **H**ealth **C**overage
UN	**U**nited **N**ations
VPF	**V**alue of **P**revented **F**atality
WHO	**W**orld **H**ealth **O**rganization
WSI	**W**ider **S**ocietal **I**mpact
WTP	**W**illingness **T**o **P**ay

This work is dedicated to every person affected by cancer.

Part I

Commentary

Chapter 1

Epidemiological Context

1.1 Health inequalities: the challenge of Universal Health Coverage

"The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition."

Constitution of the World Health Organization (WHO), 1948

Shortly after World War II, the United Nations (UN) acknowledged that except for peace, population health was to be restored and maintained, and in 1948, the Constitution of the WHO established Universal Health Coverage (UHC) as the foundation of its identity and mandate. All UN Member States signed and committed to take action towards ensuring that people, independently of their socio-economic, demographic or cultural characteristics can receive the essential health services they need, when they need it, without financial hardship. Under UHC, people can expect to access health services related to all stages of care, from health promotion and prevention to treatment, post-treatment and palliative care.

Achieving UHC and the health-related aims, as envisioned by WHO, specific and measurable goals were required. This led to the adoption of the Sustainable Development Goals (SDGs) in September 2015, with all 191 UN Member States committing to a global partnership to end poverty, hunger, inequalities, promote economic growth and sustainable development. Among the 17 goals, SDG 3 called for "Good Health and

Well-Being" and invited all UN Member States to ensure healthy lives and promote well-being for all at all ages and work towards achieving UHC.

Since then, the world has faced numerous challenges, including disease outbreaks, pandemics, conflicts, poverty and natural disasters that affected the health of millions. Almost a decade later, we are far from achieving the health-related SDGs and uneven progress between and within countries means that health inequalities are fast widening. Still, 99% of annual maternal deaths worldwide affect only the developing countries and half of all new HIV infections in the US occur among African Americans whilst they only comprise about 13% of the population [1]. In the UK, life expectancy in London decreases dramatically the further to the east one lives [2] and in Glasgow the difference in life expectancy is more than 10 years between the most and the least deprived neighbourhoods [3].

By definition, health inequities are the avoidable and unfair differences in people's health across and between population groups. In a world where UHC is the mandate, the individuals, communities and countries most in need, continue to experience disproportional difficulties in accessing health services [4], either due to availability or affordability constraints or due to organisational barriers. These inequities incur a cost in lives and resources, hinder societal progress and often contribute to violence and war.

In the UK, the National Health Service (NHS) was established in 1948. The NHS, a healthcare system based on UHC principles, was built with the aim to provide healthcare services that are free for all at the point of delivery. However, inequalities in ill-health and death rates between social classes were soon revealed. In 1980, the publication of the Black report [5], mandated by the Labour government and led by Sir Douglas Black, president of the Royal College of Physicians, was the first authoritative look on inequities in health. The report found that ill-health and death are unequally distributed among the population of Britain and suggested that these inequalities have been widening rather than diminishing since the establishment of the NHS. It concluded that the inequalities were not caused by poverty, education or lifestyle, but by lack of measures to ensure equal access to health services. The recommendations made in

this report were not well received by the Conservative government that took over shortly after, mainly due to the scale of expenditure proposed.

Since then, despite notable overall improvements in population health indicators, such as life expectancy, health inequalities remained. In recent years, the UK was faced with a stalling life expectancy - especially among women of more deprived areas, an alarming rise in infant mortality and widening inequalities in mortality from a range of causes [6]. In 2018–20, the life expectancy of people living in the 10% most deprived areas in England was almost a decade shorter than people living in the 10% least deprived areas [7]. One of the largest contributors to the social gradient in health outcomes are non-communicable diseases and in particular, cancer [8].

1.2 Cancer inequalities in the UK

Cancer is among the leading causes of morbidity and mortality in the UK, alongside cardiovascular disease (CVD), stroke and neurological disorders [9] accounting for around 30% of total deaths [10]. Poor cancer outcomes combined with geographical or socioeconomic inequalities in cancer outcomes prompted the publication of the Calman-Hine report in 1995 [11], the first-ever policy to tackle cancer and improve the quality of care in England and Wales. Since then, several other strategies [12] followed, including the first ever NHS Cancer Plan introduced in 2000 [13]. These strategies aimed to improve cancer survival to levels of other comparable countries and reduce inequalities in cancer care and outcomes.

A few large-scale international and European comparative cancer survival studies such as the EUROCARE [14] and CONCORD [15] in the late 2000s, showed that cancer survival in the UK was still consistently lower than in other comparably wealthy countries with UHC health systems. In 2009, the Department of Health in England initiated the International Cancer Benchmarking Partnership (ICBP), as a means to bring together expertise and inform policy on cancer survival across high-income countries [16].

Since then, cancer survival in England has continued to improve steadily [17, 18] as a result of an overall improvement in cancer care and a series of strategies and initiatives implemented by the government. However, it still lags behind other countries [18–20].

In terms of socio-economic inequalities, little progress has been made. Between 1996 and 2013, one-year cancer survival in the most socio-economically deprived patients remained consistently lower than in the least deprived, and for some cancers, this difference even slightly widened [21, 22]. Whilst the inequalities component has been among the aims of most cancer policies implemented in England, the focus has been mainly on modifying health behaviours such as reducing smoking rates, alcohol consumption and obesity or targeting awareness and beliefs about cancer. However, there may be structural components of people's health such as the environment where they live and work and barriers to accessing the healthcare system, that contribute to those inequalities.

1.3 PhD Aim

The aim of this PhD is two-fold: (1) to describe the increasing burden of cancer among young adults and (2) to explore the socio-economic inequalities in cancer in England and the contributing health-system factors. I will describe inequalities based on socio-demographic characteristics in the diagnostic and treatment phases of the cancer pathway.

The cancer pathway is the patient's journey from the initial suspicion of cancer, through clinical investigations, patient diagnosis, treatment and post-treatment management. It usually includes the pre-diagnostic, diagnostic, treatment/management and survivorship phases [23]. This distinction is partly because the commissioning and organisation of the cancer services are provided by different NHS bodies, either more centralised or more local to the communities.

Throughout the thesis, referring to Figure 1.1 from Morris *et al* (2020) [23], will help to contextualize the healthcare system factors that contribute to the observed inequalities.

This is a simplified version of the cancer patient pathway based on the clinical pathways developed by the National Institute for Health and Care Excellence (NICE) in the UK, and cancer patient journeys described in the literature. The authors also slightly adapted the patient pathway to reflect patient journeys in other ICBP countries.

Chapter 2 gives an overview of the methods either used in the publications or as an extension of the work, with emphasis on their application, usefulness and interpretation, rather than the technical details and the mathematics. Chapter 3 of the dissertation gives the context of the changing epidemiology and the growing burden of cancer. Chapter 4 is on socio-economic inequalities in cancer survival in England and their societal and economic impact. Chapter 5 explores some of the health system factors that contribute to inequalities occurring in the diagnostic and treatment stages of the cancer pathway. There are five published research papers included in the portfolio, described in order of relevance to the chapters.

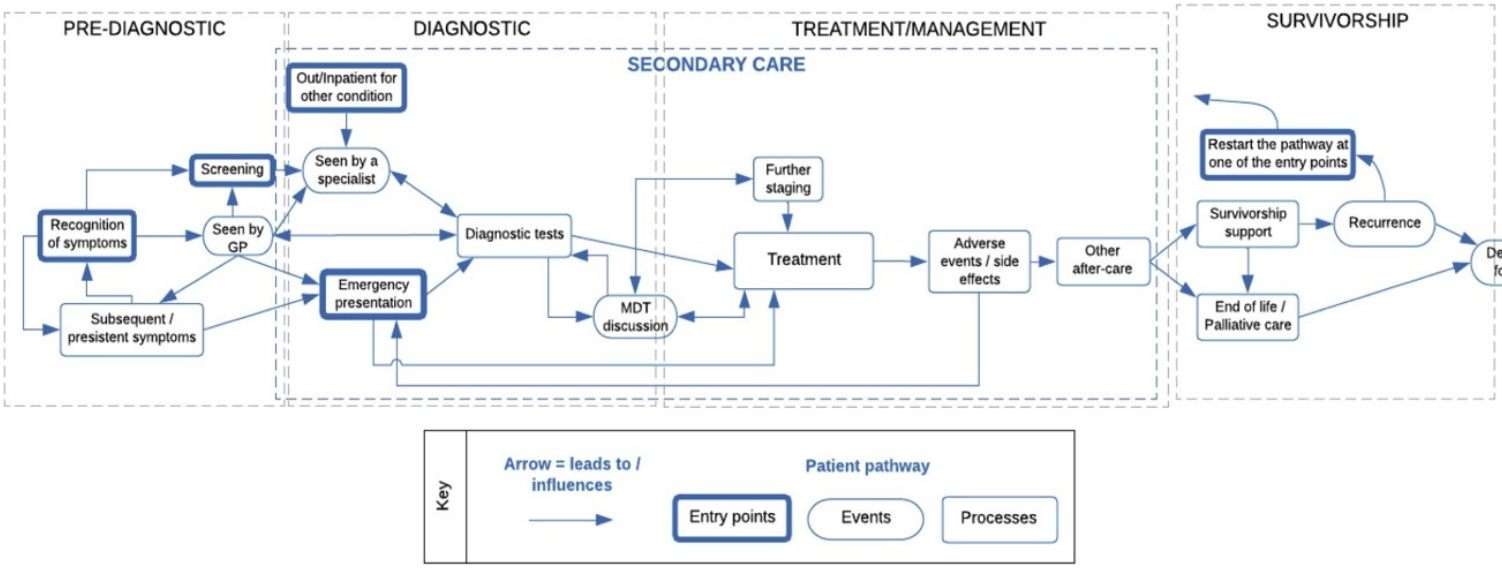

FIGURE 1.1: The Cancer Pathway

Morris et al, Journal of Cancer Policy (2020)

Chapter 2

Data and Methods

2.1 Data

Cancer records

Across all publications, the main source of data used was the National Cancer Registration Dataset, currently owned and maintained by NHS England [24]. The database is a comprehensive collection of all cancer registrations in England since 1971, and it includes information on cancer patient demographics, tumour characteristics, diagnostic details and vital status. Over time, the dataset was enriched with more accurate and detailed information on the tumour characteristics and expanded to include treatment information [25]. It is considered of high completeness as it is constantly updated and maintained at a high standard.

Detailed information on cancer patients' admissions to NHS hospitals was derived from Hospital Episode Statistics (HES) records [26]. The HES database, also owned by NHS, includes demographic, clinical, administrative and geographic information for all NHS patients. HES records comprise episodes which describe a period of time under the care of the same consultant within a particular speciality at a single hospital provider. Episodes are nested within spells, which describe a patient's entire stay in one hospital from admission to discharge. The linkage between the cancer registry and HES datasets was deterministic, based on patient and tumour pseudo-identification.

Socio-economic deprivation

Socio-economic deprivation of cancer patients was based on the English Index of Multiple Deprivation (IMD) [27], an ecological measure of relative deprivation. The IMD consists of seven sub-domains of deprivation, namely income, employment, education, skills and training, health deprivation and disability, crime, barriers to housing and services and living environment. Small administrative areas in England called Lower Layer Super Output Areas (LSOAs) are ranked based on a weighted summary IMD score from the most to the least deprived. Across all publications in the portfolio, socio-economic deprivation of cancer patients was determined by the income domain only. Cancer patients were assigned to a quintile of deprivation (from the first quintile i.e., Q1 being the "least deprived" quintile to the fifth quintile i.e., Q5, being the "most deprived") based on the LSOA of residence at the time of cancer diagnosis.

Socio-economic inequalities in cancer care and outcomes may occur due to a combination of individual and contextual factors. Access to timely and optimal cancer care may be affected by patient-related factors such as symptom awareness, language and cultural characteristics or patient's overall health and well-being. Simultaneously, factors outside of patient's direct control such as their area of residence or work and family circumstances, can equally determine cancer outcomes through for example, distance to the closest hospital, availability of out-of-hours GP appointments in the area of residence or lack of social support to attend medical appointments. As an ecological measure of deprivation, the IMD index and its sub-domains represent a summary of the contextual circumstances where people live. It can be useful to describe and suggest overall patterns of deprivation and give some indication as to which of the individual factors are in play.

The income domain of the IMD measures the proportion of the population in an area experiencing deprivation relating to low income. The use of the income domain only as a proxy for socio-economic deprivation, is based on technical and interpretation attributes. Although it is a contextual characteristic, it may reflect the individual income and socio-economic status better than other domains due to less residual confounding.

Moreover, excluding components about access to public services and therefore access to healthcare can prevent misinterpretation due to the strong association of these characteristics with inequalities in cancer survival [28]. Technically, the income domain has the highest degree of agreement with the overall composite IMD measure [29].

2.2 Measures of cancer burden: usefulness and interpretation

In cancer epidemiology, different measures are used to describe the cancer burden and evaluate cancer outcomes. Among the most common indicators routinely reported by the statistical authorities of individual countries or larger policymaker organisations are cancer incidence and mortality in the general population and cancer survival in the cancer population. These indicators are particularly useful in casting light on different dimensions of the cancer epidemic and help identify areas for improvement.

2.2.1 Cancer Incidence and Mortality

Incidence refers to the rate or frequency of disease occurrence in a population over a specified time period. Whilst cancer occurrence at the individual level may have a biological explanation, for example, genetic changes or hereditary mutated genes, cancer incidence at the population level may be driven by a demographic transition, such as population ageing, or a change in certain environmental and lifestyle risk exposures. A historical example of the latter was the discovery of the association between tobacco smoking and lung cancer. Dr. Isaac Adler, a physician from the US, observed an increase in lung cancer cases among smokers back in the 19^{th} century. Scholars of the period researched the idea more formally and noted that the rise in cigarette consumption paralleled the increase in lung cancer cases [30]. Since then, it has been established that tobacco smoking is a cause of lung cancer [31].

The introduction or alteration of health system services or medical practices may also impact cancer incidence. For instance, cancer incidence can temporarily increase due

to the introduction of cancer screening. This may occur due to earlier detection of non-symptomatic cancer cases that would have been otherwise diagnosed later or due to over-diagnosis, i.e., the detection of cancer tumours that would have never progressed. An example of this, is the approval of the Prostate-Specific Antigen (PSA) blood test in the early 1990s, as a potential diagnostic tool for early detection of prostate cancer. The blood level of PSA is often higher in people with prostate cancer, hence the FDA approved it in 1986 to monitor the progression of prostate cancer in men who had already been diagnosed with the disease. In 1994, the Food and Drug Administration (FDA) approved the PSA test to be used in conjunction with a digital rectal exam to aid in the detection of prostate cancer in men 50 years and older. This led to a peak in prostate cancer incidence rate in the US in the early 1990s at around 238 cases per 100,000, due to a rise in the detection of asymptomatic disease [32]. As more of the benefits and harms of prostate cancer screening became known, the US Preventive Services Task Force cautioned against routine use of the test for population screening [33] which eventually stabilised the incidence rate to around 180 cases per 100,000 in 2008. A screening wave was also seen in breast cancer incidence rate due to the introduction of the NHS breast cancer screening in England and Wales in 1988. The incidence rate of breast cancer increased rapidly in the screened age group (50-64 year-olds) shortly after the introduction of routine mammograms but in 1992 the rates started to level off [34].

Cancer mortality rate is the number of deaths from cancer in the general population within a specified period of time, usually a year. Although it can be used as a measure of overall progress against cancer, it is hard to distinguish if any changes in cancer mortality are due to advances in prevention, diagnosis or treatment and management of patients. This is in part because incidence rates and mortality rates do not refer to the same people. Incidence rate refers to people diagnosed in a given year, whilst mortality rate in a given year refers to people who died of cancer in that year (cancer recorded as the underlying cause of death in the death certificate). Depending on the cancer survival, the diagnosis date for those people can be many years back [35]. This makes it impossible to pinpoint what events, policies or interventions may have impacted the mortality rate in a given year and when.

2.2.2 Cancer Survival

Cancer survival, in contrast to incidence and mortality rate, is defined in the cancer population and represents the chance of a patient being alive at a specific time point after cancer diagnosis. It is widely used in clinical and epidemiological settings, either in randomised clinical trials, for instance, to assess the effectiveness of new treatment modalities or as a surveillance tool to monitor healthcare quality. With the establishment of national cancer registries in many countries around the world, it is now common to estimate population-based cancer survival [36].

2.2.3 Net survival

Many population-based cancer prognosis measures, including survival, can be estimated both in the absence (net measures) or the presence of other causes of death (crude measures) [37] requiring a different interpretation.

A net measure of cancer prognosis widely used is net survival. Net survival is the survival in the hypothetical situation where the disease under study is the only possible cause of death [38]. Although its interpretation may seem unrealistic to be of interest, net survival is particularly useful for tracking progress in the implementation and effectiveness of cancer policies or the impact of advancements in medical treatment since it is not affected by changes or differences in mortality from other causes. It has been used for comparison of cancer care between countries or continents [20, 39] and population groups [40–42].

The relative survival data setting

To estimate net survival, methods in the competing risks theory are required to account for the fact that patients can die from other causes than the cancer. In this framework of methods, the cause of death is required but since this information is usually unknown or incorrectly recorded in the cancer registries, methods in the relative survival framework can be used instead [43].

In the relative survival framework, we assume that the overall mortality hazard of a patient i at time t, $\lambda_{O_i}(t)$ can be decomposed into the disease-related hazard $\lambda_{C_i}(t)$ (also called "excess hazard") and the hazard of death from other causes $\lambda_{P_i}(t)$ (the "expected hazard"). To disentangle death from the disease (i.e., cancer) and death from other causes, it is assumed that time to death from the disease of interest and time to death from other causes are conditionally independent given population-based demographic characteristics, and that there is non-informative censoring (i.e., the time to censoring is independent of the time to death) [44]. These assumptions are summarized with an additive statistical model used to derive disease-related survival estimates. The modelling framework is known as the *relative survival setting* and it is expressed mathematically as follows:

$$\lambda_{O_i}(t) = \lambda_{C_i}(t) + \lambda_{P_i}(t) \tag{2.1}$$

The basic principle in the relative survival setting is that in the absence of the cause of death, the expected hazard can be derived from the mortality hazard in the general population where patients come from, i.e., from life tables [45, 46]. Life tables are usually publicly available from the statistics authorities of each country, and they provide information on population mortality hazards most commonly stratified by geographical area, year, age, sex, and sometimes by socio-economic deprivation. This allows for a more precise estimation of the expected hazard based on the distribution of the same socio-demographic characteristics among patients.

Net survival of an individual is the survival function acquired from the excess hazard alone (2.2). To derive the marginal net survival for the whole cancer patient cohort $i = 1, 2, ..., N$ we take the average of the individual net survival functions (2.3) [46].

$$S_{C_i}(t) = \exp\left(-\int_0^t \lambda_{C_i}(u)du\right) \tag{2.2}$$

$$S_C(t) = \frac{1}{N}\sum_{i=1}^{N} S_{C_i}(t) \tag{2.3}$$

The Pohar-Perme estimator

The Pohar-Perme estimator (P-P) has been proposed as the only consistent non-parametric estimator of net survival that does not depend on mortality from other causes [38]. At individual level, the P-P estimator is defined as the ratio of the observed to the expected survival for patient i at time t, corresponding to the hazards described in (2.1):

$$S_{C_i}(t) = \frac{S_{O_i}(t)}{S_{P_i}(t)} \tag{2.4}$$

The formula (2.4) implies that to derive the individual net survival at time t, the observed survival is weighted by the expected survival derived from the life tables. This is particularly useful when we wish to estimate long-term survival of a cancer patient population where specific groups have high competing risks of death. For instance, older cancer patients are more likely to die from other causes than the cancer itself which can potentially lead to a form of informative censoring. Weighting the overall survival of those patients with the expected survival of a group with similar demographics in the population, yields an unbiased and consistent estimate of net survival.

Using the relationship between net survival and the excess hazard in (2.2) and the definition of marginal net survival in (2.3), it can be shown that the marginal net hazard $\lambda_C(t)$ estimated by P-P, is the average of the individual excess hazards weighted with the individual net survival (2.5) [38, 46, 47].

$$\lambda_C(t) = \frac{\sum_{i=1}^{N} S_{C_i}(t)\lambda_{Ci}(t)}{\sum_{i=1}^{N} S_{C_i}(t)} \tag{2.5}$$

Other non-parametric estimators

Other non-parametric estimators of net survival have been proved to be biased i.e., the Ederer II, from Ederer and Heise, first published in 1959 [48] and later updated by Hakulinen in 1982 [49]. Alternative quantities such as the relative survival ratio can be

estimated but those have different use and interpretation, and are not independent of the population background mortality [50].

Net survival estimated with the P-P estimator has been used across most publications in the portfolio.

Excess hazard modelling

Net survival can be also estimated using an excess hazard regression modelling approach. The principle in excess hazard modelling is that individual net survival is predicted for every patient from the model and net survival for the complete cohort of cancer patients is the mean of all individual net survival estimates.

Excess hazard modelling has the advantage of estimating net survival when the number of covariates is large. In those cases, the non-parametric estimation may quickly become quite restrictive due to multiple stratification, which may also lead to dimensionality and sparsity issues. In those cases and/or when we are interested on the effect of covariates, a modelling approach has the advantage of flexibility not only in terms of the number of covariates allowed but also the ability to account for the most complex relationships between covariates and the outcome. However, modelling usually requires some assumptions as to the shape of the baseline excess hazard, i.e., the hazard of death due to the disease when all covariates are set to zero or to their reference values.

The Cox model introduced in 1972 [51], and later the Aalen model [52], set the basis for modelling overall survival and the cumulative mortality hazard from all causes. However, in the relative survival framework, where we aim to decompose death from the disease and death from other causes, most commonly it is the excess hazard which is modelled. In 1990, Estève *et al* introduced a Cox-type model for the excess hazard [45]. In the Estève model - as in the Cox model, proportional excess hazards are assumed, i.e., the effect of covariates on the hazard is constant over time, and the baseline excess hazard function is described by a piecewise constant function. Later, Giorgi *et al* extended the Estève model, to include b-spline functions to allow for non-proportional hazards [53]. Since then, further developments followed with the integration of both

non-proportional effects and non-linear effects of covariates [54] and later, with the introduction of multilevel excess hazard models to account for hierarchical structure of the data [55].

Recently, more emphasis was given to the baseline hazard and allowing its shape to be flexibly modelled either with the use of splines [55–57] or with the use of flexible parametric distributions [58]. Flexible Parametric Modelling (FPM) has been extended to include penalized terms, spatial and time-dependent effects and use advanced forms of regression splines [59].

Modelling of the excess hazard [60] has become more widespread in applied research. In a study published in 2021, authors used flexible parametric modelling of the excess hazard to estimate the socio-economic inequalities in colorectal cancer survival from colorectal cancer [61]. They were able to include time-varying covariates and estimate stage-specific excess hazard ratios and absolute differences in net survival between most and least deprived patients, adjusted for a number of factors such as sex, age, site, tumour grade, emergency presentation, receipt of major resection, number of chronic and acute comorbidities.

2.2.4 Alternative measures of cancer survival experience

Although net survival is the main measure used to describe the survival experience of cancer patients, it is often hard to interpret in the "real world" when cancer is not the only possible cause of death. It may also be difficult to communicate to a large audience or to use across science fields, such as health economics. Therefore, I estimated complementary cancer survival measures such as the Crude Probability of Death due to cancer and the Number of Life-Years Lost due to cancer to provide a different angle.

The Crude Probability of Death due to cancer (CPr) $F_C(t)$ is a continuous function describing the probability of dying from cancer before or at time t in the presence of competing causes of death [37]. In the relative survival setting and assuming the additive hazards framework (2.1), CPr can be expressed as:

$$F_C(t) = \int_0^t S(u)\lambda_C(u) \tag{2.6}$$

where $S(u)$ is the all-cause survival and $\lambda_C(u)$ is the cancer-specific cumulative hazard, i.e., the sum of all individual hazards. In the relative survival framework, combining the individual hazards in (2.1), results in:

$$\lambda_C(u) = \lambda_O(u) - \lambda_P(u) \tag{2.7}$$

where $\lambda_P(u)$ is a function of the sum of individual expected hazards acquired from life tables [38, 62, 63].

By integrating the CPr function from 0 to time t we can derive the Number of Life-Years Lost (NLYL) which can be interpreted as the mean time patients would lose due to cancer death within a specific time period $[0, t]$.

$$L_C(u) = \int_0^t F_C(u)du \tag{2.8}$$

Although a non-parametric approach in the estimation of cancer survival measures was primarily used in the portfolio of publications across the thesis, other approaches are also possible. A more recent methodological development in the field was the use of the pseudo-observation framework in the relative survival setting [64] which allows for the direct modelling of the CPr and NLYL. I describe the method and its application in the estimation of socio-economic and age inequalities in the NLYL for a few cancers in Chapter 4.

2.3 Other Methods

Other traditional statistical methods used in the publications, in particular to estimate time trends in cancer survival or in cancer incidence rates, were flexible generalised

(linear and log-linear) regression models with regression splines. In Research Paper 5, a penalised generalised mixed-effects model was used to perform a variable selection accounting for a correlated data structure (i.e., cluster data).

2.4 Data Visualisation

Across all publications, I used data visualisation methods to present the results in a concise way. As most of my research is around comparisons and contrasts of cancer survival or cancer incidence between periods, socio-demographic groups and geographical areas, the main challenge was to find a way to summarize and compare a large set of results. For example, I created dropline plots to demonstrate the trend in net survival from a range of cancers between 1996 and 2013, with the size of the line drawn from the baseline representing the size of the change (Research Paper 1). I used connected line scatterplots to describe the NLYL in the most and the least deprived, with the size of the segment between them representing the size of inequality in the NLYL (Research Paper 2). I drew funnel plots to determine whether geographical variation in cancer survival is more than what would be expected due to random variation (Research paper 5). More details can be seen in the individual papers and in the following chapters.

Chapter 3

The growing burden of cancer

3.1 The changing demographic patterns in cancer

Cancer is among the largest contributors to the burden of disease worldwide and it is projected to continue increasing for the next decades, partly due to the growing and ageing population. And despite cancer being primarily a disease of older age, there is a growing burden among adolescents and young adults in recent years. In 2019, there were 1.19 million incident cancer cases and 396,000 deaths due to cancer among people aged 15-39 years worldwide, contributing 23.5 million Disability-Adjusted Life-Years (DALYs) to the global burden of disease in this age group [65]. This corresponds to more DALYs than communicable diseases such as HIV/AIDS and sexually transmitted infections which attract most of the attention and funding for public health and research in this demographic group [65].

The increase in incidence and/or mortality among adolescents and young adults is unlikely to have occurred due to changing biology, at least for some cancers, and is most likely attributed to a shift in the distribution of risk factors, mainly tobacco smoking, alcohol consumption and obesity. Other underlying reasons may also be related to the geographic and socio-economic characteristics of the population and their access to health care. This population has not historically been the focus of research and cancer control policies, therefore it is often unclear what is causing these patterns.

Some of the age disparities in the cancer burden are also a consequence of gender and socio-economic disparities, in particular at the pre-diagnostic interval of the cancer pathway 1.1. Socio-economic inequalities in vaccination [66–68] and screening participation [69, 70] are manifested into gender disparities in cancer incidence among young

adults. Globally, over two-thirds of cancers diagnosed among adults aged 20-49 years occur in women. Female breast, cervical and female thyroid are the most common cancers among younger adults, well-demonstrating the increased risk among women. The evidence points to socio-economic inequalities in vaccination and screening participation as an underlying cause as well as overdiagnosis of thyroid cancer in some settings [71].

There is also variation in how patients are able to navigate the healthcare system and if they receive the optimal management and treatment based on their needs. Patients over 75 years in England are less likely to receive resectional surgery for colorectal cancer after adjusting for stage at diagnosis [72]. In England, women 40-59 years have an increased risk of emergency diagnosis with colorectal cancer compared to men, partly due to less specific symptoms and their more frequent attribution to benign diagnoses [73]. These disparities have a direct impact on cancer mortality and survival.

Cancer among adolescent and young adults requires to be a public health priority because - although it may be more rare and less lethal than in older ages - it has a disproportionate impact on individuals' lives and large societal and economic burden. Younger cancer patients are faced with psychosocial challenges, infertility concerns, may be more likely to drop out of education or work, seriously affecting their productivity and quality of life. They may also be more likely to have a second cancer or recurrence during their lifetime.

3.2 Increasing colorectal cancer incidence among young adults (Research Paper 1)

3.2.1 Study findings

In the current landscape of changing gender and age patterns in cancer, I set out to describe trends of colorectal cancer incidence rates in England, focusing on differences between calendar periods, sex, age, deprivation and anatomical sub-site (Research

Paper 1). The findings pointed to a steep increase in colorectal cancer (CRC) incidence among young adults aged 20-39 years in contrast to an overall stabilising trend in adults over 40 years of age.

This was the first study to describe these trends in England [74]. Several studies conducted in the US and other countries, preceding [75–79] and following the publication of this study [80–88], confirmed these findings showing an almost two-fold increase in incidence of early-onset CRC diagnosed in people younger than 50 - with a steeper rise among those less than 30 years. Large increase in incidence rates among young adults were also seen for some other obesity-related cancers such as stomach [82].

The findings of our study, highlighted the largest increase in CRC incidence among young adults predominantly in the ascending/proximal colon. However, early-onset CRC is primarily characterized by left colon - sided and rectal location tumours. This discrepancy is probably mainly due to the inclusion of the appendix and splenic flexure (ICD-10: C18.1, C18.5) with the proximal colon in the sub-site classification, which is in contrast to common practice in the literature. Incidence of appendiceal tumours in England, albeit rare, has increased significantly since 1995, especially among young adults. This may be due to a combination of factors such as an increase in the number of appendicectomies undertaken in the young population, changes in the pathological assessment methods of resected appendices or due to more frequent use of cross-sectional imaging in clinical investigation [89].

3.2.2 A comment on methods

The aim of Research Paper 1 was to describe trends in CRC incidence rates (age-standardised) in England by several socio-demographic characteristics such as sex, age and socio-economic deprivation. I used the Joinpoint Regression Program [90] to fit the simplest piecewise linear trend to the yearly incidence rates in a given calendar period between 1971 and 2014 (i.e, assuming linearity in trends). The Joinpoint Regression Program is a well-recognized method with embedded software, developed by the Cancer Research Institute to produce cancer statistics. It is the main analytic tool of

the Surveillance, Epidemiology, and End Results (SEER) Program in the US for cancer surveillance. It produces plots and outputs that are easy to read and can be compared across the literature [77, 78].

Other analytic approaches were however, possible. An age-period-cohort analysis would have been able to disentangle the effects of age, period and birth cohort on the incidence rates and isolate the birth cohort of colorectal cancer patients most affected [91]. This would help identify the potential risk factors that may have acted in the early years of those individuals to increase their risk for CRC in early adulthood.

Another potentially useful approach would be to estimate the effect of different risk factors on the incidence patterns. Based on the literature, I would include lifestyle factors such as alcohol consumption and tobacco smoking, diet and environmental exposures to identify the combination of factors that can explain the patterns in cancer incidence. Access to these data may be challenging but for instance, the Clinical Practice Research Datalink (CPRD) database in the UK [92, 93], contains individual information on demographic characteristics, diagnoses and symptoms, vaccination history, health behaviours etc. More than 2,000 primary care practices are included in the database, with more than 18 million registered and active patients, with the potential to link to cancer registry data and HES. Alternatively, if individual information is not available, I would combine data at individual and ecological level, for instance by including smoking and alcohol consumption prevalence in England or by geographical area in England. This type of data are publicly available from NHS Digital [94].

3.2.3 Potential mechanisms to explain the rise in early-onset colorectal cancer

The reasons for these trends in incidence among adolescents and young adults (AYAs) remain largely unknown, with most mechanisms pointing to a combination of genetic and lifestyle factors. Some colorectal cancers in children and young adults are linked to familial CRC or hereditary cancer predisposing syndromes such as the Lynch syndrome or inflammatory bowel disease. However, this is unlikely to explain the patterns

observed as approximately only 50% of early-onset CRC co-exist with familial CRC and hereditary cancer predisposing syndromes while the remaining 50% are of unknown etiology [95].

Lifestyle factors have been associated with CRC at all ages, but it is important to consider the timing and their duration. The rise in colorectal cancer incidence rates in England started after 1993 among 20-29 year-olds and after 2005 among 30-39 year-olds suggesting a cohort effect. In the preceding three decades, prevalence of overweight and obesity in children and adolescents increased by more than 200% since the early 1960's in England [96], with the odds of having obesity higher for birth cohorts born between 1989 and 2008 [97]. Adult-onset obesity accounts for only 11% of CRC cases [98], highlighting the fact that obesity during critical phases of growth and development may have a large effect on CRC risk [99]. Similarly, physical activity levels in children 5–15 years old have dropped by 20% since the 1960s, and in 2017, only 18% of children and young people met the Chief Medical Officer's current guidelines of at least 60 minutes of exercise per day. Other lifestyle factors such as smoking, alcohol, consumption of red or processed meat, use of non-steroidal inflammatory drugs, specific micronutrients such as calcium and Vitamin D, environmental pollutants may all play a role.

The evidence on how survival outcomes of young patients with early-onset CRC compare to the outcomes in older individuals is still conflicting. Despite younger patients being overall healthier and with less comorbidities and more likely to receive the optimal treatment [83], most studies show very little [100] to no survival advantage to older patients [101, 102]. This may imply that the young have more aggressive tumours, are over-treated or respond differently to treatment regimens developed for older patients with CRC.

3.2.4 Impact of the study

Colorectal cancer is one of the most common and deadliest cancers in ages over 50 years old and the third contributor on the burden of cancer among adolescents and

young adults - especially among high-income countries [65]. The CRC incidence trends reported with this study are alarming and may predict a surge on the CRC cases diagnosed among young adults in the future.

In the US, the screening threshold was reduced to 45 years acknowledging the need to expand the screening benefits to younger ages. Whilst this may not yet be justified in terms of case volume or feasibility for the NHS in England, this evidence should increase awareness and alertness among clinicians and young adults themselves, but also among policymakers to act on the societal environment that encourages the emergence of CRC risk factors.

Chapter 4

Socio-economic inequalities in cancer survival

4.1 Progress since the 2000 NHS Cancer Plan (Research Paper 2)

4.1.1 Study findings

In Research Paper 2, I aimed to assess the effectiveness of the NHS Cancer Plan introduced in 2000 and of subsequent strategies in reducing the difference in cancer survival between the most and the least deprived cancer patients in England - what is called the "deprivation gap". Patient and tumour information for more than 3.5 million registered patients diagnosed with one of 24 most common cancers during 1996-2013 were included from the National Cancer Registry database. I estimated net survival for every sex-cancer combination by year of diagnosis and deprivation group. The expected mortality hazard was derived from the life tables for England stratified by calendar year, sex, age, and deprivation.

Despite an improvement in cancer survival for most cancers, the deprivation gap persisted and survival in the most deprived was consistently lower than in the least deprived. A reduction in the deprivation gap was inevitably observed over time for the very good prognosis cancers due to a "ceiling effect" where survival in the less deprived is so high that it cannot improve further. These findings emphasised that socio-economic inequalities in cancer survival remain a major public health issue.

4.1.2 A comment on methods

Previous publications [17, 21, 103] had examined national trends and socio-economic inequalities in cancer survival just before the 2000 NHS Cancer Plan in England and shortly after it. These studies investigated how the trends in cancer survival and in the deprivation gap changed according to three calendar periods: 1996-2000 (before the Cancer Plan), 2001-2003 (initialisation) and 2004-2006 (implementation). They showed that survival had indeed improved since the 1990s but the deprivation gap in survival had narrowed only slightly between 2000 and 2006. In Research Paper 2, I updated those findings by extending the incidence period to 1996-2013 with follow-up to 2014, to allow for a longer latency period for these policies to take effect and provide more recent estimates of cancer survival.

In contrast to the previous studies that also provided 3-year and 5-year cancer survival, I only focused on one-year survival as most of the differences in survival between populations occur shortly after diagnosis. For example, the ICBP study [15] highlighted that international differences in survival were more marked in the first year of diagnosis. As with international differences in cancer survival, excess mortality hazards (i.e. mortality due to the cancer) differ between socio-economic deprivation levels, mainly soon after diagnosis, whereas those differences disappear, or are minimal, after the first 12-18 months since diagnosis [104]. Therefore, survival being a cumulative measure, it means that the inequalities in survival are often not wider at five years than at one year after diagnosis. All patients had at least one year of follow-up information on their vital status which allowed the cohort analysis for the estimation of net survival [105].

In previous publications, the calendar periods for the estimation of trends in cancer survival, were pre-defined by the then National Cancer Director. In contrast, in this study age-standardised net survival estimates were modelled using regression model with splines allowing for the calendar periods to vary.

4.1.3 Impact of the study

The publication of Research Paper 2 study followed extensive media coverage from newspapers including The Times [106], Daily Mail [107] and other high-impact journals such as The Lancet Oncology [108]. I got invited to give interviews and wrote a commentary in the New Scientist [109].

Shortly after the publication we were invited to contribute to the 2018 Chief Medical Officer's (CMO) report with an illustration of the number of avoidable cancer deaths if cancer survival was equitable between less and more deprived cancer patients in England [110].

This study has become a key reference when reporting socio-economic inequalities in cancer survival in England. Citations include policy documents [111] and government reports [112].

The work was extended with Research Paper 3, translating the socio-economic inequalities into Number of Life-Years Lost due to cancer non parametrically. By incorporating the quality of life component, ongoing work will use the Quality-Adjusted Life Years, a measure widely used in health economics [113–115] to reflect the health, societal and economic impact of socio-economic inequalities in cancer.

4.2 An alternative framework for the evaluation of public health policies

Although this and previous studies are useful in describing the overall progress (or the lack of it) in improving cancer survival and reducing socio-economic inequalities in cancer survival, I acknowledge the limitations to properly evaluate the impact of the 2000 NHS Cancer Plan on cancer outcomes. Between 2000 and 2013, except for the NHS Cancer Plan, more policies [12, 13, 116] were introduced with similar aims. Our study relied on cancer survival trends to assess the 2000 NHS Cancer Plan, however it

is difficult to disentangle its effect from other policies, from secular trends or from other factors such as environmental and lifestyle changes at population level.

The main challenge when it comes to the evaluation of the impact a policy brings, is the attribution of causality: is it the policy causing a change in health outcomes, or is the change attributable to other factors at play? Randomized-controlled trials are ideal for the evaluation of changes at population level but due to difficulties in controlling their implementation, observational studies are used. Such studies have low internal validity and therefore require a controlled framework to establish causal relationships between a policy and their impact. When aiming to evaluate a public health policy or intervention, a logic model can be a useful tool [117]. It provides conceptual and methodological framework to think about, manage and effectively evaluate components of a policy [118].

A logic model is a systematic and visual representation of the relationships between inputs/resources, activities, outcomes and impacts pertaining in a programme, intervention or system, which also identifies its underlying theory and assumptions. A basic logic model is drawn in Figure 4.1, adapted from W.K. Kellogg Foundation's guide to Logic Model Development [118]. It describes the flow from resources and actions to the intended results and impact.

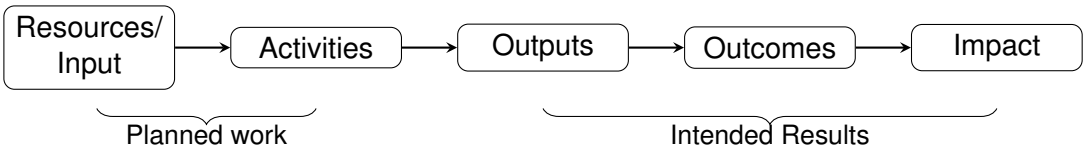

FIGURE 4.1: The Basic Logic Model

A toolkit in thinking and visualizing an intervention's anticipated causal pathway can be thought of as an "If then" exercise [117, 119]. The "If Then" principle is the conceptual link between resources and activities and the outcomes and impact expected. The 'if' states the conditions for the outputs and impact to occur and relies on probabilities, i.e., it can be evaluated but not calculated. In contrast, the "then" part which is the outputs and impact, should be measurable and time-bound.

Ideally, logic models are built prior to the implementation of public health interventions to support their introduction and structure and later their evaluation. However, as this is still not common practice, they can be used a posteriori by researchers to generate the hypotheses and model how an intervention is supposed to work. They can be as complex as one wishes to make them, referring to a single strategy or intervention, a component of a strategy or a set of public health initiatives and policies.

Logic models have been previously developed by researchers for tobacco control policies [117]. In the context of cancer survival, researchers mapped out the cancer pathway in the NHS, to visualize the complex interactions between health system factors (inputs, activities, resources etc) and how they may contribute to variation in cancer outcomes [23].

As an extension to the study in Research Paper 2, it would be useful to gather information on the policies introduced to reduce socio-economic inequalities in cancer outcomes in England, the activities and processes to implement them and the intended outcomes and impact. This would help build a logic model. Collection of data from the literature or other sources can then be analysed for the evaluation part. Since logic models are based on causal pathways, methods to evaluate components of public health interventions would largely rely on the causal inference methods framework.

4.3 Number of Life-Years Lost due to cancer (Research Paper 3)

4.3.1 Study findings

Net survival may be a key measure of cancer prognosis, especially when making comparisons between populations but it does not fully reflect the burden of the disease. Effective communication of survival statistics requires additional indicators [46, 120, 121] that can be used to describe different dimensions, including its societal and economic impact [122, 123]. In Research Paper 3, I aimed to quantify the population burden of socio-economic inequalities in cancer survival using the Crude Probability of Death and the Number of Life-Years Lost due to cancer within three years since diagnosis.

All patients diagnosed between 2010-2014 with one of 24 most common cancers were included in the analysis. I estimated the Number of Life-Years Lost (NLYL) due to cancer within 3 years since diagnosis for each cancer and stratified by sex, age and deprivation using a non-parametric approach in the relative survival framework.

For the vast majority of cancers, most deprived patients lost more life-time than the least deprived. The largest socio-economic inequalities were seen mostly in adults younger than 45 years old, with poor prognosis cancers such as brain, lung and all the upper-digestive organ cancers (pancreatic, liver, oesophagus and stomach). In this age group, the most deprived patients with lung, pancreatic and oesophageal cancer lost up to 6 additional months within three years since diagnosis than the least deprived.

For each cancer, the interpretation of these findings can vary ranging from access to screening, delays in diagnosis or barriers in receiving the optimal treatment. What stands out though, is that socio-economic inequalities are more prominent among young adults with cancers largely related to tobacco smoking. The fact that socio-economic inequalities exist across the age range, suggests that variation in patient- and tumour- related characteristics such as comorbidity, frailty and tumour stage often associated with older age do not seem to be the only explanation. There may be

structural components of the health system that affect deprived patients of all ages and sexes.

4.3.2 The pseudo-observation approach for the estimation of the Number of Life-Years Lost

The pseudo-observation method framework

In different studies, Life-Years Lost is estimated differently and may have different notation [124, 125], but it is a measure commonly used to complement mortality statistics. The NLYL measure used in Research Paper 3, was estimated non-parametrically, based on the Aalen-Johansen estimator of the crude probabilities [126] adapted for the relative survival setting [127].

However, crude probabilities can also be modelled with regression models either on the cause-specific hazards or the sub-distribution hazards [128] and more recently, with the pseudo-observation approach [64]. With this method, it is possible to compute for every individual at a given time a quantity that is fully observed despite the presence of right-censoring due to loss of follow-up. The resulting new dataset of pseudo-observations can then be used as the outcome in a regression model [64].

The pseudo-observation method was first developed for multi-state models [129] but the idea has been extended to other estimation problems in the context of incomplete time-to-event data [130, 131]. Given that for each individual $i \in (1, \ldots, n)$, Y_i describes the random time-to-event variable, we know that under right-censoring Y_i is not observed for all individuals. Therefore, any function $f(Y_i)$ is also not observed for all individuals.

The usefulness of this method is based on the inherent quality of the marginal expectation that it can be derived even with incomplete data. Assuming there is an unbiased and consistent estimator of $E[f(Y)]$, a whole set of incompletely observed random variables or their functions can be replaced by their pseudo-observations.

A pseudo-observation is computed for each individual i at time t - even for the ones that $f(Y_i)$ is observed, using the "leave-one-out" estimator. The estimator is a function of the estimator of interest using the whole sample n and the estimator using the sample obtained after removing individual i. For the NLYL, this takes the following form:

$$\tilde{L}_{C,i}(0,t) = n\hat{L}_C(0,t) - (n-1)\hat{L}_C(0,t)^{-i} \tag{4.1}$$

where $\tilde{L}_{C,i}(0,t)$ is the pseudo-observation for the NLYL within $[0,t]$ for individual i, $\hat{L}_C(0,t)$ the marginal expectation of the NLYL estimator based on the whole sample and $\hat{L}_C(0,t)^{-i}$ the marginal expectation of NLYL estimator based on the sample size after removing individual i. Computing those pseudo-observations for each individual at different time points m, results in a multi-dimensional vector which can be used as an outcome in a generalized linear model [64].

Application of the pseudo-observation approach

I used the pseudo-observation approach to estimate the impact of socio-economic deprivation and age on the NLYL due to cancer death.

I computed a set of pseudo-observations of the NLYL due to cancer within 1 year since diagnosis for patients with colon, lung, prostate and cervical cancer diagnosed between 2010-2014 in England. Cancer- and sex-specific Generalised Linear Models were fitted on the pseudo-observations as the main outcome and age at diagnosis (continuous scale) and socio-economic deprivation (categorical with values 1-5) were included as the main predictors. Cubic b-splines for the age term and an interaction term between age at diagnosis and deprivation were included, assuming a heterogeneous effect of age across levels of deprivation. The final results were the model predictions of NLYL for combinations of age and deprivation groups.

I found that the total NLYL due to cancer within one year from diagnosis increased with increasing deprivation and were the highest in patients with lung cancer among all four cancer sites (Table 4.1). The Number of Life-Years Lost before age 65 was

approximately 18% of the Total NLYL and the proportion increased with deprivation. For all cancer sites, the NLYL increased with age but the gradient was steeper in the more deprived patients.

TABLE 4.1: Total Number of Life-Years Lost (NLYL) due to cancer for all patients and for patients less than 65 years (NLYL before 65) diagnosed in England, 2010-2014

		Lung cancer			Colon cancer			Prostate cancer			Cervical cancer		
		N	Number of Life-Years Lost	NLYL before 65 (%NLYL)	N	Number of Life-Years Lost	NLYL before 65 (%NLYL)	N	Number of Life-Years Lost	NLYL before 65 (%NLYL)	N	Number of Life-Years Lost	NLYL before 65 (%NLYL)
Males	**Least deprived**	13,791	6,108	828 (13.6)	12,570	1,837	214 (11.7)	45,992	1,125	34 (3.0)	-	-	-
	2	16,907	7,801	1,168 (15.0)	12,695	1,957	222 (11.4)	43,920	1,171	48 (4.1)	-	-	-
	3	19,130	8,913	1,502 (16.9)	11,958	1,982	249 (12.5)	39,627	1,181	52 (4.4)	-	-	-
	4	22,382	10,531	1,985 (18.8)	10,949	1,947	298 (15.3)	33,438	1,144	48 (4.2)	-	-	-
	Most deprived	23,649	11,005	2,568 (23.3)	8,715	1,643	295 (17.9)	24,686	873	57 (6.5)	-	-	-
Total		***95,859***	***44,358***	***8,051 (18.2)***	***56,887***	***9,366***	***1,278 (13.6)***	***187,663***	***5,493***	***238 (4.3)***	-	-	-
Females	**Least deprived**	10,982	4,374	681 (15.6)	11,092	1,756	146 (8.3)	-	-	-	1,836	123	33 (26.5)
	2	13,553	5,619	849 (15.1)	11,370	2,029	186 (9.2)	-	-	-	2,068	154	45 (29.2)
	3	15,843	6,742	1,090 (16.2)	11,100	2,116	205 (9.7)	-	-	-	2,443	193	72 (37.3)
	4	19,089	8,238	1,447 (17.6)	10,330	2,128	226 (10.6)	-	-	-	2,875	194	75 (38.6)
	Most deprived	20,310	8,782	1,792 (20.4)	7,876	1,712	251 (14.7)	-	-	-	3,323	234	104 (44.5)
Total		***79,777***	***33,754***	***5,859 (17.4)***	***51,768***	***9,742***	***1,014 (10.4)***	-	-	-	***12,545***	***897***	***328 (36.6)***

The deprivation gradient in the NLYL was more prominent in lung, cervical and female colon cancer patients (Figure 4.2). Among patients with cervical cancer, the NLYL increased rapidly from age 25-30 years in the more deprived patients. The increase was more gradual in the less deprived patients and the deprivation gradient reduced after 60 years of age (Figure 4.3).

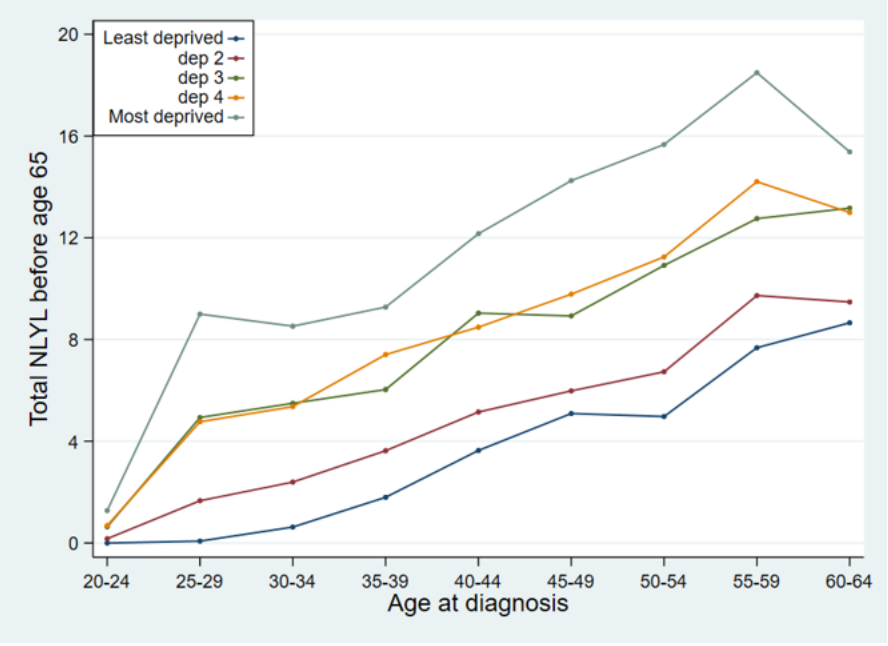

FIGURE 4.3: Number of Life-Years Lost by age and deprivation in cervical cancer patients, England 2010-2014

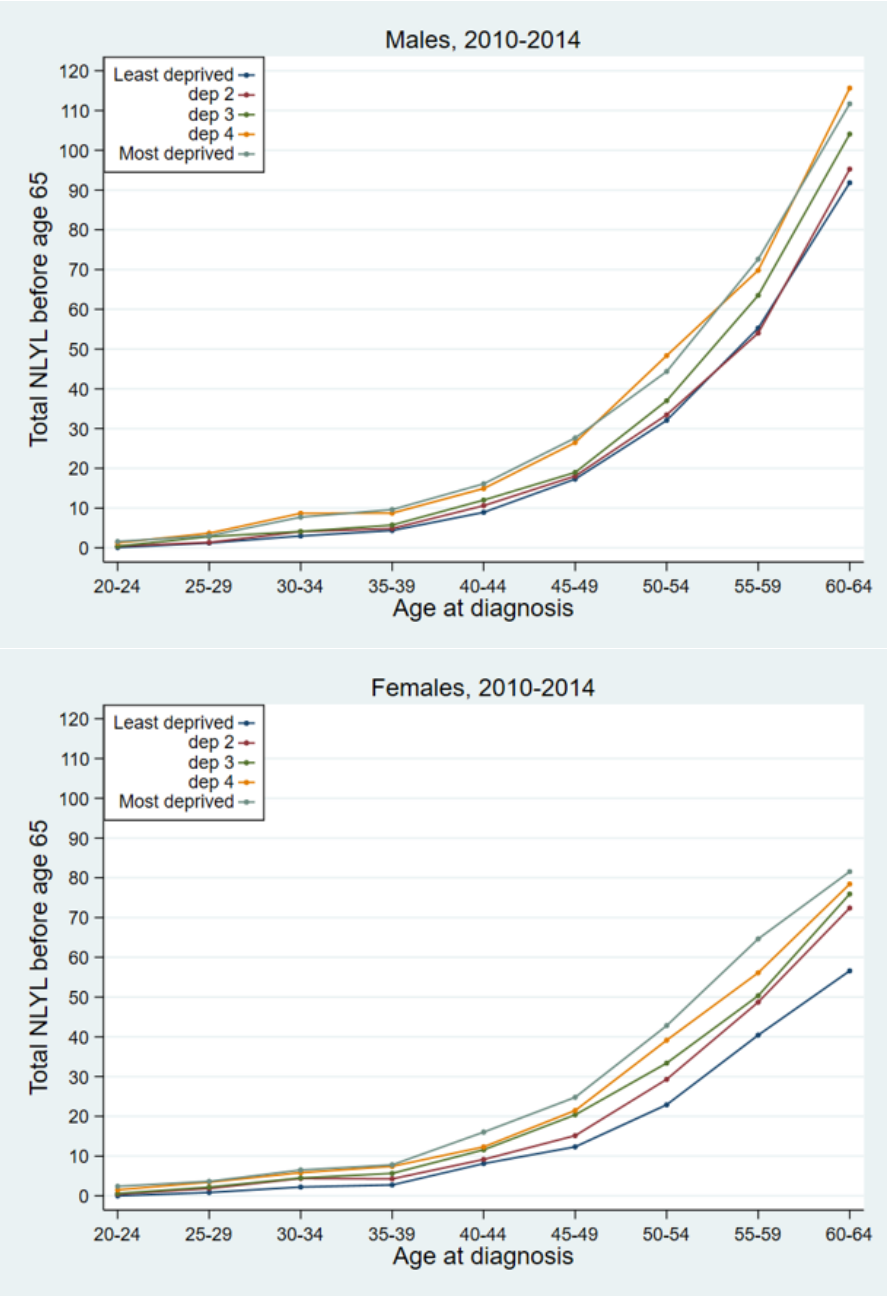

FIGURE 4.2: Number of Life-Years Lost by age and deprivation in lung cancer patients, England 2010-2014

4.4 The health and economic cost of socio-economic inequalities in cancer survival

This is another extension of the work in collaboration with health economists. I aim to use the findings from Research Paper 3 to estimate the total economic cost of

socio-economic inequalities in cancer survival. Below, I outline the strategy and a brief overview of the ongoing work.

Quality-Adjusted Life-Years (QALY) due to cancer

The first step for this work is to translate the NLYL due to cancer into QALY. The National Institute for Health and Care Excellence (NICE) defines QALY as the *measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life.* It is a measure commonly used in health economics and in particular in the cost-utility analysis of health interventions [132] to help decision-making and public health policy implementation. The cost-effectiveness of an intervention is a way to examine how its overall cost over expected health benefits compares to other proposed or existing technologies and helps determine if it is an efficient use of resources.

The basic idea underlying the QALY is the concept of "utility" which stems from political philosophy theory. Utility is the value attached to a particular state or consumable estimated by the intensity of preference for it. Utility in health describes the preference for a health state and is usually expressed on a numerical scale from 0 to 1, with 0 representing the state "Dead" and 1 the state of "Perfect Health" [133]. The QALY combines the utility of a particular health state with the length of life into a single index, e.g., a year of life lived in perfect health is worth 1 QALY (1 Year of Life x 1 utility = 1 QALY) and that a year of life lived in a state of less than this perfect health is worth less than 1.

The calculation of these utilities or quality of life scores, are obtained from individuals completing a health-related quality of life (HRQoL) questionnaire at baseline, and at one or several time points during a study period [134]. There are various instruments to measure HRQoL scores [135–139]. The most commonly used metric of HRQoL in the UK is the EQ-5D. This metric has five dimensions of quality of life (mobility, self-care, usual activities, pain and discomfort, anxiety and depression) each with three possible levels.

EQ-5D scores for the general population in England (population norms) are commonly provided by age and sex [140]. These scores are usually less than 1 as the general population is not in a state of full health and decline with age. To account for the Quality of Life (QoL) associated with a disease, a weighted estimate of QoL by ICD-10 codes at the average age of respondents is used; the difference between the population norms and the disease-related QoL is the disease decrement [140].

The total loss in QALY attributable to cancer includes both the impact of cancer on the quality of life while patient is alive and the loss in QALY due to premature cancer death. To estimate the loss in QALY due to premature cancer death, the average population EQ-5D scores by age, sex and socio-economic deprivation [115] can be applied to the NLYL estimates stratified by age-group, sex and socio-economic deprivation [63]. To estimate the loss in QALY due to cancer while patient is alive, these population weights can be further adjusted with a cancer-related decrement related to the quality of life experienced by cancer patients. These can then be applied to the average number of life-years lived - the complement to the NLYL within 3 years since cancer diagnosis.

The Total Economic Cost

To estimate the total economic cost of socioeconomic inequalities in cancer survival, the Wider Societal Impact and the societal value have to be estimated.

Besides the health loss or premature mortality, cancer has also a cost for society which includes reduced productive capacity of cancer patients and cancer survivors in paid labour as well as suspension in unpaid activities such as child-care, domestic work and volunteering. Considering that cancer patients are also consumers of resources in the healthcare system and social care, the net summary of their contribution or production of resources through paid or unpaid labour net of their consumption or utilisation of resources, constitutes the net production or the "Wider Societal Impact" (WSI). The methodology to estimate the WSI for cancer and other diseases has been developed by the Department of Health, estimating a patient's production and consumption as a function of their age, gender, condition and health-related QoL using routinely available data

[141]. To simplify the adoption of these estimates, the Department of Health has provided a summary reference estimate of WSI per QALY gained from typical treatments in each disease field. To estimate the WSI of socio-economic inequalities in cancer survival, we apply these reference estimates of WSI per QALY gained by cancer type to the total QALY lost due to specific cancers by combinations of sex, age group and deprivation level as calculated before.

Economic appraisal of a health intervention should also take into account all the resource costs and savings due to its implementation. The value of changes in the quality and quantity of life due to the socio-economic inequalities in cancer survival can be quantified in money terms using the Willingness to Pay (WTP) technique [113]. The WTP is one of the main approaches in health economics (others include the human capital approach and the restitution cost approach) to estimate the value of life and it is based on the principle that under certain conditions, what the consumer is willing to pay for a good, represents its economic value. With this approach, one can estimate the Value of a Prevented Fatality (VPF) using population surveys of stated preference for the value of a statistical life, or other data sources. Based on data from the Department of Transport, a monetised value of £60,000 (based on 2009 data) was estimated for the VPF [113]. This value can be applied to the difference in total QALY between the least and the most deprived cancer patients in England to estimate the societal value of socio-economic inequalities in cancer survival.

Potential impact of this work

By providing a tangible estimation of the societal and economic impact of socio-economic inequalities in cancer survival, it may be easier to communicate with policy-makers and stakeholders. It provides another dimension to the persisting socio-economic inequalities in cancer that will highlight the urgency to prioritise it in the design of new public health policies and strategies.

Chapter 5

Socio-economic inequalities in cancer diagnosis and treatment

In previous chapters, it was shown that cancer outcomes are worse for the more socio-economically deprived patients in England, and little or no improvement has been achieved over time.

To tackle those inequalities, most cancer policies implemented in England, emphasized prevention and early diagnosis, mainly by encouraging better health behaviours or targeting awareness and beliefs about cancer. The 2000 NHS Cancer Plan [13] - the first comprehensive cancer strategy in England - was committing among others, to address the socio-economic disparities in smoking rates in adults by 2010. More targeted strategies followed, aiming at the areas of prevention, early diagnosis, access to diagnostic tests and optimisation of referral pathways [12, 116, 142, 143]. Campaigns such as the National Awareness and Early Diagnosis Initiative [144] and "Be Clear on Cancer" [145] introduced in 2009 and 2011 respectively, targeted people from lower socio-economic groups to promote awareness of cancer symptoms and encourage them to seek help in primary care. Alongside prevention and early diagnosis, those strategies planned investment in the delivery of care and reform in cancer services.

Whilst those steps were essential to improve overall cancer outcomes in England, they have been ineffective in eliminating socio-economic inequalities in outcomes. Even among patients with similar tumour and clinical characteristics such as stage at diagnosis and comorbidities, the more deprived patients continued to experience worse outcomes [146–148]. This points to systemic factors related to the management and treatment of patients. Socio-economic inequalities have been observed in various stages

of the cancer pathway such as in screening [149] and vaccine uptake [150], as well as diagnostic intensity [151], treatment [148] or post-operative care [152].

In this chapter, I will explore some of these socio-economic differences occurring in the diagnosis and treatment of cancer.

5.1 Delays in cancer diagnosis

Delays in cancer diagnosis are a major contributor to poor cancer outcomes [153] as it exacerbates the disease or the health status of the patient which eventually determines the treatment received and its effectiveness. Tackling delays in diagnosis has been on the agenda of all cancer strategies and policies introduced in England. To achieve that, it was necessary to set measurable goals and track progress. In this context, Emergency Presentations (EP), i.e., estimated proportions of all malignant cancers where patients first presented as an emergency over the total number of hospital admissions, were introduced as an indicator and started to be published quarterly as Official Statistics by the National Disease Registration Service at NHS Digital [154].

For some cancers such as brain, liver and pancreatic cancer more than half of patients are diagnosed through Emergency Presentation, partly due to the asymptomatic progression of cancer. For other cancers, such as colorectal and lung cancers high proportion of EP can be a manifestation of both delays in recognition of symptoms as well as problems in access to and delivery of health care services. Furthermore, wide inequalities in EP are observed, with the more deprived patients and patients of non-white ethnic backgrounds at higher risk [155–157].

The higher proportion of EP among more deprived cancer patients may be a reflection of the high prevalence of comorbidities in those populations [158]. For example, individuals with high comorbidity who eventually proceed to get diagnosed with cancer, often present with more general symptoms or symptoms that may be attributed to their comorbidities, thus interfering with the cancer diagnosis [159–161]. However, large socio-economic disparities in the proportion of EP cannot be explained solely through

this mechanism. The overall use of emergency compared to elective hospital care is higher in the more deprived areas in England, and only a small proportion can be attributed to the severity of comorbidity prevalent in those areas [162, 163] pointing to alternative explanations.

To understand the mechanisms underlying the wide socio-economic inequalities in EP with cancer, I focused on exploring the link between EP and hospital admissions prior to diagnosis in colon cancer patients. The idea is that the use of emergency services in cancer patients, even for causes unrelated to cancer, varies by socio-economic status. Changes in healthcare use patterns are observed at least six months before cancer diagnosis, presenting opportunities for earlier diagnosis [164]. The aim of this study is not so much to focus on hospital admissions related to cancer diagnosis, but rather to benchmark the pattern of emergency services use in the most deprived against the least deprived cancer patients, to further understand the inequalities component. If part of the higher use of emergency services for cancer among the more deprived populations is attributed to systemic factors, there is little reason that these systemic factors do not affect other pathologies or clinical contexts.

5.1.1 Hospital Emergency Admissions prior to cancer diagnosis (Research Paper 4)

5.1.1.1 Study findings

For Research Paper 4, I examined whether more deprived cancer patients experience a higher proportion of Hospital Emergency Admissions (HEA) than the less deprived, and if the conditions for which they get hospitalised for and their admission route varies by socio-economic status in the two years prior to cancer diagnosis.

All patients diagnosed with colon cancer in England in 2013 were included in the analysis. The English Cancer registry data was linked to HES inpatient care records to acquire a complete database of patient and tumour characteristics and information on

patient history of hospitalisations prior to cancer diagnosis. Each patient had multiple hospital admissions with multiple conditions or symptoms diagnosed, creating a cluster-structured dataset. To address the first objective of this study, i.e., to find out whether more deprived colon cancer patients experience a higher number of HEA than the less deprived, I presented the monthly rate of hospital admissions per patient and the monthly proportion of patients with at least one HEA by socio-economic status. For the second study aim, i.e., identifying the combinations of conditions associated with HEA, I applied a multi-step modelling approach often referred to as Purposeful Variable Selection [165].

Whilst the rate of hospital admissions for any cause (elective and emergency included) was similar between the most and the least deprived colon cancer patients, the most deprived patients had an overall higher rate of HEA than the least deprived and this was more marked in the last 7 months prior to cancer diagnosis. The proportion of patients using the emergency services was comparable between the most and the least deprived. The patterns of conditions and the associated admission route (emergency or non-emergency) did not differ much by deprivation, except for the substantially smaller number of conditions in the most deprived.

The study findings point to an overall higher use of the emergency services as the main path, in the most deprived patients. Contrasting the proportion of patients using the emergency services, which was similar in the most and the least deprived, to the rate of HEA which was higher in the most deprived, it seems that among the most deprived, some patients were using repeatedly the emergency services. However, individual disease-specific aspects of care do not seem to explain the excess of emergency admissions in the most deprived patients, suggesting higher use of the emergency services for non-specific symptoms and conditions.

5.1.1.2 A comment on methods

The main methodological challenge of this study was to perform variable selection on a total of 42 conditions to identify the ones related to HEA. The Purposeful Variable

Selection (PVS) approach was used. Originally developed for fixed effects logistic regression [165], it was applied to the context of the mixed-effects logistic regression models to account for the correlated data structure. The PVS is a variable selection process in which, at each step, variables that are not significant and not a confounder are removed. At each step, the full model is compared to the nested model with a likelihood-ratio test (LRT) to determine the statistically significant covariates. We also used the AIC to assess the relative quality of the model at each concluding step of the selection process.

Whilst this approach performs well when the analyst is interested in risk factor modelling, more automated methods may have the benefit of testing covariates jointly. However, I prioritized the understanding of the potential causal structural relationship between variables related to the previous background knowledge, rather than the automatization of methods that do not consider the basic structural relationship between variables.

For instance, in the context of more automatized methods, penalised regression may be an option to further consider. It fits a model containing all covariates and shrinks the coefficient estimates towards zero using a gradient descent algorithm [166]. The tuning parameter, often denoted as λ, defines the level of shrinkage imposed on the coefficient estimates, with larger λ values leading to more zero coefficients. Selecting the tuning parameter requires a process where a range of values are tested and the one with the smallest cross-validation error is selected.

I performed a secondary analysis using the "glmmmixedlasso" package in R, a penalized algorithm for fitting high-dimensional generalised linear mixed models [167]. Despite testing a wide grid of λ values and pre-specifying the starting values, the algorithm retained most of the covariates. Therefore, after discussions with statistics experts and the developer of the package, I kept my strategy for variable selection and modelling, as it was clear that the LASSO behaviour of keeping all variables was due to false discovery problems associated with highly correlated covariates.

5.1.1.3 Impact of the study

Most studies related to socio-economic inequalities and delays in diagnosis focus on examining the consultation processes in primary care such as recognition of cancer symptoms [168] and referral patterns [169] as well as certain General Practitioner (GP) characteristics such as GP availability and consultation time [170]. Whilst what happens in primary care is an important piece to understanding the complexities underlying the delays in cancer diagnosis, this study proposes that the urgent and emergency care setting can provide useful insights into potential health system barriers in timely cancer diagnosis, by removing biases around patient choice or accessibility to GP. We know that more deprived patients experience longer waits in the emergency services, are less likely to be admitted for inpatient care, and are more likely to have an emergency re-admission or die shortly after attendance [171]. Combined with the findings of our study, the evidence points to system-level barriers as the potential factors associated with timely cancer diagnosis. If part of the higher use of emergency services for cancer among the more deprived populations is attributed to systemic factors, there is little reason that these systemic factors do not affect other pathologies or clinical contexts.

5.2 Variation in cancer treatment uptake

A large part of the socio-economic inequalities in cancer survival is due to the inequalities in cancer treatment received [40, 148, 172]. Whilst cancer treatment is predominantly determined by the extension of the disease and the health status of the patient, more deprived patients are more likely to experience delays in treatment or receive no optimal treatment even after accounting for patient and tumour factors such as comorbidities and tumour stage [40, 148, 172]. Large inequalities in the receipt of resectional surgery have been also proposed as one of the potential explanations why cancer survival from colorectal cancer in England lags behind other comparable countries such as Denmark, Norway and Sweden [72].

Despite continuous efforts by the NHS to bring better cancer treatments including advanced radiotherapy techniques and immunotherapies, and adopt new technological advancements, geographical variation persists with the more deprived areas experiencing more barriers to accessing the optimal treatment and experiencing worse outcomes. This geographical variation in cancer treatment may be quite dependent on the availability and sufficiency of resources across the country, such as specialist surgeons, cancer nurses, and high-dependency or intensive care units. For example, we know that geographical variation in cancer survival in London is largely accounted for by the hospitals where colon cancer patients were treated [173].

To understand better geographical variation in cancer treatment and its impact on cancer outcomes, I set out to explore the variation in resection rates for pancreatic cancer. Pancreatic cancer, despite its lethality, has not always been at the forefront of cancer policies mainly due to relatively low incidence and limited treatment options when diagnosed at a later stage. However, in the 1990s, it was recognised that oesophagogastric cancer services were inconsistent and poorly organised. For pancreatic cancer, wide disparities in surgical outcomes between District General Hospitals and specialist tertiary centres were observed [174, 175]. All this led to the introduction of "Improving Outcomes Guidance in Upper Gastro-Intestinal Cancer" [176], a reform strategy with a number of specific recommendations, including centralising curative services into specialist cancer centres and setting up multi-disciplinary teams among clinicians of each hospital [177]. Currently, specialist centres for pancreatic cancer cover a population of 2–4 million people, either as a stand-alone pancreas-specific centre or as part of a Hepato-Pancreato-Biliary (HPB) centre. Patients referred to a pancreatic centre are given a diagnosis, and the specialist Multidisciplinary Team decides the best management. Surgical resection is carried out in the specialist centre, but oncological medical therapy and palliative care are undertaken either centrally or at the referring unit.

5.2.1 The role of specialist centres in resection rates (Research Paper 5)

5.2.1.1 Study findings

The main aim of Research Paper 5 was to investigate variation in resection rates and survival from pancreatic cancer between the 23 HPB centres in England where all resections are centralised. Changes in incidence rates of pancreatic cancer were also estimated. All analyses were stratified by three broad morphologic categories: exocrine carcinomas, pancreatic neuroendocrine tumours (PNET), and other malignant cancers of the pancreas. The stratified analysis was justified as pancreatic cancers have different clinical and epidemiological characteristics. However, emphasis was given to exocrine tumours as they represent more than 97% of all pancreatic tumours.

All patients diagnosed with a pancreatic tumour during 1995–2014 were included in the analysis. The main source of information was the National Cancer Registry database which was linked to HES records and the Cancer Analysis System (CAS) to derive data on treatment and stage. With the contribution of the commissioner, Pancreatic Cancer UK, and clinical specialists, we were able to map NHS Trust hospitals, hospices and Primary Care Units where patients were assigned based on treatment or diagnostic information, to the areas covered by the 23 HPB centres in England.

For the main aim, I examined variation in regional resection rates and up to 5-year age-standardised net survival for patients diagnosed during 2000–2013. To evaluate whether regional variation in pancreatic cancer survival is higher than what would be expected due to random variation, I plotted the survival estimates in each geographical area covered by the pancreatic specialist centres around the national average survival in England using funnel plots allowing to easily identify excess of variation not due to chance [178]. This strategy of analysis was repeated in resected and non-resected patients.

Overall, survival from pancreatic cancer improved between 2000-2013 in England and survival was higher among resected than non-resected patients. The resection rate remained low; at the national level, only 8.9% of the 23,415 patients diagnosed with

an exocrine tumour in 2010–2013 were resected. Between centres the number of resections varied, but it did not seem to explain the variation in one-year net survival for patients who were resected.

5.2.1.2 A comment on methods

The main limitation of this study was the potential residual confounding. Variations in pancreatic cancer survival between specialist centres cannot be fully explained by the number of resection performed in each centre. Although the approach aimed to provide a proxy for the system-level factors attributed to high-volume centers, such as surgeon experience, availability of cancer nurses, infrastructure and technology, it is not possible to explain the variation without also adjusting for the case-mix of patients receiving treatment in the specialist centres. In particular, adjusting for the stage at diagnosis, routes to diagnosis, socio-economic deprivation and comorbidities would have provided a more accurate insight as to the systemic components contributing to the variation observed. However, more than 60% of the stage was missing for pancreatic cancer patients diagnosed between 2010-2013, which made it impossible to perform any stage-specific analysis. In recent years, the completeness of stage data for all cancers diagnosed in England has increased to almost 90% [179]. A similar improvement was seen for pancreatic cancer.

Further, the design of the study was more descriptive than explanatory. To adjust for a range of covariates, patient- or system-related, hierarchical modelling could be applied. This would allow to model pancreatic cancer survival, adjusting for fixed effects of patient- and system-level variables and random effects at the hospital level.

Alternatively, a causal framework for observational data would help disentangle the causal effect of each variable. The use of Directed Acyclic Graph (DAG), would help identify, based on the understanding of the structural relationship between variables, which variables have to be considered to study the association between resection rates and cancer survival. Furthermore, identifying the ones that are available and the ones that are missing would have helped to understand the potential spurious associations

due to selection and collider biases. Additionally, we would aim to estimate the total causal effect as well as the effects mediated by system (e.g. hospital characteristics) and patient (e.g. stage) factors, an important step towards clinical intervention.

5.2.1.3 Impact of the study

This is the first study to evaluate national incidence and survival trends for pancreatic cancer and to assess variation in survival between areas covered by the 23 pancreatic cancer specialist centres for all patients in England. Commissioning this study was part of the Pancreatic Cancer UK charity's effort to inform the public, support its campaigns to raise money for research and press parliament and other bodies for more research.

The study showed that the incidence of pancreatic cancer in England has increased slightly in the last 20 years pointing to changes in the prevalence of lifestyle and environmental factors. Survival remains particularly poor for pancreatic cancer patients, especially those diagnosed with exocrine tumours. This means that the burden of pancreatic cancer will likely increase in the next years and steps need to be taken to prevent it.

The lack of specific early symptoms, advanced stage at diagnosis, and rapid progression are all obstacles to timely diagnosis and treatment. Emergency presentation is still the most common route of diagnosis, particularly among patients living in more deprived areas [180]. Centralisation of cancer care in high-volume providers has led to lower post-operative mortality and morbidity for cancer and other non-communicable diseases [181, 182]. This was mainly attributed to the clinical teams of experienced surgeons, skilled multidisciplinary teams, the use of advanced tumour imaging methods, and better postoperative care facilities [183, 184]. Despite this reform, resection rates for pancreatic cancer in England remain low and large geographical variation in outcomes point to alternative healthcare system and organisational factors. Variation in the quality of oncological care in the palliative and adjuvant settings, the number of specialised surgeons or clinical nurses in each centre, and referral patterns between local or specialist hospitals may have all played a role. More research has to be conducted

around the implementation of centralisation, distribution of resources and access to treatment.

Chapter 6

Discussion

Reflecting on the aim of this PhD dissertation, the findings confirmed that the more socio-economically deprived patients in England experience worse cancer survival and lose more life-time due to cancer than the less deprived patients with the same tumour and demographic characteristics. The introduction of the NHS Cancer Plan in 2000 and subsequent cancer policies improved cancer survival for all but made little to no difference in reducing the socio-economic inequalities in cancer survival at least until 2013.

Inequalities in cancer outcomes, either by socio-economic status or demographic characteristics are the summary of inequalities that occur along the cancer pathway. It is not clear what causes those inequalities but more than 20 years of cancer policies and initiatives can provide some indication as to what has worked and what not.

In the pre-diagnostic stage, socio-economic inequalities in vaccination and screening participation disproportionately affect female cancers such as breast and cervical cancers [69, 70]. A social gradient has also been seen in the NHS bowel cancer screening with lower uptake among more deprived people and particularly women [149]. In the diagnostic stage of the cancer pathway, inequalities are manifested with disproportional delays in diagnosis among more deprived populations and ethnic minorities, with a higher proportion of Emergency Presentation [157], more advanced stage at diagnosis or longer interval from the first primary care presentation to cancer diagnosis and treatment [153].

From early on, cancer policymakers emphasized the role of patient-related factors such as health behaviours and cancer awareness. After the 2000 NHS Cancer Plan, cancer

policies such as the 2007 "Cancer Reform Strategy" [12] and the 2011 "Improving Outcomes: A strategy for cancer" [142], laid out plans on how to improve cancer outcomes which included a range of activities from cancer prevention, early diagnosis and better access to treatments. As a response to these strategies, the "Be Clear on Cancer" [145], one of the largest awareness programmes was launched in 2010 with the aim to promote early diagnosis and early recognition of signs and symptoms of cancer, targeting people from lower socio-economic status wherever possible. The programme was run for almost a decade and included several campaigns for various cancer sites, engaging with the public through a range of mass media outlets and platforms.

Indeed, cancer patients from more socio-economically deprived areas tend to delay presentation to their GP [185], have lower cancer awareness and report more perceived barriers to seeking medical help [186] than their more affluent counterparts. Repeated evaluations of the "Be Clear on Cancer" campaigns showed an overall positive impact on cancer awareness, GP attendance rates and cases diagnosed however, it was not clear whether they had any impact on cancer survival [187] and in particular, on socio-economic inequalities in cancer survival.

I showed that more deprived colon cancer patients have similar hospital admission rates as the less deprived, suggesting that there is no considerable difference between those groups in the way they engage with health services. At the primary care level, we know that the GP consultation rate is similar between the emergency presenters and non-emergency presenters [188] and that patients with comorbidities consult more frequently with cancer symptoms at least one year before cancer diagnosis [159]. Given that Emergency Presentation and comorbidity burden are higher among more deprived patients, this pattern in primary care suggests that discrepancies in cancer outcomes between socio-economic groups cannot be totally explained by the individuals' failure to see their GP. In contrast, the fact that the more deprived have a higher use of emergency hospital services and that most of these admissions are for non-specific symptoms, reinforces the hypothesis that there may be successive barriers in access to primary and secondary care that lead patients to seek help in an emergency setting. It

is unlikely that patients choose to bypass primary care, given the long waits [189] and risks of infections in A&E departments.

In primary care, virtual or form-based online triage and online appointments, may present access barriers to individuals with limited digital skills. GP consultation length at around 9 minutes for face-to-face and 5 minutes for telephone appointments is among the shortest in Europe and is even lower for more deprived populations [190–192]. Although it is unclear how GP consultation length affects outcomes [193], it may be an important parameter for a more efficient communication with more deprived patients or other under-served populations [194].

Another indication of structural barriers in cancer diagnosis, is the use of referral pathways, and in particular the contrast between the higher use of EP and the lower use of the Two-Week Wait (TWW) referral pathway among more deprived populations. The TWW along with the NHS Cancer Waiting Times standards set the acceptable timeframe between the GP referral to the first consultant appointment or the initiation of cancer treatment [195]. The Two-Week Wait (TWW) urgent referral route was introduced for urgent GP referral to consultant appointment within 14 days, drawing from the updated NICE referral guidelines [196]. Those standards were implemented nationally and reporting the number of people seen within those standards were routinely published as official statistics to monitor progress [197]. Whilst the referral and detection rates increased steadily since the implementation of the standards, the conversion rate, i.e., cases that turn out to be cancer, declined from around 11% to 7% between 2010 and 2020. Additionally, the referral, detection and conversion rates were all lower in the more deprived than the less deprived [198]. All these combined, point to a potential misuse of the pathway which may have also impacted on other referral pathways, such as EP. Despite a small reduction from around 30% in 2006 to 23.1% in 2018, EP is still high among more deprived patients.

On the treatment phase of the cancer pathway, inequalities often occur due to barriers in access to treatment and variation in clinical practice. Access to optimal treatment and hospital care seems to be socially and geographically patterned [173, 199]. More deprived patients are less likely to receive the optimal treatment [46, 199] and more

likely to be re-admitted as an emergency after discharge [200]. Under-treatment and wide geographical variation in treatment modalities across England for the same tumour and patient characteristics have also been observed [201, 202].

A strategy to minimize variation in outcomes and ensure better quality of care and, in particular, of surgery, is the centralisation of cancer care into high-volume centres. In England, this happened gradually for prostate, bladder, kidney, and oesophagogastric cancers [182]. The evidence suggests that the advantages are due to the higher degree of specialisation and experience among the teams performing a large number of surgeries, often accompanied by better equipment and infrastructure [203, 204]. Implementation of centralisation has been particularly beneficial for low-volume cancers or cancers that require high-risk resection [205–207].

However, as I demonstrated in my dissertation, for pancreatic cancer, centralisation of resections into the HPB centres did not have the anticipated impact on outcomes. Years after its implementation between 2001 and 2006, there is still considerable geographical variation in pancreatic cancer survival and low resection rates across England. Travel time has often been cited as a drawback of centralisation [204, 208–211] which results from reducing the number of surgical or care centres where patients can receive treatment.

The type of treatment received by patients is often influenced by geographical distance or access to the hospital [211–213]. This may be even more exacerbated among more deprived patients who often lack the means, the social support or even the time required to travel further for their treatment. For instance, in London, patients from more deprived areas rarely travel outside of their Clinical Commissioning Group (CCG) to receive treatment in hospitals other than their local hospital, in contrast to patients residing in more affluent areas [173].

In recent years, NHS spending on healthcare has increased at a much slower pace than a decade earlier, despite the increasing inflation. It now accounts for around 9% of the Gross Domestic Product (GDP) which ranks the UK around or below the average spending of other comparable OECD countries. This restriction of spending has had

a significant impact on cancer services and especially on workforce shortages among clinical oncologists, nurses, radiologists and other specialties.

The vast majority of the NHS budget is allocated to the newly introduced integrated care boards (ICBs). ICBs are health administrative areas that are responsible for planning and commissioning health and care services in the geographical area under their jurisdiction. Those include primary and secondary care services, and emergency and community care. In 2022, ICBs replaced the CCGs that existed since 2013, and previous to the CCGs other health geographies that were in place such as the Primary Care Trusts (PCTs). Although allocation of NHS funding to ICBs is based on a statistical formula that calculates the target funding allocation based on their population's needs, often it is not what they receive [214]. Frequent changes in the organisation and commissioning of cancer services have been an obstacle in the assessment of resources allocation and its impact on socio-economic and geographical variation in cancer outcomes.

The structural complexity of the NHS as a health system is also reflected on the cancer pathway [23]. There are numerous inputs and decisions taken by NHS staff at each step of patients' journey from the cancer diagnosis to treatment, on which they have little control. Their time with health professionals is often limited and may often be left unsure as to what follows in their journey. The extent of this has been recognised and the role of cancer pathway navigator was introduced in the 10-year Cancer Plan, to assist patients and clinicians [215]. It may be early days to evaluate the impact this will have on inequalities in cancer but it seems as a complex solution to an obvious problem. Instead, simplifying the cancer pathway as well as the access to and delivery of cancer care could have the desired impact.

6.1 Conclusions

Socio-economic inequalities in cancer outcomes have been persistent in England, costing in lives and resources. With the rising cancer incidence among young adults and the growing burden of cancer, these are likely to become worse.

The source of these inequalities is not clear but potentially stems from the interaction of patients' complex needs and the complexities of the healthcare system. My PhD dissertation highlights health system barriers in diagnosis and treatment of cancer that disproportionately affect under-served populations and those most in need. Focusing more on cancer awareness and patient-related factors than health-system factors, and introducing new policy interventions without prior consideration of their impact on socio-economic inequalities may be two key lessons learnt from over 20 years of cancer policies in England.

Future policies and interventions should prioritise inequalities and focus on building a health care system that does not require resources and education or rely on disproportional initiative from individuals to provide the optimal care. Reducing barriers in access, simplifying the cancer pathway and keeping cancer patients well-informed on their journey can have an positive impact on reducing socio-economic and other demographic inequalities in cancer outcomes.

6.2 Final comment

Cancer is a disease that affects people's lives every day, in a profound way. Every person diagnosed with cancer should feel hopeful that they will have the same opportunity to live a longer and healthier life, no matter their income, ethnic or religious background. Researchers and policymakers should all work together to make this happen.

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Part II

Portfolio of publications

Research Paper 1

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1604651	**Title**	Ms
First Name(s)	Aimilia		
Surname/Family Name	Exarchakou		
Thesis Title	Inequalities in cancer care in England: from diagnosis to treatment		
Primary Supervisor	Professor Bernard Rachet		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLoS One		
When was the work published?	5 December 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	PhD by Prior Publication		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the lead author of this publication. I decided the analytic strategy, conducted the data analysis and produced the plots and figures. I drafted the first version of the manuscript.

SECTION E

Student Signature	[redacted]
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Supervisor Signature	[redacted]
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PLOS ONE

RESEARCH ARTICLE

Colorectal cancer incidence among young adults in England: Trends by anatomical sub-site and deprivation

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Abstract

Background

Colorectal cancer incidence in the UK and other high-income countries has been increasing rapidly among young adults. This is the first analysis of colorectal cancer incidence trends by sub-site and socioeconomic deprivation in young adults in a European country.

Methods

We examined age-specific national trends in colorectal cancer incidence among all adults (20–99 years) diagnosed during 1971–2014, using Joinpoint regression to analyse data from the population-based cancer registry for England. We fitted a generalised linear model to the incidence rates, with a maximum of two knots. We present the annual percentage change in incidence rates in up to three successive calendar periods, by sex, age, deprivation and anatomical sub-site.

Results

Annual incidence rates among the youngest adults (20–39 years) fell slightly between 1971 and the early 1990s, but increased rapidly from then onwards. Incidence Rates (IR) among adults 20–29 years rose from 0.8 per 100,000 in 1993 to 2.8 per 100,000 in 2014, an average annual increase of 8%. An annual increase of 8.1% was observed for adults aged 30–39 years during 2005–2014. Among the two youngest age groups (20–39 years), the average annual increase for the right colon was 5.2% between 1991 and 2010, rising to 19.4% per year between 2010 (IR = 1.2) and 2014 (IR = 2.5). The large increase in incidence rates for cancers of the right colon since 2010 were more marked among the most affluent young adults. Smaller but substantial increases were observed for cancers of the left colon and rectum. Incidence rates in those aged 50 years and older remained stable or decreased over the same periods.

sensitive data. Detailed information on the application process can be found at https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data. Population counts are publicly available from the Office for National Statistics (ONS) at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates. The authors did not have special access privileges.

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Conclusions

Despite the overall stabilising trend of colorectal cancer incidence in England, incidence rates have increased rapidly among young adults (aged 20–39 years). Changes in the prevalence of obesity and other risk factors may have affected the young population but more research is needed on the cause of the observed birth cohort effect. Extension of mass screening may not be justifiable due to the low number of newly diagnosed cases but clinicians should be alert to this trend.

Introduction

Colorectal cancer is one of the commonest cancers worldwide. In 2016, it was the third most frequent cancer among men and women in England, accounting for 12% of all new cancer cases [1]. It is predominantly a disease of older people, with the highest incidence rates amongst adults aged 70 years and over [2].

In several high-income countries, including the United States, Australia and Canada, incidence of invasive colorectal cancer has declined in older men and women, partly because of screening programmes for colorectal cancer [3–5], which enable the detection and removal of pre-invasive polyps. In the United Kingdom, the National Health Service (NHS), introduced population-based screening in 2006 for all people aged 60 years and over, using the faecal occult blood test.

Recent population-based studies have shown that colorectal cancer incidence has been increasing in age groups not currently targeted by screening programmes, especially adolescents and young adults [6–10]. In the United States, colorectal cancer incidence in the under-50s is higher now than it was in the mid-1990s, with marked differences between the sexes and between racial and ethnic groups [11–13]. In the United Kingdom, age-standardised incidence rates have remained stable, but rates in adults aged 20–39 have accelerated rapidly in the last 25 years [9].

Socioeconomic variation in colorectal cancer incidence in the UK, has shifted. In the 1980s, affluence carried a higher risk of colorectal cancer, but during the 1990s, surveillance data pointed to an increased risk for adults, especially men, in areas of higher deprivation. Since then, in the period 1996 to 2010, an association has emerged between colorectal cancer incidence and deprivation in men, but not in women [14, 15]. However, a deprivation gradient in women became apparent in 2010–2012 [16].

In this study, we describe colorectal cancer incidence trends among young adults in England over a 44-year period. We also examine differences in these trends by anatomical sub-site and between socioeconomic groups.

Methods

Study design and participants

This is a longitudinal study, analysing trends in population incidence rates of colorectal cancer over the period 1971–2014 in England.

We obtained anonymised individual records from the National Cancer Registry for England, held by the Office for National Statistics (ONS) for persons diagnosed with colorectal cancer between 1971 and 2014.

ONS uses standardised procedures to ensure high-quality data. We applied additional checks to identify and exclude incomplete, ineligible or inconsistent tumour records [17], as well as records of a second primary tumour in the colon or rectum in the same person. We excluded less than 5% of all records, leaving 1,073,624 adults aged 20–99 years diagnosed with a primary, invasive malignancy of the large bowel during 1971–2014. We grouped cancers into anatomical sub-sites: left colon (153.2–154.0, C18.5-C18.7), right colon (153.0–153.6, C18.0-C18.4), rectum (154.1, C19-C20) and unspecified tumours of the colon (153.8–153.9, C18.8-C18.9) [18–20].

We examined overall incidence trends for seven age groups (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–99 years), chosen to enable comparisons with studies in the United States and Australia [8, 21]. We further analysed incidence trends by deprivation and anatomical sub-site for young adults, aged 20–39 years.

We obtained information on deprivation from the Index of Multiple Deprivation (IMD 2015) [22], an ecological measure based on scores in seven distinct domains of deprivation assigned to each of the so-called Lower-Layer Super Output Areas (LSOAs). LSOAs comprise 32,844 small administrative areas that cover the whole of England. They are designed to be relatively homogeneous for a range of socio-economic variables, with an average population of only 1,500 [23]. IMD 2015 uses the geographic boundaries of LSOAs, as revised following the 2011 Census. IMD scores for each domain can be used individually or combined for a summary measure of deprivation. For this study, we used the combined IMD scores, ranked in five quintiles. These were defined by the national distribution of LSOA scores in seven domains: Income, Employment, Education, Health and Disability, Crime, Barriers to Housing and Services and Living Environment Deprivation. Patients were assigned to one of five deprivation levels from 1 ("least deprived", or "most affluent") to 5 ("most deprived") according to the patient's postcode of residence at the time of diagnosis.

The number of colorectal cancer registrations between years 1971 and 2014, by year, sex and age group were applied to the corresponding populations from ONS to obtain the annual incidence rates [24].

Incidence trends by sub-site and deprivation level were focused on the most recent period (2001–2014), because population counts by IMD 2015 deprivation score have only been available since 2001 [25].

Ethical approval

The data used in this study were analysed under approvals from the UK's statutory Health Research Authority (PIAG 1-05(c)/2007; ECC 1-05(a)2010) and NHS Research Ethics Committee (13/LO/0610).

Statistical analyses

We used the Joinpoint Regression Program from the US National Cancer Institute [26] to analyse trends in the incidence rate. This methodology fits the simplest linear trend to the data in a given calendar period. The linear trends within successive calendar periods are joined at knots or "joinpoints", which mark statistically significant changes (increase or decrease) in the slope. The location (calendar year) of the knots is determined by a Monte Carlo permutation test with a two-sided statistical significance of $\alpha = 5\%$. This gives a piecewise linear trend over the entire period covered by the data.

We fitted a generalised linear model (log-linear) to the incidence rates, with a maximum of two knots, allowing us to describe trends in the incidence rate as the annual percentage change (APC) during up to three successive calendar periods. The knots, and therefore the length of

the calendar periods, may differ between analyses. The maximum length of the incidence trends was between 1971 and 2014 for the rates by sex, age group and sub-site and between 2001 and 2014 for the rates by sub-site and deprivation. For the age-standardised rates we used the European Standard Population weights, modified to reflect only the adult population (15–99 years).

Results

Incidence by age group

During 1971–2014, 1,073,624 people aged between 20–99 years were diagnosed with colorectal cancer in England (Table 1 and S1 Table), of whom 562,833 were males (52.4%) and 510,791 females (47.5%).

The age distribution is shifted to older ages with 81.3% of cases aged over 60 years old. Only 3,148 colorectal cases (0.2%) were aged 20–29 years and 11,643 (1.0%) aged 30–39 years (S1 Table).

Age-standardised incidence rates in males increased by 1.3% (95% confidence interval (CI): 1.1–1.4%) per year between 1971 and 1998 but stabilised during 1998–2012 and decreased by 3.4% (95% CI: -6.3- -0.5%) per year during 2012–2014 (S1 Fig). Rates among females remained relatively stable in 1971–2014 (0.6% per year; 95% CI: 0.5–0.6%).

Colorectal cancer incidence rates in young adults (aged 20–39 years) remained 40–180 times lower than in persons aged 60–69 years during 1971–2014 (S2 Table). Among those aged 20–29 years, the incidence rate was 0.7 per 100,000 in 1971 and fell by an average 1.5% per year during 1971–1993. The decline was similar in 30-39-year-olds (1.7% per year; 1971–1990) (Table 1). Among those aged 40–49 years, the decrease in incidence rates was smaller (0.3% per year, 1971–2003).

From the early 1990s, incidence rates increased substantially among adults aged 20–39 years.

For the youngest age group (20–29 years), the average annual increase was 8% (95% CI: 7.1–8.8%) per year, rising from 0.8 per 100,000 in 1993 to 2.8 per 100,000 in 2014 (S2 Table). For those aged 30–39 years, the annual increase after 2005 was 8.1% (95% CI: 6.2–10.0%) per year. In 2005, the incidence rate was 3.9 per 100,000, rising to 7.6 per 100,000 by 2014. We found a smaller annual increase in adults aged 40–49 years during 2003–2014 (1.5% per year).

In adults over 50 years of age, incidence rates remained stable or increased less rapidly, around 1% per year. For those aged 60–69 years, incidence rates actually fell by 4.7% per year from 2011 to 2014.

Incidence trends among young adults (20–39 years)

Anatomical sub-site. The increasing trend in colorectal cancer incidence in adults aged 20–39 years was more marked for cancers of the right colon than left colon and rectum. Incidence rates increased by an average 5.2% per year from 0.5 per 100,000 in 1991 to 1.2 per 100,000 in 2010. During 2010–2014, the rate of the increase accelerated sharply to 19.4% (95% CI: 14.5–24.6%) per year (Fig 1 and S3 Table), with the rate rising to 2.5 per 100,000 in 2014.

For left-sided colon cancer, incidence rates increased less rapidly, by 5.7% per year during 1998–2014 (Fig 2 and S3 Table).

Incidence rates for rectal cancer also increased in younger adults, by an average of 4.4% per year during 1990–2014 (Fig 3 and S3 Table). In contrast, incidence rates of colon tumours with unspecified sub-site fell by an average 3.2% per year between 1996 and 2014 (S3 Table).

Table 1. Annual Percentage Change (APC, %) in colorectal cancer incidence rates by sex, age and calendar period (segment) of diagnosis: England, 1971–2014.

	Persons* (N = 1,073,624)					Males* (N = 562,833)					Females* N = 510,791)				
Age (years)	Segment	APC (%)	95% CI			Segment	APC (%)	95% CI			Segment	APC (%)	95% CI		
20–29	**1971–1993**	-1.5	-2.6	to	-0.5	**1971–1994**	-0.7	-1.9	to	0.6	**1971–1993**	-2.2	-3.6	to	-0.7
	1993–2014	8.0	7.1	to	8.8	**1994–2014**	7.3	6.1	to	8.4	**1993–2014**	8.9	7.8	to	10.1
30–39	**1971–1990**	-1.7	-2.4	to	-1.0	**1971–1990**	-1.4	-2.3	to	-0.6	**1971–1994**	-1.8	-2.4	to	-1.1
	1990–2005	1.2	0.0	to	2.3	**1990–2006**	1.2	0.0	to	2.3	**1994–2009**	3.0	1.7	to	4.3
	2005–2014	8.1	6.2	to	10.0	**2006–2014**	8.4	6.3	to	10.6	**2009–2014**	12.0	6.5	to	17.7
40–49	**1971–2003**	-0.3	-0.4	to	-0.1	**1971–2008**	0.0	-0.2	to	0.2	**1971–2003**	-0.5	-0.7	to	-0.3
	2003–2014	1.5	0.7	to	2.3	**2008–2014**	1.9	0.1	to	3.8	**2003–2014**	1.9	1.0	to	2.8
50–59	**1971–1993**	0.7	0.5	to	0.9	**1971–1995**	1.2	1.0	to	1.5	**1971–2009**	0.0	-0.1	to	0.1
	1993–2014	0.1	-0.1	to	0.3	**1995–2014**	0.0	-0.3	to	0.3	**2009–2014**	2.0	0.1	to	3.9
60–69	**1971–2011**	1.1	1.0	to	1.2	**1971–1996**	1.7	1.4	to	2.0	**1971–2011**	0.6	0.5	to	0.7
	2011–2014	-4.7	-7.8	to	-1.5	**1996–2011**	0.8	0.3	to	1.3	**2011–2014**	-4.0	-8.0	to	0.2
						2011–2014	-4.9	-9.8	to	0.2					
70–79	**1971–1987**	0.7	0.4	to	1.1	**1971–1987**	0.8	0.4	to	1.2	**1971–2011**	0.8	0.7	to	0.9
	1987–2000	1.9	1.4	to	2.3	**1987–2000**	2.1	1.6	to	2.7	**2011–2014**	-3.1	-6.0	to	0.0
	2000–2014	0.1	-0.2	to	0.4	**2000–2014**	-0.2	-0.5	to	0.2					
80–99	**1971–2014**	0.9	0.8	to	1.0	**1971–2009**	1.1	1.1	to	1.2	**1971–2014**	0.6	0.6	to	0.7
						2009–2014	-0.4	-1.7	to	0.9					

* Diagnosed with colorectal cancer

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Socio-economic deprivation (2001–2014). Incidence rates in the two youngest age groups (20–39 years) were generally higher in the more deprived groups than in the less deprived (Table 2).

Whilst incidence rates increased consistently in all deprivation groups and at each anatomical sub-site, the increasing trend for cancers of the right colon accelerated sharply in the most affluent group, from 4.7% per year during 2001–2010 to 25.2% (95% CI: 12–39.9%) per year during 2010–2014. Crude incidence rates increased from 0.5 per 100,000 in 2001 to 3.0 per 100,000 in 2014. The rates of increase in the other deprivation groups were smaller, but still substantial, at 10–12% per year (Table 2).

Discussion

To our knowledge, this is the first study to examine incidence trends for colorectal cancer in relation to socio-economic deprivation and anatomical site in the younger population of England.

Whilst age-standardised colorectal cancer incidence rate in England has stabilised over the last decade, we found a sharp increase in the rate for young adults. This observation is in line with studies in Europe, the United States, Canada and Australia [6, 8, 9, 21, 27]. It is striking that incidence rates amongst young men and women aged 20–29 years and 30–39 years almost tripled between 1990 and 2014. Increases in incidence among men and women aged 40–49 years were much smaller. Rates in older age groups either remained stable or slightly decreased.

The rise in colorectal cancer incidence rates in England started after 1993 among 20-29-year-olds and after 2005 among 30-39-year-olds suggesting a cohort effect. In the preceding three decades, risk factors such as overweight and obesity had become more prevalent [28].

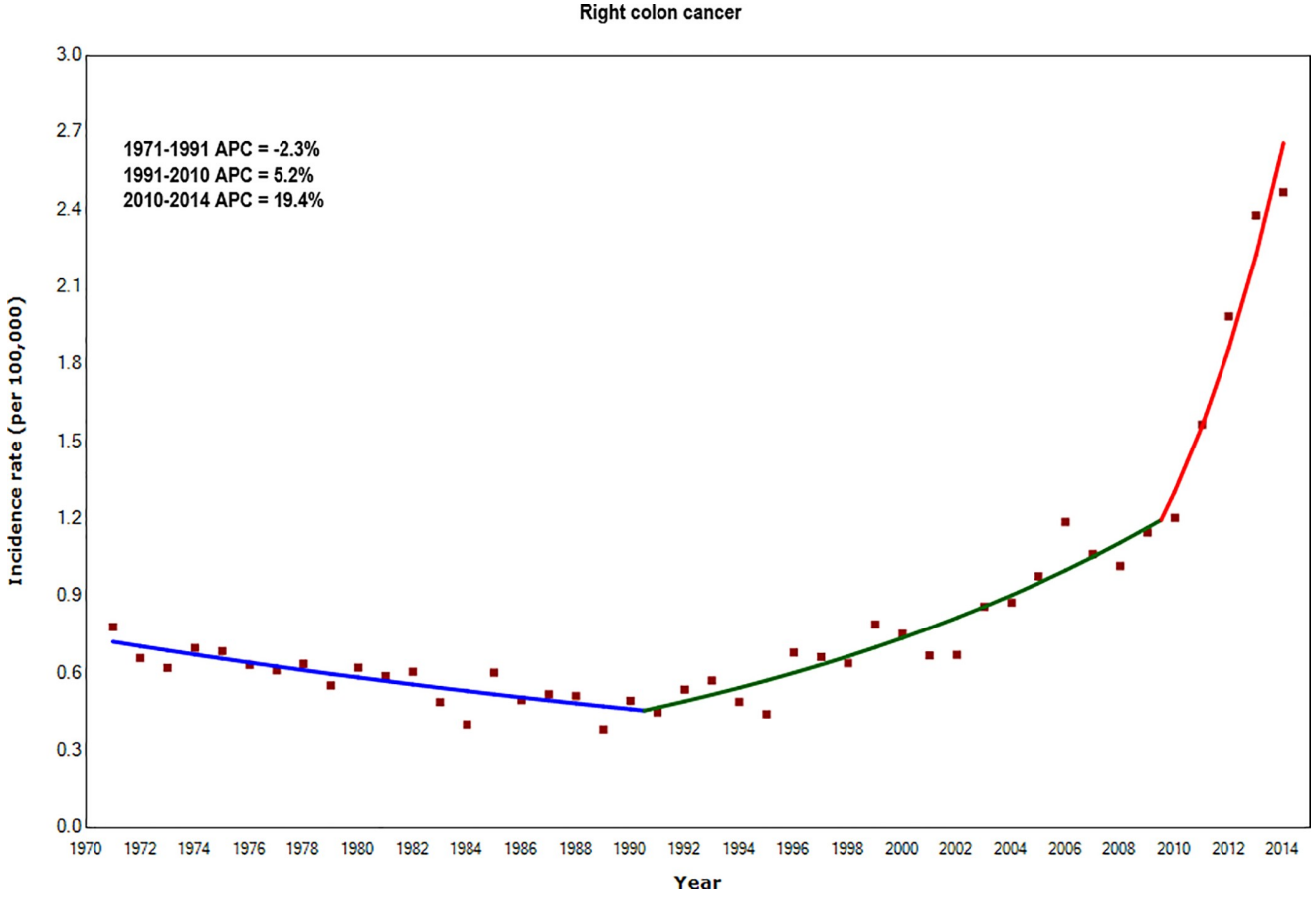

Fig 1. Annual Percentage Change (APC) in incidence rates of right colon cancer for adults aged 20–39 years: England 1971–2014.

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These risk factors would need to have acted early in life, probably childhood or adolescence, to account for an increase in colorectal cancer risk mainly restricted to young adults [29]. In England, overweight and obesity among children aged 2–15 years rose from 25% in 1995 to 30% in 2017 [30]. The prevalence of obesity is also related to the level of physical activity in the population. Activity levels in children 5–15 years old have dropped by 20% since the 1960s, and in 2017, only 18% of children and young people met the Chief Medical Officer's current guidelines of at least 60 minutes of exercise per day [30].

In the International Agency for Research on Cancer 2018 monograph, consumption of red meat was classified as "probably carcinogenic" and processed meat as "carcinogenic" [31]. Alcohol use and reduced consumption of dietary fibre are also associated with an increased risk of colorectal cancer [32]. Adolescents and young adults have been acquiring less of their energy intake at home and more at restaurants and fast-food outlets [33, 34], increasing their exposure to a poor-quality and potentially carcinogenic diet. However, evidence on the consumption of specific foods or nutrients during early life and the risk of colorectal cancer later in life is sparse and conflicting [35].

In contrast to the US studies [5, 21], we found that for young adults (20–39 years) the increases in incidence were more marked for cancers of the right colon, especially since 2010. Given that distribution of risk factors in the UK and the US are similar [36], we hypothesise that the shift to an increase in right-sided colon cancers in the UK could be due to different

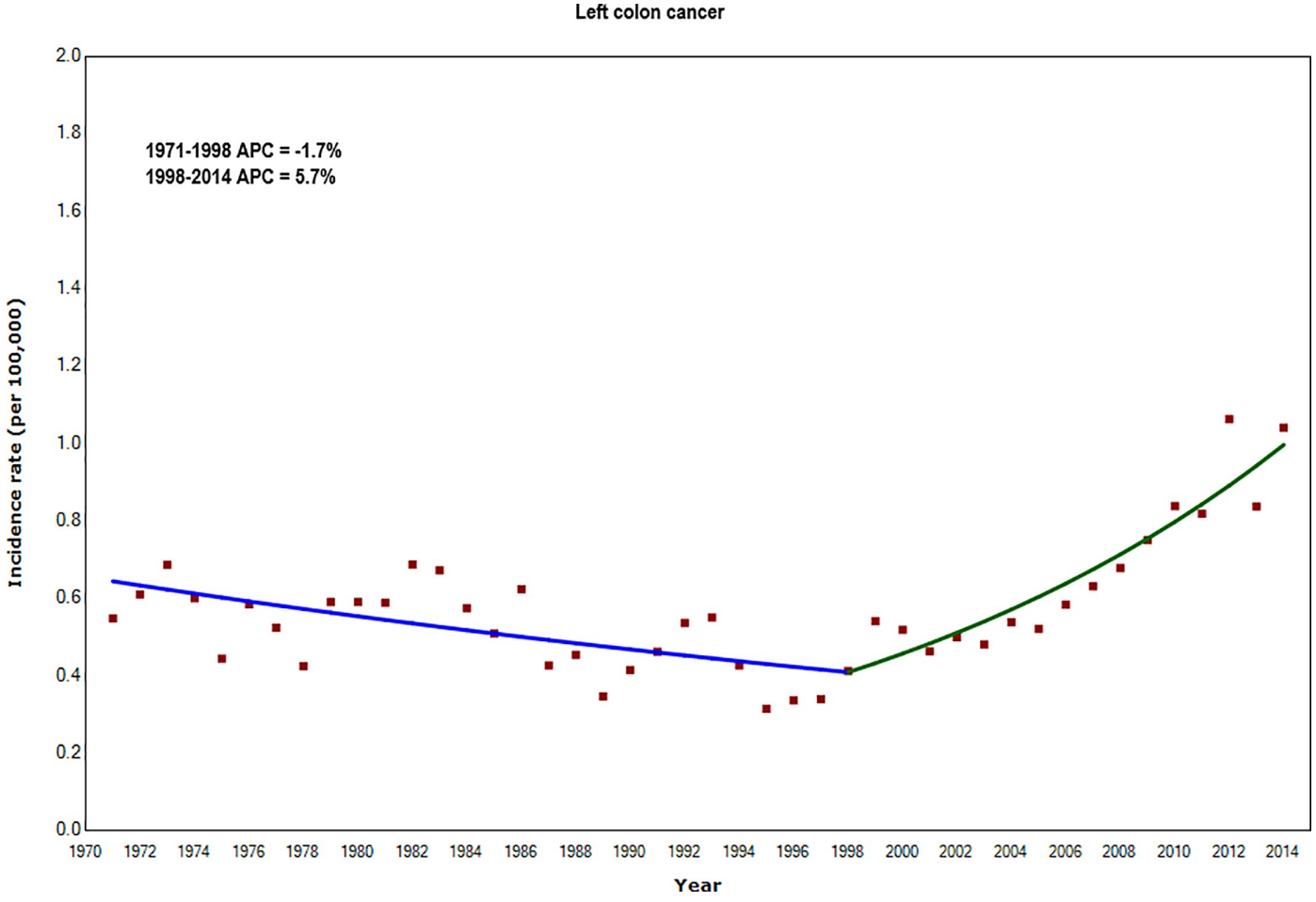

Fig 2. Annual Percentage Change (APC) in incidence rates of left colon cancer for adults aged 20–39 years: England 1971–2014.

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referral patterns and clinical management. The UK National Institute for Health and Care Excellence (NICE) guidelines do not recommend endoscopy or imaging for patients with IBS (Irritable Bowel Syndrome). By contrast, 45% of 200,000 US patients with IBS received an endoscopy during 2001–12, and 36% received at least three gastrointestinal medical procedures [37], suggesting that sub-clinical, early-stage tumours of the rectum and left colon might be detected more often.

Incidence rates in young adults increased for all deprivation groups and anatomical subsites. However, the increase in incidence rates for right-sided colon cancer was largely attributable to the trend in the most affluent persons: the sharp increases coincided in time and were similar in magnitude. Common risk factors such as obesity and diabetes are mainly associated with deprivation [38–40], but colorectal cancer screening uptake [41] and other health-seeking behaviours are more common among affluent groups, which could lead to a more timely diagnosis [42]. Clinical suspicion for colorectal cancer among young adults is generally low, while greater awareness of symptoms and better navigation of the health system could help explain the excess of right-sided colon cancer among the most affluent.

We have described an increasing incidence of colorectal cancer in young adults at the population level, but colorectal cancer in this age group remains uncommon, and clinical suspicion

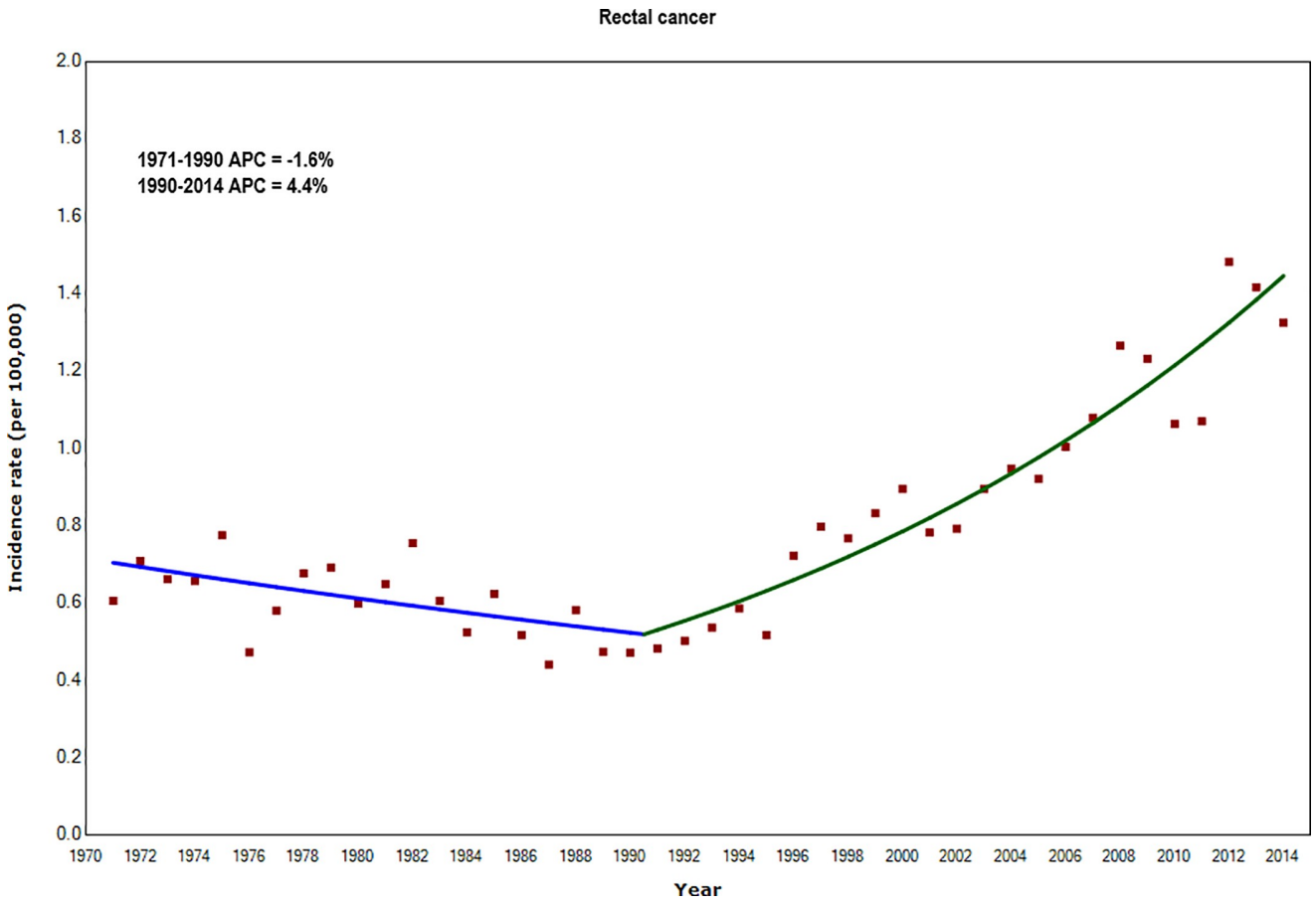

Fig 3. Annual Percentage Change (APC) in incidence rates of rectal cancer for adults aged 20–39 years: England 1971–2014.

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for colorectal cancer in a young adult will inevitably be lower than in an older adult. Nevertheless, red-flag symptoms in a younger person such as persistent changes in bowel function, rectal bleeding or abdominal pain should not be lightly dismissed as being unlikely to stem from a serious cause. It is important that clinical guidelines for colorectal cancer and postgraduate education curricula address this need, to enable primary care physicians to identify the right patients for referral, and to avoid additional strain on health service diagnostic resources.

The United Kingdom's national screening programme for colorectal cancer targets adults aged 60 years and over. Extension of mass screening to much younger age groups is not likely to be justifiable in public health terms [43] and is unlikely to become policy. However, if it were possible to delineate high-risk groups of young adults with sufficient precision, identifying symptomatic individuals for targeted colonoscopy could prove beneficial in preventing invasive malignancy or promptly diagnosing any invasive colorectal cancer.

In 2011, in the United Kingdom, the "*Be Clear on Cancer*" campaign [44] was launched to raise awareness of colorectal cancer symptoms and signs at a regional and national level. It was particularly successful in fighting the embarrassment associated with alarming symptoms [45]. However, it was specifically aimed at people aged over 55 years, and the message may have been less relevant to the younger population. Increasing awareness of the symptoms and signs of colorectal cancer among both the general population of younger adults and clinicians could

Table 2. Annual Percentage Change (APC) in colorectal cancer incidence rates by anatomical sub-site and deprivation for adults aged 20–39: England, 2001–2014.

Anatomical sub-site		Crude incidence rate		Trends in incidence				
		2001	2014	Segments	APC (%)	95% CI		
Right colon	Most affluent	0.49	2.90	2001–2010	4.7	- 0.4	to	10.1
				2010–2014	25.2	12.0	to	39.9
	2	0.79	1.80	2001–2014	9.8	6.3	to	13.4
	3	0.46	2.17	2001–2014	11.9	8.7	to	15.2
	4	0.65	2.70	2001–2014	11.4	8.7	to	14.2
	Most deprived	0.92	2.71	2001–2014	10.0	6.9	to	13.1
Left colon	Most affluent	0.44	1.33	2001–2014	7.8	3.7	to	12.0
	2	0.49	1.02	2001–2014	5.5	2.4	to	8.6
	3	0.46	1.10	2001–2014	8.6	6.0	to	11.3
	4	0.36	1.07	2001–2014	8.7	6.5	to	10.9
	Most deprived	0.56	0.77	2001–2014	4.6	2.0	to	7.3
Rectum	Most affluent	0.73	1.24	2001–2014	6.1	2.0	to	10.5
	2	0.86	1.57	2001–2014	4.5	1.9	to	7.2
	3	0.92	1.35	2001–2014	3.3	- 0.6	to	7.3
	4	0.62	1.28	2001–2014	4.8	1.7	to	8.0
	Most deprived	0.79	1.22	2001–2014	3.8	0.6	to	7.2
Colon, unspecified	Most affluent	0.20	0.23	2001–2014	2.4	- 1.6	to	6.6
	2	0.41	0.12	2001–2014	- 1.0	- 8.3	to	6.8
	3	0.32	0.17	2001–2014	- 7.6	- 11.9	to	- 3.1
	4	0.13	0.03	2001–2014	3.4	- 2.4	to	9.5
	Most deprived	0.30	0.15	2001–2014	- 7.7	- 11.5	to	- 3.8
All sub-sites	Most affluent	1.86	5.70	2001–2014	7.7	5.6	to	9.8
	2	2.55	4.51	2001–2014	6.1	4.1	to	8.1
	3	2.16	4.79	2001–2014	6.9	5.1	to	8.7
	4	1.76	5.07	2001–2014	8.0	7.2	to	8.8
	Most deprived	2.57	4.86	2001–2014	5.4	4.0	to	7.0

https://doi.org/10.1371/journal.pone.0225547.t002

be beneficial. Online symptom-checkers for the public and for primary care physicians could also be helpful [46].

Limitations

In 14% of colorectal cancers diagnosed during 1971–1990, the anatomical sub-site was not specified, but this proportion fell to 6% during 2003–2014 (S1 Table), probably due to better pathological reporting and improved cancer registration and coding. The bias introduced by any misclassification affected all age groups, hence it is unlikely to explain the observed trends.

The Index of Multiple Deprivation (IMD) is an ecological measure based on the characteristics of the area in which each individual is resident, but socio-economic heterogeneity among individuals in the same category of the IMD would bias any differences towards the null. This means that the differences in incidence trends between the five socio-economic levels we report here are likely to be an underestimation of the true differences.

Conclusion

More detailed studies are warranted to investigate the interplay between behavioural and environmental risk factors and its impact on the rapidly increasing incidence of colorectal cancer in young adults.

Despite the magnitude of the increase in incidence rates among young adults 20–39 years, the number of newly diagnosed cases remains far lower than in adults aged 50 years or more. Incidence rates in the over-50s decreased or barely changed. However, if the trend we report in this recent birth cohort were to continue unchecked, it would foreshadow a very substantial increase in the number of older adults being diagnosed with colorectal cancer over the next 20–30 years.

Supporting information

S1 Table. Characteristics of colorectal cancer patients in three calendar periods of diagnosis: England, 1971–2014.
(DOCX)

S2 Table. Annual incidence rates of colorectal cancer (per 100,000) by age group: England, 1971–2014.
(DOCX)

S3 Table. Annual Percentage Change (APC) in colorectal cancer incidence rates by anatomical sub-site and calendar period of diagnosis in adults aged 20–39 years: England, 1971–2014.
(DOCX)

S1 Fig. Annual Percentage Change (APC) in age-standardised colorectal cancer incidence rates (adults): England, 1971–2014.
(TIFF)

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Writing – review & editing: Aimilia Exarchakou, Liam J. Donaldson, Fabio Girardi, Michel P. Coleman.

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Research Paper 1 - Supplementary Material

S1 Table. Characteristics of colorectal cancer patients in three calendar periods of diagnosis: England, 1971-2014

	1971-1990			1991-2002			2003-2014		
	N	**%**	**%**	**N**	**%**	**%**	**N**	**%**	**%**
Sex									
Men	191,002	48.9		163,947	53.1		207,884	56	
Women	199,648	51.1		144,990	46.9		166,153	44	
Age (years)									
20-29	911	0.2		604	0.2		1,633	0.4	
30-39	4,445	1.1		2,893	0.9		4,305	1.2	
40-49	16,724	4.3		11,603	3.8		14,023	3.7	
50-59	51,265	13.1		35,527	11.5		41,261	11.0	
60-69	107,654	27.6		75,938	24.6		92,291	25	
70-79	133,638	34.2		106,433	34.5		118,764	32	
80-99	76,013	19.5		75,939	24.6		101,760	27	
Anatomical subsite									
Right colon									
153.0 (ICD-9)	26,105	28.3		1,344	1.8				
153.1 (ICD-9)	23,728	25.8		3,680	4.9				
153.4 (ICD-9)	29,736	32.3		12,028	15.9				
153.5 (ICD-9)	772	0.8		375	0.5				
153.6 (ICD-9)	11,745	12.8		4,489	5.9				
C18.0 (ICD-10)				28,692	38.0		53,225	46	
C18.1 (ICD-10)				1,162	1.5		4,490	3.9	
C18.2 (ICD-10)				11,380	15.1		29,650	26	
C18.3 (ICD-10)				3,835	5.1		10,521	9.0	
C18.4 (ICD-10)				8,500	11.3		18,429	16	
Right Colon total	*92,086*	*100*		*75,485*	*100*		*116,315*	*100*	
Right colon % of colorectal			*24%*			*24%*			*28%*
Left colon									
153.2 (ICD-9)	13,585	12.0		2,439	3.1				
153.3 (ICD-9)	71,734	63.6		17,617	22.6				
153.7 (ICD-9)	5,310	4.7		1,673	2.1				
154.0 (ICD-9)	22,243	19.7		6,750	8.6				
C18.5 (ICD-10)				3,901	5.0		8,002	6.0	
C18.6 (ICD-10)				5,268	6.7		10,577	7.9	
C18.7 (ICD-10)				40,467	51.8		78,709	58.6	
Left Colon Total	*112,872*	*100*		*78,115*	*100*		*134,311*	*100*	
Left colon % of colorectal			*29%*			*25%*			*33%*
Rectum									
1541 (ICD-9)	130,520	100		28,871	26.7				
C19.0 (ICD-10)				16,406	15.2		27,224	20	
C20.0 (ICD-10)				62,874	58.1		107,087	80	
Rectum total	*130,520*	*100*		*108,151*	*100*		*134,311*	*100*	
Rectum % of colorectal			*33%*			*35%*			*33%*
Colon, unspecified									
153.8 (ICD-9)	19,445	35.2		470	1.0				
153.9 (ICD-9)	35,727	64.8		17,021	36.1				
C18.8 (ICD-10)				955	2.0		1,007	3.9	
C18.9 (ICD-10)				28,740	60.9		25,116	96	
Colon, unspecified total	*55,172*	*100*		*47,186*	*100*		*26,123*	*100*	
Colon, unspecified % of colorectal			*14%*			*15%*			*6%*

S2 Table. Annual incidence rates of colorectal cancer (per 100,000) by age group: England, 1971-2014

	Age groups						
Year	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-99**
1971	0.7	4.4	16.5	49.4	117.6	234.2	321.7
1972	0.8	4.2	15.9	46.4	119.8	227.0	317.3
1973	0.6	4.2	15.9	48.5	119.3	243.7	355.1
1974	1.1	3.9	16.5	49.1	121.2	240.4	319.2
1975	0.8	4.0	17.2	48.9	123.8	253.9	320.0
1976	0.5	4.0	16.4	52.4	125.1	241.8	325.6
1977	0.7	3.4	14.3	44.4	114.6	223.6	309.3
1978	0.7	3.4	13.9	49.8	121.8	238.3	327.4
1979	0.6	3.9	16.8	55.1	129.3	249.1	342.2
1980	0.6	3.6	14.8	53.1	130.0	260.5	372.0
1981	0.6	3.6	18.0	53.5	129.2	254.7	372.0
1982	0.8	4.2	15.5	55.4	130.5	254.8	344.7
1983	0.7	3.6	16.9	52.8	132.7	256.8	382.1
1984	0.5	3.2	15.3	56.5	135.9	257.1	359.7
1985	0.7	3.6	14.8	56.3	136.6	262.4	371.0
1986	0.7	3.4	15.3	53.7	133.4	260.5	363.8
1987	0.7	3.1	15.7	53.8	133.2	251.5	360.2
1988	0.7	3.8	15.1	56.2	143.0	269.3	370.7
1989	0.6	3.0	15.7	56.7	153.8	284.2	384.4
1990	0.7	3.1	15.6	61.0	150.5	290.2	398.0
1991	0.5	3.3	15.5	60.5	159.2	278.9	396.0
1992	0.7	3.4	16.8	64.6	165.7	294.7	407.7
1993	0.8	3.8	16.3	63.9	173.0	304.3	414.7
1994	0.6	3.3	16.0	60.2	166.1	304.0	412.1
1995	0.5	2.9	14.9	63.3	167.1	298.6	413.0
1996	1.0	3.4	17.4	63.0	181.7	317.0	434.3
1997	0.7	3.7	17.4	62.3	178.3	329.3	424.0
1998	1.1	2.9	16.3	62.8	181.6	336.7	413.7
1999	1.0	4.0	16.6	63.0	176.0	340.0	439.5
2000	0.7	3.9	15.0	63.5	180.5	351.3	439.8
2001	1.0	3.5	14.7	62.0	171.3	332.7	441.1
2002	0.9	3.1	16.0	61.4	173.2	331.7	445.2
2003	1.4	3.7	15.0	60.7	174.2	332.3	440.2
2004	1.2	4.2	15.8	62.1	175.2	344.2	456.7
2005	1.6	3.9	16.4	66.2	167.9	348.9	453.0
2006	1.7	4.2	16.6	66.3	174.1	346.9	457.7
2007	1.6	4.2	15.5	61.0	181.5	345.7	455.1
2008	2.2	4.8	15.8	60.3	197.3	345.6	473.8
2009	1.6	5.6	16.6	59.9	196.2	346.6	490.1
2010	1.6	4.5	16.5	60.9	199.3	346.1	473.7
2011	2.3	5.8	17.0	63.9	192.7	352.5	464.4
2012	2.2	7.0	18.2	65.6	183.3	346.4	490.3
2013	2.4	7.2	17.5	64.8	172.3	327.7	462.3
2014	2.8	7.6	17.5	60.1	165.9	311.7	469.6

S3 Table. Annual Percentage Change (APC) in colorectal cancer incidence rates by anatomical sub-site and calendar period of diagnosis in adults aged 20-39 years: England, 1971-2014

	Persons (N=14,791)					Men (N=7,639)					Women (N=7,152)				
Anatomical sub-site	**Segments**	**APC (%)**	**95% CI**			**Segments**	**APC (%)**	**95% CI**			**Segments**	**APC (%)**	**95% CI**		
Right colon	**1971-1991**	-2.3	-3.3	to	-1.4	**1971-1989**	-2.2	-3.5	to	-0.8	**1971-1991**	-2.7	-4.1	to	-1.4
	1991-2010	5.2	4.3	to	6.1	**1989-2010**	4.5	3.4	to	5.6	**1991-2009**	5.8	4.3	to	7.4
	2010-2014	19.4	14.5	to	24.6	**2010-2014**	17.6	11.1	to	24.4	**2009-2014**	20.4	13.2	to	28.1
Left colon	**1971-1998**	-1.7	-2.5	to	-0.8	**1971-2002**	-0.7	-1.6	to	0.2	**1971-1997**	-2.3	-3.1	to	-1.4
	1998-2014	5.7	4.2	to	7.3	**2002-2014**	7.3	4.0	to	10.6	**1997-2014**	5.7	4.2	to	7.2
Rectum	**1971-1990**	-1.6	-2.7	to	-0.5	**1971-1991**	-1.8	-3.0	to	-0.7	**1971-1990**	-1.1	-2.7	to	0.5
	1990-2014	4.4	3.8	to	5.1	**1991-2014**	4.7	4.0	to	5.5	**1990-2014**	4.1	3.2	to	5.1
Colon, unspecified	**1971-1996**	0.2	-0.7	to	1.0	**1971-1996**	0.8	-0.5	to	2.1	**1971-2014**	-1.2	-1.7	to	-0.6
	1996-2014	-3.2	-4.8	to	-1.6	**1996-2014**	-3.7	-6.0	to	-1.4					

Research Paper 2

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Primary Supervisor	Professor Bernard Rachet		

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Impact of national cancer policies on cancer survival trends and socioeconomic inequalities in England, 1996-2013: population based study

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ABSTRACT

OBJECTIVE

To assess the effectiveness of the NHS Cancer Plan (2000) and subsequent national cancer policy initiatives in improving cancer survival and reducing socioeconomic inequalities in survival in England.

DESIGN

Population based cohort study.

SETTING

England.

POPULATION

More than 3.5 million registered patients aged 15-99 with a diagnosis of one of the 24 most common primary, malignant, invasive neoplasms between 1996 and 2013.

MAIN OUTCOME MEASURES

Age standardised net survival estimates by cancer, sex, year, and deprivation group. These estimates were modelled using regression model with splines to explore changes in the cancer survival trends and in the socioeconomic inequalities in survival.

RESULTS

One year net survival improved steadily from 1996 for 26 of 41 sex-cancer combinations studied, and only from 2001 or 2006 for four cancers. Trends in survival accelerated after 2006 for five cancers. The deprivation gap observed for all 41 sex-cancer combinations among patients with a diagnosis in 1996 persisted until 2013. However, the gap slightly decreased for six cancers among men for which one year survival was more than 65% in 1996, and for cervical and uterine cancers, for which survival was more than 75% in 1996. The deprivation gap widened notably for brain tumours in men and for lung cancer in women.

CONCLUSIONS

Little evidence was found of a direct impact of national cancer strategies on one year survival, and no evidence for a reduction in socioeconomic inequalities in cancer survival. These findings emphasise that socioeconomic inequalities in survival remain a major public health problem for a healthcare system founded on equity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Cancer survival in England has been improving steadily for all deprivation groups since the 1970s, but still lags behind that seen in comparable countries in Europe

A "deprivation gap" in survival persists between the least and the most deprived in England

WHAT THIS STUDY ADDS

Even though increasing cancer survival and reducing inequalities in survival have been among the main targets of national cancer policy initiatives implemented since 2000, this study found little evidence of a direct impact of these strategies on one year survival, and no evidence for a reduction in socioeconomic inequalities in survival

Introduction

Differences in cancer survival between less and more deprived patients have been well documented for most types of cancer and in different geographical settings.[1-7] There is evidence for some explanations related to patient, tumour, and healthcare characteristics, but these can only explain part of the differences depending on the cancer type and healthcare system.[8 9] Cancer survival in England has been improving steadily since the 1970s,[10] but socioeconomic inequalities in survival persist for most cancers,[11] despite concerted efforts and investment in the National Health Service.

After the Calman-Hine report in 1995,[12] the first fully detailed strategy to tackle cancer in England was the NHS Cancer Plan,[13] introduced in 2000. It set out the government's plans for investment and reform, aiming at improving prevention, delivery of care (including implementation of multidisciplinary teams), and research. It led to an inflation adjusted increase of 35% in annual expenditure on cancer services between 2001 and 2004. Among the main aims were improving cancer survival to levels comparable with the rest of Europe and reducing socioeconomic inequalities. In 2007, the Cancer Reform Strategy[14] focused on consolidation of progress made since publication of the NHS Cancer Plan and set out plans for cancer services over the ensuing five years. Again, tackling inequalities and promoting equality in access to cancer services in England were central to the strategy, which also led to the foundation of the National Cancer Equality Initiative in 2008, a multidisciplinary initiative dedicated to this purpose.[15] In 2008, the National Awareness and Early Diagnosis Initiative (NAEDI) was launched, with the purpose of stimulating action to diagnose cancer earlier and improve cancer outcomes. Some of the key target areas were tackling negative attitudes to cancer and the barriers to seeing a doctor, supporting primary care, and optimising access to diagnostic tests and referral pathways. These initiatives occurred concomitantly with major reorganisation of the NHS and funding pressure on NHS spending (reduction of the health spend as a proportion of the gross domestic product) after publication of a white paper in 2010.[16]

We investigated the effectiveness of the NHS Cancer Plan and subsequent strategies in improving one year survival and reducing socioeconomic inequalities in cancer survival, up to 14 years after the introduction

of the plan, in the context of major changes in the NHS since 2010. We focused on one year survival because most inequalities in cancer survival in England arise shortly after diagnosis.[17] We examined trends in cancer survival and in the deprivation gap in survival for patients receiving a diagnosis in three predefined calendar periods: 1996-2000 (before the cancer plan), 2001-05 (initialisation period), and 2006-13 (implementation period), with follow-up to 2014. This allowed comparison of trends before and after introduction of the NHS Cancer Plan, including an initialisation period to reflect the latency before such an extensive and wide ranging strategy might take effect. We also analysed the changes in survival patterns without fixing the calendar periods a priori, to examine survival trends after the successive cancer policy initiatives but without imposing assumptions on the calendar periods during which those changes might occur.

Methods

Data

We extracted data from the population based National Cancer Registry database held by the Office for National Statistics (ONS). The primary source of cancer registration records is a range of healthcare providers, such as hospitals, pathology laboratories, and other services that provide all the information on the cancer diagnoses in a given year. This information is collected and maintained by the National Cancer Registration and Analysis Service in Public Health England, which actively updates the database for up to nine months after the registration year. The vital status of registered patients with cancer (alive, emigrated, dead, not traced) is updated by ONS and the HSCIC (Health and Social Care Information Centre, now known as NHS Digital). The estimated completeness of this dynamic database is 98% at the registration calendar year, but it can reach 100% within five years.[18 19]

We included all young people and adults (age 15-99 years) with a diagnosis of one of the 24 most common primary, malignant (ICD-O (international classification of diseases for oncology) behaviour code 3), invasive neoplasms between 1996 and 2013, with potential follow-up until the end of 2014. These represent about 91% of all cancers diagnosed in England. Tumour site was coded according to ICD-10 (international classification of diseases, 10th revision),[20] whereas morphology and behaviour were coded according to the international classification of diseases for oncology, second edition (ICD-O-2).[21] The data owners undertake various cleaning procedures to ensure high quality of the data, but we also apply a standard set of additional checks for cancer survival analysis, aiming to flag or exclude incomplete, ineligible, or incoherent tumour records, as well as second or higher order tumours arising in the same organ as a previous primary cancer.[22] Overall, these procedures led to exclusion of less than 5% of patients. The analyses included over 3.5 million patients.

Deprivation

The index of multiple deprivation (IMD 2004)[23] is an ecological measure of deprivation, with seven distinct domains and a combined measure, assigned to individuals living within a given Lower-layer Super Output Area (LSOA). LSOAs are administrative geographical areas established to improve reporting of small area statistics in England and Wales. Patients with cancer were assigned to one of 32 482 LSOAs in England (mean population 1500) on the basis of their postcode of residence at diagnosis. For our study we used the income domain score, which measures the proportion of the population with low income in a given LSOA. The five deprivation categories were based on the fifths of the national distribution of scores for the 32 482 LSOAs in England and patients with cancer were assigned to the deprivation category of their LSOA (from 1 indicating "least deprived," or affluent, to 5 indicating "most deprived").

Net survival estimation

We estimated one year net survival for each cancer by sex, year of diagnosis (1996 to 2013), and deprivation category. Patients with a diagnosis between 1996 and 2013 had the potential to be followed up for at least one year, so we used the classic cohort approach.

Net survival is the probability of survival if cancer were the only possible cause of death. It is the only survival measure enabling comparisons between populations (ie, between periods and socioeconomic levels) in which mortality hazard from other causes may differ, because this measure does not depend on these hazards. Estimation of net survival requires the comparison of the overall mortality hazard experienced by the patients with cancer to their expected mortality hazard—that is, hazard from other causes of death. This leads to an estimate of the excess mortality hazard (ie, hazard of death due to the cancer of interest), which mathematically is the complement of net survival.[24] Because the cause of death is not considered as reliable in population based data, the expected mortality hazard of the patients with cancer is estimated in the general population that the patients come from. We therefore built life tables for the England general population by calendar year, sex, age, and deprivation.[25 26] In the absence of data on recent deaths in the general population, we used the 2011 mortality rates for 2012 and 2013.

We estimated net survival using the consistent non-parametric estimator defined by Pohar-Perme.[27] This estimator accounts for the informative censoring due to patient factors such as age—that is, when some groups of patients are more likely to be censored because of death from other causes. The estimator is implemented in Stata 14[28] within the *stns* command.[29]

Age standardisation

Survival estimates for all ages combined were age standardised with the International Cancer Survival Standard weights.[30] Age standardisation required to estimate survival in 18 450 unique combinations

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of cancer (20 in men and 21 in women), sex, year of diagnosis (18 years), deprivation (five categories), and age groups (five groups). In 562 of these combinations it was not possible to estimate survival owing to sparse data. In those cases, we combined the data for adjacent age groups and assigned the pooled survival estimate to both age groups, the corresponding weights for these age groups being also combined. If survival estimates were missing for more than one age group, we report only the unstandardised survival estimate (382 combinations). These issues arose mostly for mesothelioma, thyroid and testicular cancer, Hodgkin lymphoma, and myeloma, which tend to be rare in either very young or very old patients.

Trends in survival, deprivation gap, and trends in deprivation gap

We used multivariable linear regression to investigate the survival patterns for each cancer and by sex. The outcome was one year age standardised net survival and the predictors were year of diagnosis (representing the trend) and deprivation. The model also included an interaction between year of diagnosis and deprivation, which defined the temporal trend in the deprivation gap: the significance level of this term was set at 0.05. This allowed us to test the statistical significance of the interaction and to decide if there was evidence for a change in the deprivation gap.

A continuous linear effect was considered for the effect of deprivation. We tested a series of linear restricted regression splines with constrained knot location for the effect of year and the interaction term. Knots were fixed at the calendar years 2001 and 2006, to align with the three periods we defined in relation to the NHS Cancer Plan. The final number of knots was determined with an algorithm embedded in the *mvrs* program in STATA.[31] Starting with the model of maximum complexity, this closed-test algorithm uses a backward elimination to choose the best fitting spline, while the overall type I error is kept at a predefined level (here 5%).

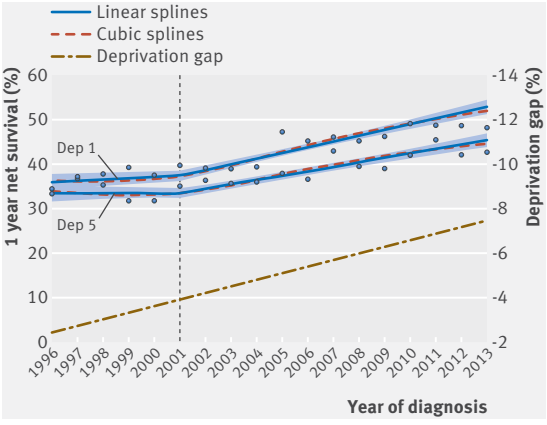

Fig 1 | Trends in one year net survival in the least and most deprived, and trends in deprivation gap (absolute difference between least and most deprived categories) for brain cancer in men

From the regression models applied to the entire dataset for each sex-cancer combination we estimated both survival and the deprivation gap in survival for each year. Survival is the predicted age standardised one year net survival for patients with a diagnosis in each calendar year. The deprivation gap is the absolute difference between the predicted net survival estimates for the most affluent and most deprived groups (fig 1). By convention, a negative value for the deprivation gap implies that survival was lower in deprived than in affluent patients. We derived 95% confidence intervals from the linear combination of coefficients acquired from the flexible models.

Relaxed assumptions

Our main analysis incorporated the assumption that 2001 and 2006 were starting points for any change in the slope of the trend in survival or in the deprivation gap in survival. We then relaxed this assumption by including an internal knot for each year in the initial model, again allowing the knots to be selected by the algorithm embedded in the command.[31] The deprivation gap was derived from the same final models as described previously. We performed similar analyses using cubic splines to allow for the possibility of non-linear trends.

Patient involvement

This study is part of the Cancer Survival Group's commitment to describe and explain inequalities in cancer survival affecting older patients, patients of low socioeconomic status, and all patients living in England and in the UK, where cancer survival still lags behind survival in other comparably wealthy countries.

We repeatedly receive feedback from patients with cancer and advocacy bodies at national and international meetings to the effect that the cancer survival statistics we produce are an invaluable support for their efforts to lobby for improved care of patients with cancer. We have a longstanding collaboration with the National Cancer Research Institute Consumer Liaison Group—a group of patients' representatives that is actively involved in our research. We organise regular meetings at which we discuss our research, exchange ideas, and receive valuable feedback. More than 40 members of this group participated in our most recent meeting, on 13 February 2017, at which our research (including this study) was presented and discussed in plenary session and in small groups. Two patients are also members of the Advisory Panel for the Cancer Survival Programme, of which this study is a component part. We recently received special recognition from Cancer Research UK for the involvement and engagement of patients in the design and delivery of our research.

Our international research programme on cancer survival is also officially endorsed by many cancer patient bodies, including the Association of European Cancer Leagues (Brussels, Belgium), the European Institute for Women's Health (Dublin, Ireland), and the European Cancer Patient Coalition. These agencies

Table 1 | Age standardised one year net survival (%) in men and women with a diagnosis of one of 24 cancers in 1996, and mean annual change (%) in successive calendar periods 1996-2013, England

	Men				Women			
		Mean annual change (95% CI)				Mean annual change (95% CI)		
Malignancy	Survival* 1996 (95% CI)	1996-2000	2001-05	2006-13	Survival* 1996 (95% CI)	1996-2000	2001-05	2006-13
Oesophagus	29.4 (28.1 to 30.7)	1.1 (1.0 to 1.2)			31.7 (30.0 to 33.3)	1.0 (0.8 to 1.1)		
Stomach	34.9 (33.7 to 36.1)	0.9 (0.7 to 1.0)			35.9 (34.5 to 37.3)	0.7 (0.6 to 0.8)		
Colon	67.0 (65.9 to 68.2)	0.7 (0.5 to 0.8)			78.7 (77.6 to 79.8)	0.6 (0.4 to 0.7)		
Rectum	73.2 (71.9 to 74.5)	0.6 (0.5 to 0.7)			74.3 (73.1 to 75.4)	0.5 (0.4 to 0.6)		
Liver	18.7 (17.3 to 20.1)	1.1 (0.9 to 1.2)			21.1 (19.1 to 23.0)	0.7 (0.5 to 0.9)		
Pancreas	13.2 (12.0 to 14.4)	0.7 (0.5 to 0.8)			13.4 (12.3 to 14.5)	0.9 (0.7 to 1.0)		
Larynx	82.7 (81.4 to 84.0)	0.1 (0.0 to 0.3)						
Lung	24.0 (23.0 to 24.9)	0.5 (0.4 to 0.7)		1.0 (0.8 to 1.3)	25.4 (24.5 to 26.4)	0.8 (0.6 to 0.9)		
Mesothelioma	28.3 (26.3 to 30.3)	0.2 (-0.3 to 0.8)	1.3 (1.1 to 1.5)		28.4 (26.0 to 30.8)	1.1 (0.8 to 1.3)		
Melanoma	92.2 (91.4 to 93.0)	0.3 (0.2 to 0.3)			95.6 (95.2 to 96.0)	0.2 (0.1 to 0.2)		
Breast					90.1 (89.5 to 90.6)	0.4 (0.3 to 0.4)		
Cervix					78.7 (77.6 to 79.8)	0.2 (0.1 to 0.3)		
Uterus					83.8 (83.0 to 84.6)	0.4 (0.3 to 0.5)		
Ovary					58.4 (57.2 to 59.5)	0.8 (0.7 to 1.0)		
Prostate	81.3 (80.4 to 82.2)	1.2 (0.9 to 1.5)	0.1 (-0.1 to 0.3)	0.6 (0.5 to 0.8)				
Testis	95.9 (84.7 to 97.2)	0.0 (-0.1 to 0.2)						
Bladder	82.9 (81.4 to 84.5)	-0.9 (-1.4 to -0.5)	0.1 (0.0 to 0.3)		75.1 (72.6 to 77.6)	-1.4 (-2.1 to 0.7)	-0.1 (-0.3 to 0.2)	
Kidney	60.9 (59.4 to 62.4)	0.6 (0.4 to 0.9)		1.4 (1.1 to 1.8)	59.3 (57.8 to 60.8)	0.8 (0.6 to 1.0)		1.5 (1.2 to 1.9)
Brain	34.7 (32.9 to 36.4)	0.2 (-0.3 to 0.6)	1.1 (1.0 to 1.3)		33.7 (32.4 to 34.9)	0.9 (0.8 to 1.0)		
Thyroid	83.1 (81.1 to 85.1)	0.0 (-0.3 to 0.4)		1.1 (0.6 to 1.5)	83.1 (81.8 to 84.3)	0.7 (0.5 to 0.8)		
Non-Hodgkin lymphoma	63.9 (62.6 to 65.1)	0.9 (0.8 to 1.0)			66.9 (65.7 to 68.0)	0.9 (0.8 to 1.0)		
Hodgkin lymphoma	87.5 (86.3 to 88.7)	0.1 (-0.1 to 0.2)			89.1 (87.6 to 90.5)	0.0 (-0.3 to 0.2)		0.5 (0.1 to 0.8)
Myeloma	63.1 (61.6 to 64.6)	0.8 (0.5 to 1.0)		1.9 (1.6 to 2.2)	62.3 (61.1 to 63.4)	1.1 (1.0 to 1.2)		
Leukaemia	62.4 (61.1 to 63.7)	0.3 (0.1 to 0.5)		1.0 (0.7 to 1.3)	59.2 (57.9 to 60.5)	0.6 (0.4 to 0.7)		

*Derived from the best fitting linear regression model for each cancer.

have all used our cancer survival estimates to press for improvements in cancer care locally, but also to improve cancer policy nationally.

Results

Trends in one year net survival

One year survival improved for 20 of the 21 cancers examined in women and 16 of the 20 cancers examined in men (table 1).

The largest improvements were observed for cancers that were of poor or intermediate prognosis in the 1990s (<65% for those with a diagnosis in 1996), such as cancers of the oesophagus, liver (men), lung (women), and kidney, mesothelioma, and myeloma. For these cancers, the average annual absolute increase in one year age standardised net survival was often greater than 1% over the whole study period (fig 2). Survival for men diagnosed as having cancer of the larynx or testis, or Hodgkin lymphoma, was already high in the 1990s, and it improved little by 2013.

For 26 of the 41 cancer-sex combinations, survival improved steadily from 1996, but with no statistically significant acceleration after 2006, ie, after the predefined implementation period. This was the case for eight of the 20 malignancies in men: six cancers of the digestive tract, melanoma, and non-Hodgkin lymphoma; and for 18 of 21 malignancies in women: six cancers of the digestive tract, lung cancer, mesothelioma, melanoma, four gynaecological cancers, brain cancer, thyroid cancer, non-Hodgkin lymphoma, myeloma, and leukaemia.

Changes in the survival trend were observed for several cancers. For mesothelioma in men, one year survival changed little during 1996-2000 (mean annual increase 0.2%), but accelerated to 1.3% each year during 2001-13 (table 1). A similar change occurred for brain tumours in men at the same time point (0.2% to 1.1% each year).

For thyroid cancer in men, one year survival changed little during the 10 year period 1996-2005, but then increased by 1.1% each year between 2006 and 2013. A similar pattern was seen for Hodgkin lymphoma in women, which increased by 0.5% a year between 2006 and 2013.

The one year survival trends seen during 1996-2005 accelerated from 2006 for lung cancer, myeloma, and leukaemia in men, and for kidney cancer in both sexes. The average annual increases during 1996-2005 were less than 1% a year, but increased up to 2% a year between 2006 and 2013. For kidney cancer, the annual rate of increase in one year survival doubled from 2006, increasing from 0.6% to 1.4% a year in men, and from 0.8% to 1.5% a year in women.

For prostate cancer, the mean annual increase in one year survival was 1.2% during 1996-2000, null during 2001-05, and 0.6% during 2006-13; by 2013, one year survival had reached 92.1%.

When we relaxed the assumption that the trend could only change in 2001 or 2006, fitting flexible splines that allow the trend to change from year to year, the results differed little (data not shown).

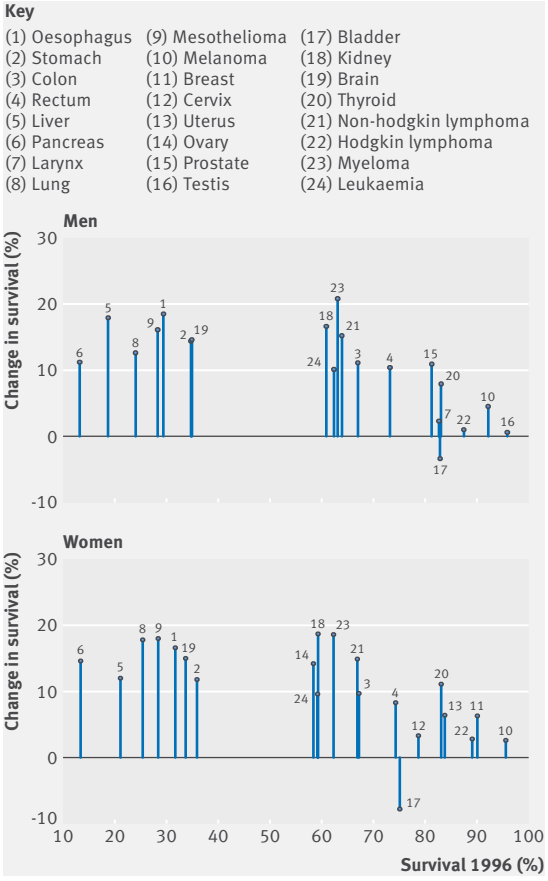

Fig 2 | Change in one year net survival between 1996 and 2013 for 20 cancers in men and 21 cancers in women, arrayed by ICD-10

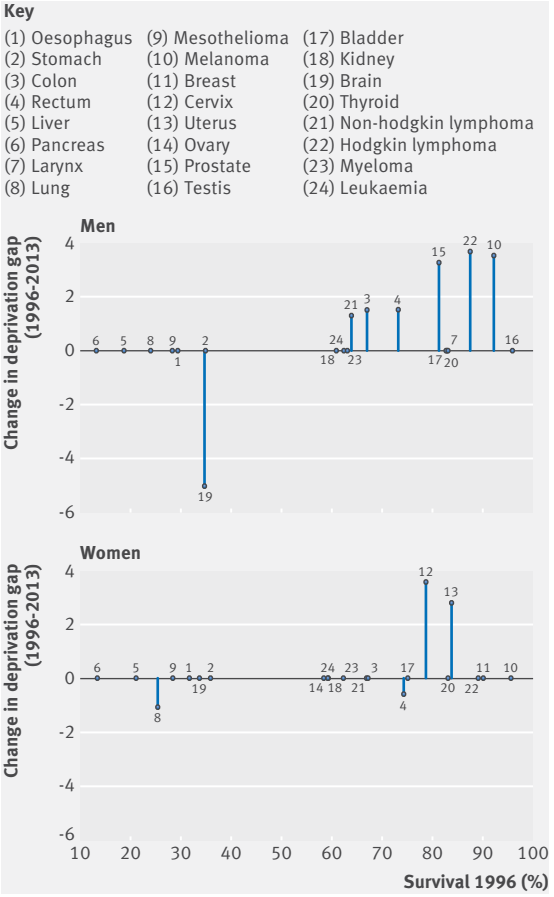

Fig 3 | Change in deprivation gap in one year net survival between 1996 and 2013 for 20 cancers in men and 21 cancers in women, arrayed by ICD-10

Deprivation gap in one year net survival and trends

When survival increased, it concerned all deprivation groups for most sex-cancer combinations. Survival nevertheless remained consistently lower among more deprived patients than the less deprived, and the deprivation gap in one year net survival remained unchanged for 13 cancers in men and 17 cancers in women between 1996 and 2013 (fig 3). The survival gap narrowed only in six out of 20 cancers among men and in two out of 21 cancers among women, and widened for three cancers. All these changes were linear. The deprivation gaps were more similar between men and women in 2013 than in 1996.

In 1996 there was a clear deprivation gradient in one year survival, which was lower among more deprived than less deprived patients, for all cancers and in both sexes (tables 2 and 3). Seventeen years later, in 2013, survival was still lower among the more deprived groups for all cancers, except Hodgkin lymphoma in men. A narrowing in the deprivation gap was observed for cancers with survival in 1996 near or higher than 65% among men and 75% among women.

In 1996, the largest deprivation gap in men was observed for rectal cancer (−9.4%) and non-Hodgkin lymphoma (−8.2%). The deprivation gap narrowed slightly by 1.6% during 1996-2013 for both colon and rectal cancer, and by 1.3% for non-Hodgkin lymphoma. However, the largest reduction was seen for Hodgkin lymphoma (3.7%) and prostate cancer (3.2%). For melanoma of the skin, the deprivation gap decreased by 3.5% between 1996 and 2013. The deprivation gap for these cancers ranged from −6.2% to −4.6% in 1996. In 2013, the largest deprivation gap was for rectal cancer (−7.8%) and brain cancer (−7.5%).

In women, the largest deprivation gap in 1996, as in 2013, was for bladder cancer (−8.6%), mesothelioma (−8.3%), and oesophageal cancer (−8%). A reduction was only seen for cervical cancer (from −7.0% in 1996 to −3.5% in 2013) and uterine cancer (from −5.8% to −2.8%, respectively).

The deprivation gap in survival widened for brain tumours in men and lung cancer in women, by 5.1% (from −2.4% in 1996 to-7.5% in 2013) and 1.1% (from −3.7% in 1996 to −4.8% in 2013), respectively.

The deprivation gap was narrow in 1996 for a few malignancies and remained among the narrowest in 2013: Hodgkin lymphoma (−1.9%) and skin melanoma (−1.9%) in women, and thyroid (−2.7%) and testicular cancers (−2.8%) in men.

Discussion

A steady improvement in one year net survival was seen between 1996 and 2013 in England for nearly

Table 2 | Adjusted one year survival and change in net survival for men with a diagnosis of one of 20 cancers between 1996 and 2013

	1996		2001		2006		2013		1996-2013
Malignancy	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Change in deprivation gap (%)
Oesophagus	32.4 (31.4 to 33.3)	−7.3 (−8.4 to −6.3)	38.6 (37.9 to 39.3)	−7.3 (−8.4 to −6.3)	44.8 (44.0 to 45.7)	−7.3 (−8.4 to −6.3)	50.6 (49.5 to 51.7)	−7.3 (−8.4 to −6.3)	0.0
Stomach	37.8 (36.8 to 38.9)	−5.8 (−7.1 to −4.6)	42.1 (41.3 to 42.9)	−5.8 (−7.1 to −4.6)	46.4 (45.6 to 47.1)	−5.8 (−7.1 to −4.6)	52.4 (51.3 to 53.4)	−5.8 (−7.1 to −4.6)	0.0
Colon	71.0 (70.1 to 72.0)	−7.9 (−9.2 to −6.5)	73.5 (72.9 to 74.1)	−7.4 (−8.3 to −6.5)	76.0 (75.3 to 76.7)	−7.0 (−7.7 to −6.2)	81.6 (80.6 to 82.5)	−6.3 (−7.7 to −5.0)	1.6
Rectum	77.9 (77.0 to 78.8)	−9.4 (−10.7 to −8.0)	80.0 (79.5 to 80.6)	−8.9 (−9.8 to −8.0)	82.2 (81.5 to 82.8)	−8.5 (−9.2 to −7.7)	87.7 (86.8 to 88.7)	−7.8 (−9.2 to −6.5)	1.6
Liver	21.5 (20.1 to 22.9)	−5.7 (−7.4 to −3.9)	26.8 (25.6 to 27.9)	−5.7 (−7.4 to −3.9)	32.0 (31.0 to 33.1)	−5.7 (−7.4 to −3.9)	39.4 (38.0 to 40.8)	−5.7 (−7.4 to −3.9)	0.0
Pancreas	16.2 (15.1 to 17.2)	−5.9 (−7.1 to −4.7)	19.5 (18.7 to 20.3)	−5.9 (−7.1 to −4.7)	22.8 (22.0 to 23.5)	−5.9 (−7.1 to −4.7)	27.4 (26.3 to 28.4)	−5.9 (−7.1 to −4.7)	0.0
Larynx	85.9 (84.7 to 87.1)	−6.3 (−7.8 to −4.9)	86.5 (85.6 to 87.5)	−6.3 (−7.8 to −4.9)	87.2 (86.4 to 88.1)	−6.3 (−7.8 to −4.9)	88.2 (87.0 to 89.4)	−6.3 (−7.8 to −4.9)	0.0
Lung	25.9 (25.2 to 26.7)	−4.0 (−4.7 to −3.2)	28.6 (28.1 to 29.1)	−4.0 (−4.7 to −3.2)	31.3 (30.6 to 32.0)	−4.0 (−4.7 to −3.2)	38.6 (37.7 to 39.4)	−4.0 (−4.7 to −3.2)	0.0
Mesothelioma	29.7 (27.6 to 31.9)	−2.9 (−4.7 to −1.0)	30.9 (29.3 to 32.5)	−2.9 (−4.7 to −1.0)	37.1 (36 to 38.3)	−2.9 (−4.7 to −1.0)	45.9 (44.2 to 47.6)	−2.9 (−4.7 to −1.0)	0.0
Melanoma	94.8 (93.9 to 95.6)	−6.2 (−7.6 to −4.8)	95.6 (95.0 to 96.1)	−5.2 (−6.0 to −4.3)	96.4 (95.9 to 96.9)	−4.1 (−4.9 to −3.4)	97.5 (96.6 to 98.3)	−2.7 (−4.1 to −1.3)	3.5
Prostate	83.6 (82.8 to 84.4)	−4.6 (−5.7 to −3.6)	89.0 (88.5 to 89.6)	−3.7 (−4.3 to −3.0)	89.1 (88.6 to 89.6)	−2.7 (−3.3 to −2.1)	92.8 (92.1 to 93.5)	−1.4 (−2.4 to −0.3)	3.2
Testis	97.3 (95.9 to 98.8)	−2.8 (−4.5 to −1.1)	97.5 (96.4 to 98.7)	−2.8 (−4.5 to −1.1)	97.7 (96.7 to 98.8)	−2.8 (−4.5 to −1.1)	98.0 (96.5 to 99.4)	−2.8 (−4.5 to −1.1)	0.0
Bladder	85.6 (84.6 to 86.6)	−5.8 (−6.6 to −4.9)	81.7 (80.9 to 82.5)	−5.8 (−6.6 to −4.9)	80.9 (80.1 to 81.7)	−5.8 (−6.6 to −4.9)	83.0 (82.1 to 83.9)	−5.8 (−6.6 to −4.9)	0.0
Kidney	64.1 (62.9 to 65.3)	−6.3 (−7.6 to −5.1)	67.3 (66.5 to 68.1)	−6.3 (−7.6 to −5.1)	70.5 (69.5 to 71.6)	−6.3 (−7.6 to −5.1)	80.7 (79.4 to 82.0)	−6.3 (−7.6 to −5.1)	0.0
Brain	35.9 (34.1 to 37.7)	−2.4 (−4.9 to 0.1)	37.4 (36.2 to 38.6)	−3.9 (−5.5 to −2.3)	43.8 (43.0 to 44.7)	−5.4 (−6.7 to −4.0)	52.8 (51.2 to 54.4)	−7.5 (−10.0 to −5.0)	−5.1
Thyroid	84.4 (82.1 to 86.7)	−2.7 (−5.1 to −0.3)	84.6 (83.1 to 86.2)	−2.7 (−5.1 to −0.3)	84.9 (82.8 to 86.9)	−2.7 (−5.1 to −0.3)	92.3 (89.8 to 94.8)	−2.7 (−5.1 to −0.3)	0.0
Non-Hodgkin lymphoma	67.4 (66.2 to 68.5)	−8.2 (−9.9 to −6.4)	71.6 (70.9 to 72.4)	−7.8 (−8.9 to −6.7)	75.9 (75.2 to 76.6)	−7.4 (−8.4 to −6.5)	81.9 (80.8 to 83.0)	−6.9 (−8.6 to −5.1)	1.3
Hodgkin lymphoma	90.4 (88.3 to 92.5)	−5.1 (−8.3 to −2.0)	89.0 (87.8 to 90.3)	−4.0 (−6.1 to −2.0)	87.6 (86.2 to 89.1)	−3.0 (−4.7 to −1.2)	90.0 (87.8 to 92.1)	−1.4 (−4.6 to 1.7)	3.7
Myeloma	65.9 (64.6 to 67.2)	−5.6 (−7.0 to −4.3)	69.7 (68.8 to 70.6)	−5.6 (−7.0 to −4.3)	73.4 (72.3 to 74.6)	−5.6 (−7.0 to −4.3)	86.7 (85.3 to 88.2)	−5.6 (−7.0 to −4.3)	0.0
Leukaemia	65.1 (64.0 to 66.2)	−5.3 (−6.4 to −4.2)	66.6 (65.9 to 67.4)	−5.3 (−6.4 to −4.2)	68.2 (67.2 to 69.1)	−5.3 (−6.4 to −4.2)	75.2 (74.0 to 76.4)	−5.3 (−6.4 to −4.2)	0.0

all 41 cancer-sex combinations. In 2013, one year net survival was higher than 80% for 17 cancer-sex combinations, but this encouraging picture is moderated by the 14 poor prognosis combinations with one year survival still below 50%. Acceleration of this overall improvement was rarely observed, offering little evidence for a direct impact of the NHS Cancer Plan (2000) and later policy initiatives on short term cancer survival. Meanwhile, the deprivation gap in one year net survival remained unchanged for most cancers, with a clear, persistent pattern of lower survival among more deprived patients. Reduction of socioeconomic inequalities was seen only among some cancers for which one year survival was already more than 65% in 1996, especially among men, suggesting a ceiling effect in that survival has reached a maximum among the least deprived patients.

The successive national policy initiatives, including the 2000 Cancer Plan for England, aimed to improve cancer survival, with the target of bringing survival to the level of comparably wealthy countries, and to reduce the inequalities in cancer survival. The lack of consistent results between men and women, as well as the lack of general patterns across cancer types, provide little evidence for any strong impact of the national cancer policies on short term cancer survival. The evidence is even weaker for their impact on the socioeconomic inequalities in cancer survival.

Strengths and weaknesses of this study

A major strength of this study is that it is based on virtually all cancer cases registered in England, and the quality and completeness of the English cancer registry data are acknowledged to be high.[32] The study also updates by seven years our previous evaluations,[11 17 33] with a total of 18 years of incidence data. These extra years of data allowed us to estimate the trends more accurately.

Since our previous evaluations new, more flexible methodologies were introduced. The assumption that trends in survival and in deprivation gap should be different in three predefined periods[11] was now relaxed

Table 3 | Adjusted one year survival and change in net survival for women with a diagnosis of one of 21 cancers between 1996 and 2013

	1996		2001		2006		2013		1996-2013
Malignancy	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Survival in most affluent (95% CI)	Deprivation gap (95% CI)	Change in deprivation gap (%)
Oesophagus	35.7 (34.2 to 37.2)	−8.0 (−9.9 to −6.2)	40.6 (39.4 to 41.8)	−8.0 (−9.9 to −6.2)	45.5 (44.4 to 46.6)	−8.0 (−9.9 to −6.2)	52.3 (50.8 to 53.8)	−8.0 (−9.9 to −6.2)	0.0
Stomach	38.2 (36.7 to 39.7)	−4.6 (−6.4 to −2.8)	41.7 (40.5 to 42.9)	−4.6 (−6.4 to −2.8)	45.2 (44.1 to 46.3)	−4.6 (−6.4 to −2.8)	50.0 (48.5 to 51.6)	−4.6 (−6.4 to −2.8)	0.0
Colon	70.9 (70.2 to 71.6)	−7.4 (−8.3 to −6.5)	73.7 (73.2 to 74.3)	−7.4 (−8.3 to −6.5)	76.6 (76.1 to 77.1)	−7.4 (−8.3 to −6.5)	80.6 (79.9 to 81.3)	−7.4 (−8.3 to −6.5)	0.0
Rectum	75.8 (74.4 to 77.2)	−5.9 (−7.5 to −4.3)	80.0 (79.0 to 81.0)	−6.1 (−7.1 to −5.0)	80.5 (79.7 to 81.4)	−6.3 (−7.1 to −5.4)	86.8 (85.7 to 87.9)	−6.5 (−8.1 to −4.9)	−0.6
Liver	23.7 (21.5 to 26.0)	−5.4 (−8.1 to −2.6)	27.3 (25.5 to 29.0)	−5.4 (−8.1 to −2.6)	30.8 (29.1 to 32.5)	−5.4 (−8.1 to −2.6)	35.7 (33.4 to 38.0)	−5.4 (−8.1 to −2.6)	0.0
Pancreas	16.3 (15.4 to 17.2)	−5.8 (−6.9 to −4.8)	20.6 (19.9 to 21.3)	−5.8 (−6.9 to −4.8)	24.9 (24.2 to 25.5)	−5.8 (−6.9 to −4.8)	30.9 (30.0 to 31.8)	−5.8 (−6.9 to −4.8)	0.0
Lung	27.2 (26.1 to 28.3)	−3.7 (−5.1 to −2.4)	32.5 (31.7 to 33.3)	−4.0 (−4.9 to −3.2)	35.0 (34.3 to 35.7)	−4.3 (−5.1 to −3.6)	45.8 (44.9 to 46.7)	−4.8 (−6.1 to −3.5)	−1.1
Mesothelioma	32.6 (29.9 to 35.2)	−8.3 (−11.5 to −5.1)	37.9 (35.8 to 39.9)	−8.3 (−11.5 to −5.1)	43.2 (41.2 to 45.1)	−8.3 (−11.5 to −5.1)	50.6 (47.9 to 53.2)	−8.3 (−11.5 to −5.1)	0.0
Melanoma	96.9 (96.5 to 97.3)	−1.9 (−2.3 to −1.6)	97.3 (97.0 to 97.5)	−1.9 (−2.3 to −1.6)	97.7 (97.4 to 98.0)	−1.9 (−2.3 to −1.6)	99.6 (99.2 to 100)	−1.9 (−2.3 to −1.6)	0.0
Breast	91.1 (90.7 to 91.5)	−3.2 (−3.6 to −2.8)	93.9 (93.6 to 94.2)	−3.2 (−3.6 to −2.8)	95.5 (95.2 to 95.7)	−3.2 (−3.6 to −2.8)	97.7 (97.4 to 98.1)	−3.2 (−3.6 to −2.8)	0.0
Cervix	84.9 (83.0 to 86.8)	−7.0 (−9.3 to −4.7)	82.8 (81.5 to 84.0)	−6.0 (−7.4 to −4.5)	83.4 (82.5 to 84.3)	−4.9 (−6.2 to −3.7)	84.3 (82.9 to 85.7)	−3.5 (−5.7 to −1.2)	3.5
Uterus	86.2 (85.3 to 87.1)	−5.8 (−7.2 to −4.4)	87.7 (87.1 to 88.2)	−5.0 (−5.9 to −4.1)	89.1 (88.6 to 89.6)	−4.2 (−4.9 to −3.4)	91.2 (90.3 to 92.0)	−3.0 (−4.4 to −1.6)	2.8
Ovary	62.5 (61.6 to 63.4)	−6.8 (−7.7 to −5.8)	65.8 (65.2 to 66.4)	−6.8 (−7.7 to −5.8)	69.1 (68.3 to 70.0)	−6.8 (−7.7 to −5.8)	76.9 (75.9 to 77.9)	−6.8 (−7.7 to −5.8)	0.0
Bladder	79.4 (77.6 to 81.2)	−8.6 (−10.2 to −7.1)	72.5 (71.1 to 73.8)	−8.6 (−10.2 to −7.1)	72.1 (71.1 to 73.1)	−8.6 (−10.2 to −7.1)	71.6 (70.1 to 73)	−8.6 (−10.2 to −7.1)	0.0
Kidney	61.7 (60.2 to 63.1)	−4.7 (−6.2 to −3.1)	65.6 (64.6 to 66.6)	−4.7 (−6.2 to −3.1)	69.5 (68.2 to 70.8)	−4.7 (−6.2 to −3.1)	80.3 (78.7 to 81.9)	−4.7 (−6.2 to −3.1)	0.0
Brain	35.8 (34.4 to 37.1)	−4.2 (−5.9 to −2.6)	40.2 (39.1 to 41.2)	−4.2 (−5.9 to −2.6)	44.6 (43.6 to 45.6)	−4.2 (−5.9 to −2.6)	50.8 (49.4 to 52.1)	−4.2 (−5.9 to −2.6)	0.0
Thyroid	84.4 (82.9 to 85.9)	−2.6 (−4.4 to −0.9)	87.7 (86.5 to 88.8)	−2.6 (−4.4 to −0.9)	90.9 (89.9 to 92)	−2.6 (−4.4 to −0.9)	95.5 (94.1 to 97.0)	−2.6 (−4.4 to −0.9)	0.0
Non-Hodgkin lymphoma	70.4 (69.7 to 71.2)	−7.1 (−8.0 to −6.2)	74.8 (74.2 to 75.4)	−7.1 (−8.0 to −6.2)	79.2 (78.6 to 79.7)	−7.1 (−8.0 to −6.2)	85.3 (84.6 to 86.1)	−7.1 (−8.0 to −6.2)	0.0
Hodgkin lymphoma	88.9 (86.9 to 90.8)	−1.9 (−3.6 to −0.2)	91.1 (89.4 to 92.8)	−1.9 (−3.6 to −0.2)	88.9 (87.3 to 90.5)	−1.9 (−3.6 to −0.2)	93.0 (91.3 to 94.8)	−1.9 (−3.6 to −0.2)	0.0
Myeloma	63.9 (62.6 to 65.2)	−3.4 (−4.9 to −1.8)	69.4 (68.4 to 70.4)	−3.4 (−4.9 to −1.8)	74.9 (73.9 to 75.9)	−3.4 (−4.9 to −1.8)	82.6 (81.3 to 83.9)	−3.4 (−4.9 to −1.8)	0.0
Leukaemia	62.4 (61.2 to 63.6)	−6.5 (−7.9 to −5.0)	65.3 (64.3 to 66.2)	−6.5 (−7.9 to −5.0)	68.1 (67.2 to 69.0)	−6.5 (−7.9 to −5.0)	72.1 (70.9 to 73.3)	−6.5 (−7.9 to −5.0)	0.0

and the periods could vary substantially. The initial assumption was that changes would be expected after 2001 or 2006, or both but further analyses were conducted using more flexible models, which enabled the number and location of the knots to vary across all years of diagnosis. The estimates were not all identical, but they did not affect our main conclusions, in particular on the common absence of inflexion points in the trends in survival and in deprivation gap.

Short term net survival mostly reflects the speed of patient management (including diagnosis, staging, and first definitive treatment) as well as the quality of the surgical treatment and postoperative care. A persistent deficit in short term cancer survival in England (and more generally in the UK) compared with most wealthy countries has been observed for decades.[34 35] Meanwhile, the wide socioeconomic inequalities in cancer survival, also seen for decades, are mostly due to higher short term mortality in more deprived patients.[4]

Although trends in cancer survival have been regularly used to inform governments on the progress towards the aims of their cancer policies,[36 37] to our knowledge, little has been specifically published on the evaluation of how cancer policies impact survival and inequalities at national level. Most studies were at subnational level [38] or focused on very specific interventions, such as screening.[39] By contrast, our study was designed to evaluate such policies. We acknowledge that changes in the survival trends are decided solely on acceleration in survival, and comparison with countries of similar wealth would put any observed improvements in perspective. This limitation, however, does not apply to our findings on the persistent socioeconomic inequalities in cancer survival. Furthermore, the weak evidence for an acceleration in cancer survival echoes the constant gap in cancer survival between England and some other wealthy countries.[40] Our study also may be too early to detect the full impact of the recently implemented

cancer initiatives, although it confirms the findings of our earlier studies.[11 33] Such studies should be regularly updated.

Meaning of the study

Since the introduction of the NHS Cancer Plan (2000), acceleration in the positive survival trends was witnessed only for a few cancers and mostly among men, who experienced a lower initial increase compared with women (cancer of the lung, brain, and thyroid, mesothelioma, myeloma, and leukaemia). No such acceleration was found among women. For lung cancer, and more specifically non-small cell carcinoma, the proportion of patients receiving a surgical treatment was low in England,[41] but this proportion increased from around 10% until 2008[42] to 17% in 2015.[43] This improvement may be partly the result of a higher number of specialised surgeons[44] and a higher proportion of patients managed in specialised centres, which could reduce the variability in postoperative mortality.[45] These changes may have impacted the outcome for mesothelioma, too. The continuous expansion in the availability of diagnostic tools (eg, computed tomography, magnetic resonance imaging, ultrasound machines) in England is likely to have increased the proportion of brain and thyroid tumours diagnosed at an earlier stage.[46] Survival pattern for bladder cancer is particular as one year survival decreased slightly between 1996 and 2001, then stabilised. It reflects a change in coding around 2000, under which papillomas were reclassified from invasive to uncertain (whether benign or malignant), therefore excluded from survival analyses. Omitting these tumours with a good prognosis resulted in a decrease in cancer survival.[47] Despite these improvements in survival there was no reduction in the inequalities in survival from lung, brain, or thyroid tumour, or from mesothelioma.

Particular efforts were dedicated in England to high incidence cancers with intermediate prognosis (one year survival between 40% and 65% in 1996) such as colon and rectal cancers, and one could have expected a faster improvement in survival and a reduction of the deprivation gap after the policy initiatives. Survival from these cancers in England remained behind internationally,[40 48] and inequalities in survival from these cancers hardly narrowed. Short term survival increased dramatically since 1996 for most other digestive cancers with poor prognosis (one year survival <40% in 1996), but the more deprived patients still experienced lower survival.

It is likely that the longstanding deficit in survival and the socioeconomic inequalities in survival in England share the same causal factors, which can be grouped into patient, tumour, and healthcare system factors. The National Awareness and Early Diagnosis Initiative[49] and the Be Clear on Cancer Campaign[50] aimed specifically to tackle some of the patient related (cancer awareness, barriers) and tumour related (tumour stage) issues. Although cancer awareness varies internationally[51] and by deprivation,[52] it seems to explain none of the international disparities in cancer survival[51] and little of socioeconomic inequalities.[53] A lot of effort has also gone into diagnosing cancers at an earlier stage. Patients tend to have a diagnosis of more advanced tumours in England compared with wealthy countries,[54-57] and among the more deprived patients compared with the least deprived.[9] However, as stage specific survival tends to be lower in England, more advanced stage would explain only part of the international[54-57] and socioeconomic inequalities in cancer survival.[58 59] A higher proportion of patients are now receiving a diagnosis through Two Week Wait or GP referral while for some cancers there is a major decrease in emergency presentation.[60] Although stage distribution might have slightly moved towards earlier stages, the picture remains patchy and there was no evidence to suggest a narrowing of these gaps in survival.

These policy initiatives put a greater emphasis on individual factors than on the observed suboptimal management of patients with cancer. The variations in cancer management (eg, differential route to diagnosis, staging investigation, treatment) are likely to explain some of the low survival observed in England and among more deprived patients, whereas the role of the individual factors in the observed variations in management seems minor. For example, the background consultation rate in primary care of patients with cancer does not differ between routes to cancer diagnosis (emergency presentation or not).[61 62] In contrast, interventions on healthcare system factors might have a large impact on cancer survival, as shown by the recent changes in the management of patients with lung cancer.[43] However, such interventions have not influenced the socioeconomic inequalities in cancer survival yet, possibly because they do not directly address the differential interactions between the healthcare system and the patients, which could lead to suboptimal management of subgroups of the population.

Conclusion and policy implications

Little evidence has been found about the acceleration in cancer survival after the successive national cancer policy initiatives. Survival in the most deprived has been consistently lower and the deprivation gap has shown little change over the years for patients with a diagnosis during 1971-90[2] and 1986-99[63] in England and Wales. This study contributes with more recent data and updates evidence that the deprivation gap persisted in England even after the introduction of successive national policies, which among other goals targeted social inequalities related to cancer.[11]

These findings should be taken into consideration by cancer policy makers and inform future initiatives. Shifting the focus from individual factors to healthcare system factors might prove to be beneficial in improving cancer outcomes among the most disadvantaged. Further research on these factors can help shed light and improve the efficacy of future cancer policies.

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Contributors: AE did the analysis. AE, CM, AB, and BR designed the analytic strategies. AE and BR wrote the article. All co-authors interpreted the findings and reviewed the article. BR is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the Confidentiality Advisory Group and the Research Ethics Committee (PIAG 1-05(c)/2007 and REC 13/LO/0610). The analysed data were anonymised and none of the results is at individual level and for small groups. Patients are data subjects under the Data Protection Act 1998, but not participants in the research, in the sense that they are not invited to participate because it is observational research for public health surveillance, not interventional research, which certainly would require informed patient consent under law. Furthermore, consent from the patients or their proxies was not sought as it would not be feasible for over 3.5 million cancer patients, many already deceased. The impracticality of seeking consent from such large numbers of patients has been recognised from various bodies that the Cancer Survival Group has sought approvals from such as the Patient Information Advisory Group, the National Information Governance Board and the Confidentiality Advisory Group. All those bodies have acknowledged in the past that obtaining consent is not a viable proposition for population-based research on cancer survival that requires national data from cancer registries. They have always granted permission for this type of research to proceed without consent under Section 251 of the NHS Act 2006 (and previously under Section 60 of the Health and Social Care Act 2001).

Data sharing: This study was based on the English national cancer registry data. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, eg, publications). At the time of request data were provided by the Office for National Statistics but now all cancer registrations are owned and maintained by Public Health England.

Transparency: The lead author (AE) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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First Name(s)	Aimilia		
Surname/Family Name	Exarchakou		
Thesis Title	Inequalities in cancer care in England: from diagnosis to treatment		
Primary Supervisor	Professor Bernard Rachet		

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Socio-economic inequalities in cancer survival: how do they translate into Number of Life-Years Lost?

Aimilia Exarchakou[1]✉, Dimitra-Kleio Kipourou[1], Aurélien Belot[1] and Bernard Rachet[1]

BACKGROUND: We aimed to investigate the impact of socio-economic inequalities in cancer survival in England on the Number of Life-Years Lost (NLYL) due to cancer.
METHODS: We analysed 1.2 million patients diagnosed with one of the 23 most common cancers (92.3% of all incident cancers in England) between 2010 and 2014. Socio-economic deprivation of patients was based on the income domain of the English Index of Deprivation. We estimated the NLYL due to cancer within 3 years since diagnosis for each cancer and stratified by sex, age and deprivation, using a non-parametric approach. The relative survival framework enables us to disentangle death from cancer and death from other causes without the information on the cause of death.
RESULTS: The largest socio-economic inequalities were seen mostly in adults <45 years with poor-prognosis cancers. In this age group, the most deprived patients with lung, pancreatic and oesophageal cancer lost up to 6 additional months within 3 years since diagnosis than the least deprived. For most moderate/good prognosis cancers, the socio-economic inequalities widened with age.
CONCLUSIONS: More deprived patients and particularly the young with more lethal cancers, lose systematically more life-years than the less deprived. To reduce these inequalities, cancer policies should systematically encompass the inequities component.

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BACKGROUND

Patients living in more socioeconomically deprived areas (referred hereafter as 'more deprived' patients) tend to have worse cancer outcomes than those living in less deprived areas ('less deprived' patients), in the UK and other countries [1–4]. In England, in order to improve cancer survival and reduce the inequalities, the first-ever NHS Cancer Plan was implemented in 2000, followed by several successive policy initiatives, mainly focusing on promoting early diagnosis, optimising treatment pathways and maximising available resources to bring better treatment options, care and infrastructure [5–9]. However, the indisputable overall increase in cancer survival over the last 25 years has been accompanied by a minimal or lack of improvement in socio-economic inequalities, reflected on persistent poorer cancer prognosis of the more deprived patients [10]. Similar patterns have been repeatedly reported regarding cancer screening uptake [11, 12] and vaccine coverage [13–17]. Such inequalities pose a challenge for the National Health Service (NHS) which is committed to equity of access in healthcare, i.e. equal access for equal need for the whole population.

Research has shown that cancer awareness, clinical (comorbidities) and tumour-related (tumour stage) factors can only explain part of the inequalities in England [18–20] and that more emphasis should be given to the observed variation in cancer screening uptake [21–23] and management of patients [24–26]. However, communication of these epidemiological findings with political forces and stakeholders has been suboptimal, evidenced by the lack of initiative to target inequalities in a more methodical fashion.

Socio-economic inequalities in England have been described previously through survival or mortality probabilities [4, 10, 27]. Although these measures are necessary for evaluating the patients' prognosis, they do not fully reflect the burden on the society, unlike alternative measures such as the crude probability of death from cancer (CPr) [28] or the Number of Life-Years Lost (NLYL) due to cancer [29, 30]. The NLYL measures how many years patients diagnosed with cancer can lose due to their cancer. The measure, easy to communicate to a large audience [29], can also be translated into societal or economic cost.

This study aims to quantify the population burden of socio-economic inequalities (measured with the income deprivation domain of the Index of Multiple Deprivation for a given area) in cancer survival using the CPr and NLYL due to cancer, to identify specific components for improvement, and to consider how this can be integrated with public health policy and resource allocation.

METHODS

England National Cancer Registry data

The main source of data was the population-based National Cancer Registry of England. We included all patients aged 15–99 years, diagnosed with a primary, invasive, malignant (ICD-O behaviour code 3) neoplasm between 1 January 2010 and 31 December 2014 and followed up to 31 December 2015. The tumour site was coded according to the tenth

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revision of the International Classification of Diseases (ICD-10) [31] while the second edition of the International Classification of Diseases for Oncology (ICD-O-2) was used for morphology and behaviour [32]. We included 23 of the most common cancers in males and females.

Socio-economic deprivation of patients was based on the income domain of the English Index of Multiple Deprivation (IMD 2004) [33], an ecological measure of relative deprivation. The income domain score measures the proportion of the population with low income living in a given Lower layer Super Output Area (LSOA) [34]. LSOAs are census-based administrative spatial areas developed by the Office for National Statistics (ONS) and designed for reporting small area statistics in England and Wales. Cancer patients were assigned to their LSOA of residence at diagnosis (32,482 LSOAs in England, mean population 1500). They were allocated to a deprivation category (from 1, 'least deprived', to 5, 'most deprived') based on the quintiles of the national distribution of all LSOA-level income domain scores of the IMD 2004.

Among the seven domains of the IMD, we used the income domain firstly because of its overall high degree of agreement with the overall composite IMD measure [35]. Also, using the overall IMD can lead to misinterpretation because it contains components about access to public services, therefore access to optimal care, which is strongly linked to inequalities in cancer survival.

Cancer survival measures

The estimation of cancer survival measures requires competing risks methods to account for the fact that cancer patients may die from causes other than the cancer under study [29, 36, 37]. However, as the cause of death is often unavailable or unreliable in population-based data, survival measures are estimated using methods from the relative survival framework. Assuming that the overall mortality hazard can be expressed as the sum of the cancer-related hazard ('excess hazard') and the hazard of death from other causes ('expected hazard'), the basic principle in the relative survival framework is that the expected hazard is derived from the mortality hazard in the general population where patients come from, i.e. lifetables. The England lifetables are here defined by sex, age (0–99 by 1-year age groups), deprivation (1–5 using IMD) and for the calendar period 2010–2015 (by calendar year for 2010 and 2011, and assuming a plateau afterwards) and extracted from a dedicated website [38].

The NLYL can be estimated directly from the CPr, which is the probability of dying from cancer before or at time t in the presence of competing causes of death [39]. By integrating the CPr function from 0 to time t we can derive the NLYL which can be interpreted as the meantime patients would lose due to cancer death within a specific time period $[0,t]$ [40, 41]. Although we provide a brief explanation in the Appendix, methods to estimate the CPr from a given cause in the relative survival framework have been fully described elsewhere [39–43]. NLYL is estimated in a pre-specified follow-up time window to account for the inability to estimate the entire survival function due to right-censoring.

We estimated the CPr and the NLYL due to cancer within 1 and 3 years after cancer diagnosis according to deprivation, age and sex. We present here the comparison of Life-Years Lost (LYL) within 3 years since diagnosis between the least and the most deprived patients. More detailed results (in particular for 1 year since diagnosis and all deprivation levels) are presented in the Supplementary file and the web-tool (https://CPr of death and NLYL due to cancer by deprivation/). Calculations were performed with R software version 4.0.4 and the package 'relsurv' version 2.2-3 [40]. To estimate 95% confidence intervals for the NLYL, we used the R-package 'boot' [44] version 1.3-28, for non-parametric bootstrap (1000 bootstrap replicates).

To describe the (cancer j)-specific burden among all different cancers combined in each group of patients defined by the combination of sex, age group and deprivation, we also present the proportion of NLYL due to each cancer over the total NLYL due to all cancers under study ($k = 1,\ldots, 23$) for this group of patients. This quantity is weighted with the cancer-specific proportion of patients with each cancer over the total number of cancer patients in that group of patients. So, within a combination of sex/age/deprivation, this proportion can be expressed mathematically as follows:

$$P_j = \frac{NLYL_j}{\sum_k NLYL_k} \cdot \frac{n_j}{\sum_k n_k}$$

where $j = 1,\ldots, 23$ defines the cancer and n_j the number of cases observed for that cancer and the specific subgroup studied.

RESULTS

During 2010–2014, more than 1.2 million patients were diagnosed with one of the 23 cancer sites in England, representing 92.3% of all incident cancers in England. Based on the area of residence at diagnosis, 20–21% of the patients were in each of the deprivation levels 1 (least deprived) to 4, contrasting with 17% in the most deprived group (level 5).

Among the most frequent cancers, colon, prostate and breast (female) cancers were more common in the less deprived whilst lung cancer largely predominated in the more deprived patients (Table 1). Cervical, stomach, liver and oesophageal cancers were more frequent in the more deprived than the less deprived patients. In contrast, pancreatic cancer was equally common in all deprivation groups.

Number of Life-Years Lost due to the cancer

The estimates of CPr and NLYL within 3 years divide naturally the cancer sites in 'good' (CPr: 0–0.25) or 'moderate' (CPr: 0.25–0.75) and 'poor' (CPr: 0.75–1) prognosis (Fig. 1; Supplementary Fig. 1). The cancer sites with the highest probability of death due to cancer within 3 years since diagnosis were brain, lung and all the upper-digestive organ cancers (pancreatic, liver, oesophagus and stomach) (Supplementary Fig. 1). For these cancers, the CPr within 3 years was between 0.75 and 1 and the NLYL within 3 years was between 1.75 and 2.3 years (Fig. 1).

Cancer sites with relatively low CPr within 3 years (<0.25) and NLYL of less than 0.5 years within 3 years, were Hodgkin lymphoma, thyroid, skin melanoma, female breast cancer and cancers of the reproductive organs, such as prostate and testicular cancer in male, and cervical and uterine cancers in female. The remaining cancers presented an intermediate CPr within 3 years (0.25–0.50), with 0.5–1.2 LYL within 3 years, and included the cancers of colon, rectum, kidney, bladder, larynx (men), ovary and leukaemia, myeloma and Non-Hodgkin lymphoma (NHL) (Fig. 1).

Number of Life-Years Lost in different deprivation groups

The NLYL within 3 years was consistently higher in the older age groups in both sexes (Figs. 2, 3), reflecting an overall worsening cancer prognosis with increasing age. Also, the most deprived patients had more LYL due to cancer than the least deprived for most of the cancer sites considered. However, the magnitude of the inequalities in the NLYL varied by sex and age group.

For the group of poor-prognosis cancers, the largest socio-economic inequalities were seen mostly in younger adults less than 45 years old. In particular, the most deprived male patients with pancreatic cancer lost 1.81 years within 3 years (95% CI: 1.56, 2.07) in contrast to the least deprived who lost 1.38 years (95% CI: 1.05, 1.71). Similarly, the most deprived female patients of less than 45 years old with lung cancer lost 1.49 years (95% CI: 1.34, 1.63), 0.54 years more than the least deprived (0.95; 95% CI: 0.77, 1.16) (Fig. 2; Supplementary Table 1). In contrast, an almost non-existent deprivation 'gap' was seen for brain cancer in (particularly male) patients more than 65 years old, with the NLYL within 3 years reaching nearly 2.5 years.

For the majority of the moderate and good-prognosis cancers (colon, rectum, kidney, leukaemia (female), myeloma (male), Non-Hodgkin lymphoma, testis, female breast, ovary, uterus), the difference in the NLYL between the most and least deprived mostly widened with age. For thyroid cancer, the deprivation difference peaked at 65 plus with no pattern in the other age groups. In contrast, the deprivation gap narrowed with age for bladder cancer in females and laryngeal cancer in males (Fig. 3; Supplementary Table 2; Supplementary Table 3).

One of the most striking socio-economic inequalities among all cancer-sex-age combinations for the moderate/good prognosis cancers was observed for Hodgkin lymphoma particularly in patients aged 55–64. In this age group, most deprived patients

Table 1. Number of cases and proportion of cancer patients in each deprivation level diagnosed with one of 23 cancer sites, 2010–2014.

	Deprivation					
	1 (least deprived) (*N* = 258,682)	**2 (*N* = 264,762)**	**3 (*N* = 259,183)**	**4 (*N* = 249,154)**	**5 (most deprived) (*N* = 210,420)**	**Total (*N* = 1,242,201)**
Cancer						
Bladder	8600 (3.3%)	9170 (3.5%)	9269 (3.6%)	8845 (3.6%)	7124 (3.4%)	43,008 (3.5%)
Brain	4186 (1.6%)	4288 (1.6%)	4011 (1.5%)	3684 (1.5%)	2922 (1.4%)	19,091 (1.5%)
Breast (female)	45,831 (17.7%)	44,486 (16.8%)	42,635 (16.4%)	38,982 (15.6%)	29,902 (14.2%)	201,836 (16.2%)
Cervix	1836 (0.7%)	2068 (0.8%)	2443 (0.9%)	2875 (1.2%)	3323 (1.6%)	12,545 (1.0%)
Colon	23,662 (9.1%)	24,065 (9.1%)	23,058 (8.9%)	21,279 (8.5%)	16,591 (7.9%)	108,655 (8.7%)
Hodgkin lymphoma	1416 (0.5%)	1514 (0.6%)	1491 (0.6%)	1683 (0.7%)	1629 (0.8%)	7733 (0.6%)
Kidney	8875 (3.4%)	9481 (3.6%)	9335 (3.6%)	9124 (3.7%)	7709 (3.7%)	44,524 (3.6%)
Larynx (male)	1046 (0.4%)	1310 (0.5%)	1400 (0.5%)	1854 (0.7%)	1969 (0.9%)	7579 (0.6%)
Leukaemia	7776 (3.0%)	7856 (3.0%)	7589 (2.9%)	6968 (2.8%)	5684 (2.7%)	35,873 (2.9%)
Liver	3393 (1.3%)	3603 (1.4%)	4022 (1.6%)	4232 (1.7%)	4498 (2.1%)	19,748 (1.6%)
Lung	24,773 (9.6%)	30,460 (11.5%)	34,973 (13.5%)	41,471 (16.6%)	43,959 (20.9%)	175,636 (14.1%)
Melanoma	15,587 (6.0%)	13,695 (5.2%)	12,099 (4.7%)	9646 (3.9%)	5709 (2.7%)	56,736 (4.6%)
Myeloma	4781 (1.8%)	4807 (1.8%)	4437 (1.7%)	4063 (1.6%)	3385 (1.6%)	21,473 (1.7%)
Non-Hodgkin lymphoma	11,874 (4.6%)	11,981 (4.5%)	11,367 (4.4%)	10,454 (4.2%)	8288 (3.9%)	53,964 (4.3%)
Oesophagus	6593 (2.5%)	7376 (2.8%)	7451 (2.9%)	7475 (3.0%)	6535 (3.1%)	35,430 (2.9%)
Ovary	6193 (2.4%)	6402 (2.4%)	6195 (2.4%)	5976 (2.4%)	4813 (2.3%)	29,579 (2.4%)
Pancreas	7535 (2.9%)	8048 (3.0%)	7906 (3.1%)	7550 (3.0%)	6186 (2.9%)	37,225 (3.0%)
Prostate	45,992 (17.8%)	43,920 (16.6%)	39,627 (15.3%)	33,438 (13.4%)	24,686 (11.7%)	187,663 (15.1%)
Rectum	12,135 (4.7%)	12,649 (4.8%)	12,106 (4.7%)	11,569 (4.6%)	9344 (4.4%)	57,803 (4.7%)
Stomach	4723 (1.8%)	5484 (2.1%)	5668 (2.2%)	6110 (2.5%)	5979 (2.8%)	27,964 (2.3%)
Testis	1755 (0.7%)	1836 (0.7%)	1962 (0.8%)	1952 (0.8%)	1819 (0.9%)	9324 (0.8%)
Thyroid	2726 (1.1%)	2520 (1.0%)	2469 (1.0%)	2606 (1.0%)	2444 (1.2%)	12,765 (1.0%)
Uterus	7394 (2.9%)	7743 (2.9%)	7670 (3.0%)	7318 (2.9%)	5922 (2.8%)	36,047 (2.9%)
Gender						
Male	134,648 (52.1%)	137,151 (51.8%)	132,468 (51.1%)	125,252 (50.3%)	106,557 (50.6%)	636,076 (51.2%)
Female	124,034 (47.9%)	127,611 (48.2%)	126,715 (48.9%)	123,902 (49.7%)	103,863 (49.4%)	606,125 (48.8%)
Age in years						
15–44	14,757 (5.7%)	15,130 (5.7%)	16,033 (6.2%)	17,669 (7.1%)	17,580 (8.4%)	81,169 (6.5%)
45–54	26,086 (10.1%)	24,998 (9.4%)	24,371 (9.4%)	25,282 (10.1%)	23,434 (11.1%)	124,171 (10.0%)
55–64	49,996 (19.3%)	49,648 (18.8%)	48,399 (18.7%)	47,080 (18.9%)	42,298 (20.1%)	237,421 (19.1%)
65 plus	167,843 (64.9%)	174,986 (66.1%)	170,380 (65.7%)	159,123 (63.9%)	127,108 (60.4%)	799,440 (64.4%)

lost almost 0.4 additional years (within 3 years) compared to the least deprived in both male and female patients (Fig. 3; Supplementary Table 3) while no such wide inequalities were seen in the younger or the older age groups. In females, the largest difference was seen for bladder cancer in young women less than 45 years old, although deprivation differences -albeit smaller- were observed in most age groups. The NLYL in the most deprived women less than 45 years with bladder cancer was 1.26 years within three years (95% CI: 0.89, 1.65), 0.63 years more than the least deprived (NLYL = 0.63; 95% CI: 0.16, 1.15). In males, in addition to Hodgkin lymphoma, the deprivation difference was also particularly high for laryngeal cancer in adults less than 45 years and, thyroid and testicular cancer in the over 65 year olds (Fig. 3; Supplementary Table 2; Supplementary Table 3).

In contrast, the deprivation gap in the NLYL was small for skin melanoma in both male and female patients. Also, small variations between age groups and relatively small deprivation inequalities were seen for prostate cancer and for cervical and thyroid cancer in women. A reversal of the difference was observed for ovarian cancer in patients less than 45 years and Hodgkin lymphoma in female patients more than 65 years old.

The proportion of Life-Years Lost

More life-years were lost due to cancer among most deprived patients, compared to the least deprived, although the age pattern of these inequalities varies according to cancer prognosis. The observations slightly differed when focussing on the proportion of the total LYL instead of their number.

Poor-prognosis cancers still accounted for the largest proportion of the total LYL for all cancers regardless of age and deprivation. However, figures can vary widely by deprivation. For example, in the most deprived, lung cancer contribution ranges from 13% (young female) to over 40% in age group 65+ (both sexes) (Fig. 4), while lung cancer represents only 21% of all incident cancers included in this deprivation group (Table 1). In the least deprived, the highest lung cancer contribution remains

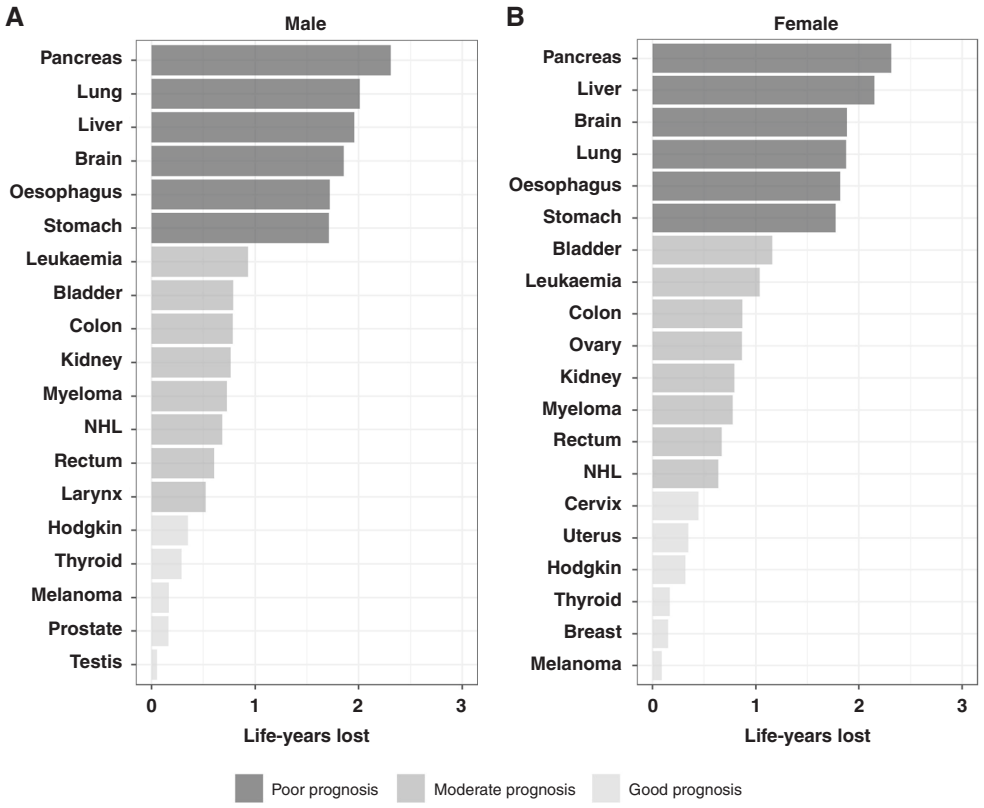

Fig. 1 Number of life-years lost within 3 years due to a given cancer. A Male and **B** female patients diagnosed in 2010–2014. NHL non-hodgkin lymphoma.

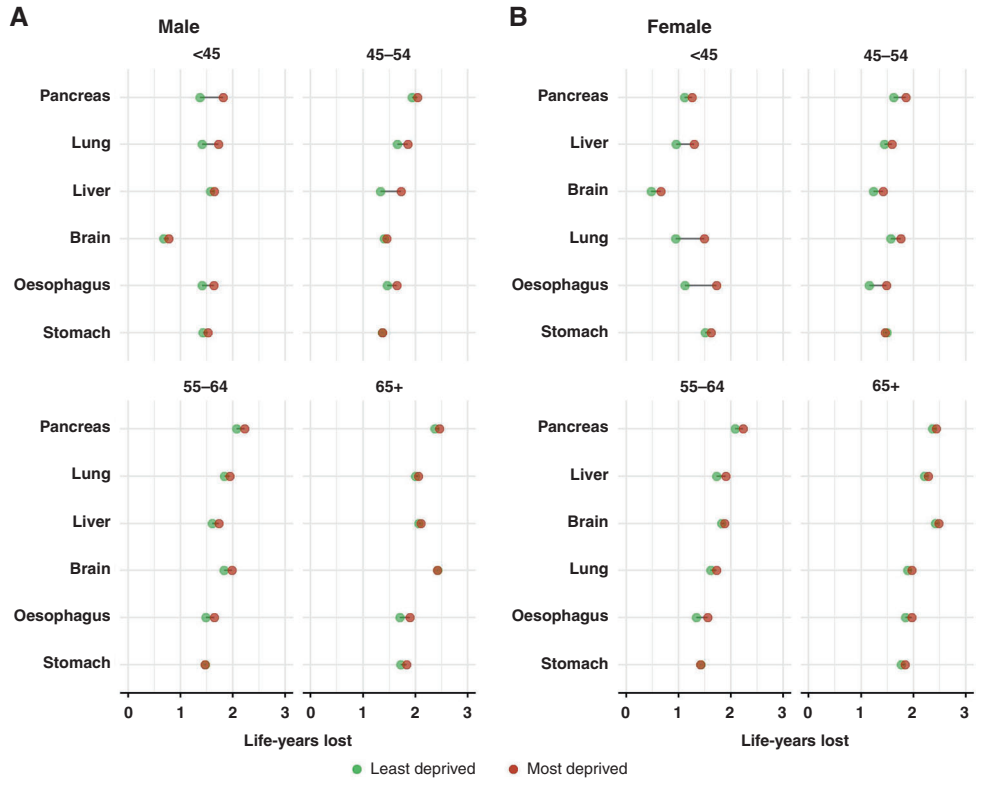

Fig. 2 Number of life-years lost within 3 years due to a given cancer in the most and the least deprived by age group, for the group of poor-prognosis cancers. A Male, **B** female; cancers sorted as in Fig. 1.

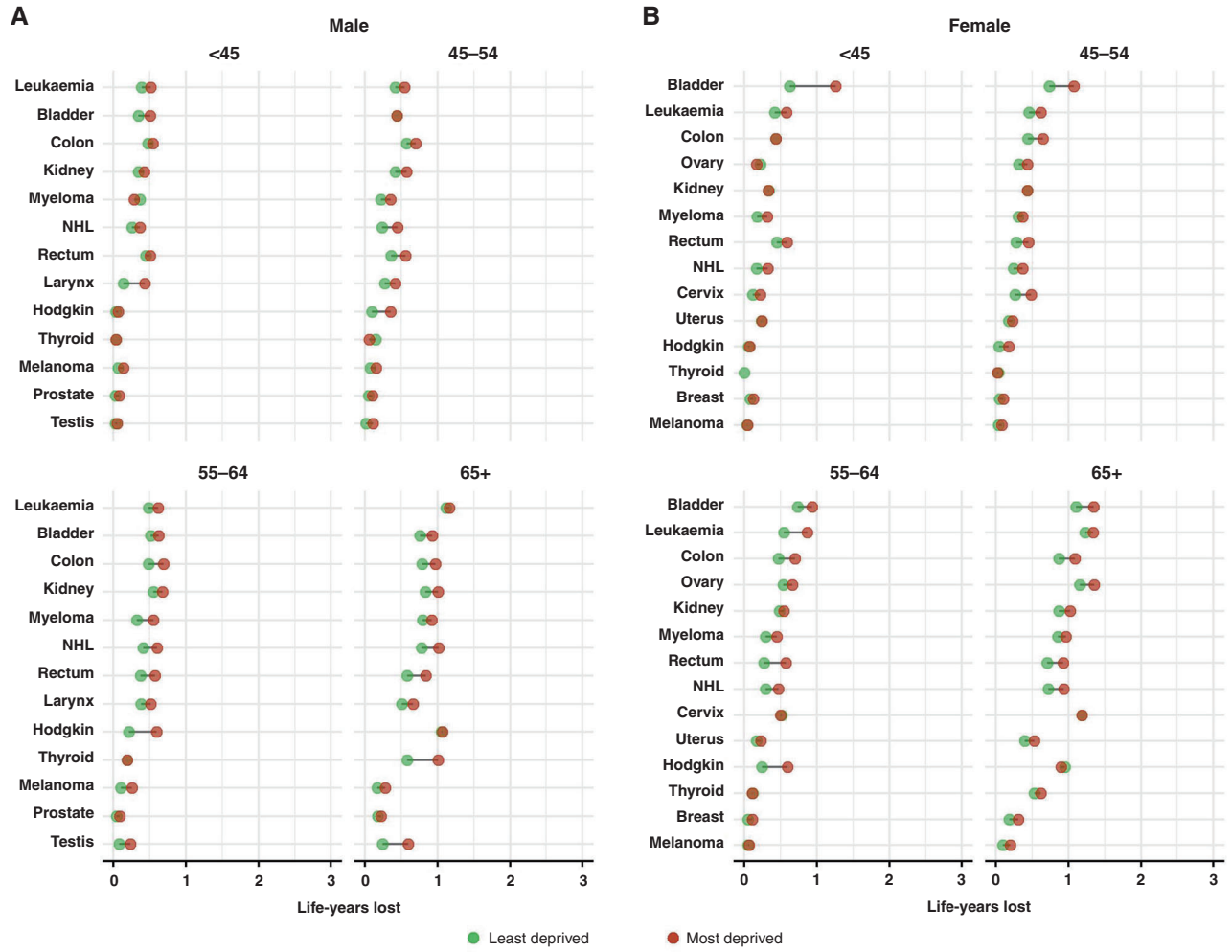

Fig. 3 Number of life-years lost within 3 years due to a given cancer in the most and the least deprived by age group, for the group of moderate and good prognosis cancers. A Male, **B** female. NHL non-hodgkin lymphoma; cancers are sorted as in Fig. 1.

below 30% of LYL (65+ male) (Fig. 4) while 10% of cancers are from lung in this group (Table 1). Lung cancer remains the largest contributor of NLYL in all age groups, with the exception of female patients, aged 15–44 years, for whom the largest contributors of NLYL were breast cancer (least and most deprived) and cervical cancer (most deprived) (Fig. 4). A few cancer sites, such as brain, bowel, leukaemia, ovary and breast, are larger contributors of LYL in the least deprived than in the most deprived groups.

DISCUSSION

Our study, including the additional online infographic, clearly show that more deprived patients systematically lose more lifetime due to cancer, and that most deprived patients tend to stand out from the other deprivation categories with generally much higher NLYL. Those living in the most socioeconomically deprived neighbourhoods in England, accounting for around 17% of the incident cancers included in this study, lost 1.5 times more NLYL than the least deprived (0.98 years vs. 0.67 within 3 years; results not shown). To obtain these results, we used a relative survival approach, which allows the competing risks of death from other causes to be controlled without any information on the cause of death. Overall, the burden of poor-prognosis cancers is the highest, both regarding the NLYL and their proportions.

The largest socio-economic inequalities in NLYL were seen mostly in younger adults less than 45 years diagnosed with poor-prognosis cancers whilst for the moderate/good prognosis cancers the socio-economic inequalities varied substantially but with an overall widening, counterintuitive, trend with increasing age. The disproportionate socio-economic inequalities in younger adults were more specifically seen for the cancers related to tobacco smoking, such as pancreatic, lung and oesophageal cancers which presented the largest gaps in this age group. The prognosis of these cancers is so poor in older patients that survival differences can no longer be observed. In contrast, the narrow socio-economic inequalities from the good prognosis cancers, particularly among young patients, may be due to the 'ceiling effect', when survival in the less deprived is so high that it cannot improve further [4, 10].

Pancreatic cancer illustrates well this age-related pattern. In the age group less than 45 years, the most deprived male patients lost about 5 months more than the least deprived within 3 years, while in the age group 65 plus, this difference is only about 1 month. This is more likely due to very low survival probabilities, rather than reduced inequalities in the oldest age group. Five-year net survival from pancreatic cancer in England ranges between 36% in patients less than 45 years and 3% in those over 75 [45], which makes it almost impossible to detect any differences in this age group. The lack of early symptoms and advanced stage at diagnosis dramatically affect the probability of receiving surgical resection which is the only curative treatment for pancreatic cancer [46].

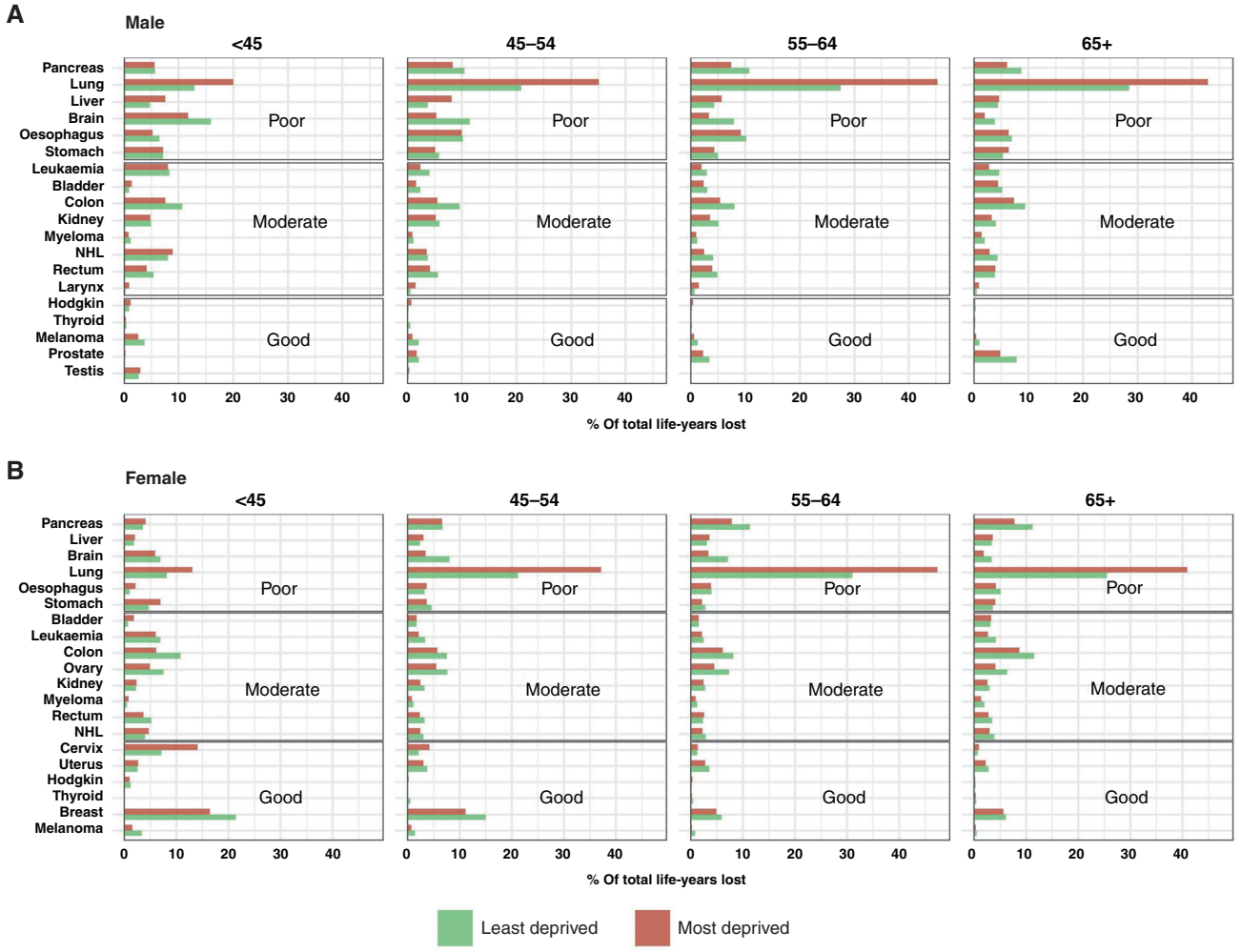

Fig. 4 Proportion of number of life-years lost within 3 years due to the cancer indicated, in the most and the least deprived group, by age group and according to cancer prognosis (poor, moderate, good). A Male, **B** female; NHL non-hodgkin lymphoma.

Similar phenomenon combined with lower use of a potentially curative treatment particularly in young deprived patients could explain the larger deprivation inequalities observed for lung cancer in younger patients. Surgical resection remains the major potentially curative treatment of lung cancer (particularly non-small-cell carcinoma). The receipt of surgical treatment decreases dramatically with age and deprivation, even after accounting for comorbidity [24], which is less of a concern among younger patients because of low comorbidity prevalence [47]. With the exceptions of youngest females and youngest least deprived males, lung cancer is also the largest contributor to LYL (Fig. 4). In the most deprived group, lung cancer represents a fifth of the incident cases (Table 1) and accounts for around 13–42% of all NLYL from all cancers combined, depending on sex and age. This highlights that a targeted lung cancer screening is justifiable given a large number of LYL that could be avoided [48, 49].

In addition to the aforementioned cancers, the largest socio-economic inequalities in NLYL overall were also seen for bladder cancer in young female patients and for laryngeal cancer in young male patients, both cancers related to tobacco smoking. Bladder [50] and colon [51] cancer cases illustrate the persisting gender inequalities in diagnosis, with early symptoms such as haematuria and pelvic pain less prone to further diagnostic investigations among women [51]. These inequalities are probably exacerbated among more deprived patients, who may not get access to a specialised healthcare facility for urologic surgery, either because of greater travel distance or lack of social support [52]. Regarding laryngeal cancer, the large deprivation gap in LYL seen in young men is unlikely to be explained by late diagnosis (i.e., advanced stage) [53], and more likely by suboptimal care, such as delayed treatment [54], or because of the poorer ability of deprived patients in navigating the complex laryngeal cancer pathway [55].

Cervical cancer is another important contributor, especially in women younger than 45 years, where it accounts for 15% and 7% of all LYL in most and least deprived patients, respectively, illustrating the need for increasing the cervical cancer screening uptake and HPV vaccine coverage among young women, particularly in more deprived population.

The study findings highlight the fact that reducing inequalities in younger adults is equally as important as tackling inequalities in the older population as it would result in many life-years gained. From a societal aspect, the LYL due to cancer in adults of working age can have a significant societal and economic impact. Studies in the US and Europe have consistently shown that premature loss of life attributed to cancer, results in reduced productive capacity and therefore loss in labour force earnings [56–59]. In the UK, it was estimated that in a single year over 50,000 people of working age lose their lives from cancer and in 2014 these people could have contributed £585 million to the UK economy [60]. Loss in productivity can also affect cancer survivors, especially those with

short survival cancers or other co-morbid chronic diseases [61]. It is estimated that among cancer survivors only around 63.5% will return to employment with the majority reducing the working hours and limiting voluntary activities and caregiving [62].

Literature on the societal and economic impact of socio-economic inequalities in cancer remains scarce [63, 64]. Moreover, similar studies on this topic have mostly used the loss in life expectancy, which requires extrapolation of cancer survival of the cohort individuals up to the end of their expected life [65]. Our metric of LYL does not rely on such extrapolation as it is time-bound to the point where all patients have been followed up. We acknowledge that the social and economic costs of a patient death go far beyond 3 years. However, our estimates bounded at 3 years make the costs easier to estimate by health economists and more usable politically and for health policy planning.

From a public health policy perspective, it is vital to address these inequalities as this will reduce the overall impact of cancer on society. The wider inequalities among young patients potentially emphasise the structural components that may play a key role and pose a serious challenge to the healthcare system and society. Moreover, the range of these across-cancer inequalities poses the question of their causes. Mechanisms underlying such inequalities within a universal health coverage setting are still not well understood [66].

In a context of an increasing shortage of resources in both primary and secondary care sectors [67], the COVID-19 pandemic has exacerbated the inequalities [68, 69]. It also emphasised that the suboptimal distribution of resources between areas according to their deprivation level [70, 71] is likely to play an important role in the inequalities in accessing optimal healthcare [72] and, ultimately, in cancer outcomes [73]. The inequities component should be systematically and carefully considered in any policies aiming at improving cancer outcomes (including for earlier detection or new treatment) before their implementation in order to reduce these inequalities or even avoid further widening.

DATA AVAILABILITY

The data used for this study are the English National Cancer Registry data 1971–2014. Cancer registration data consist of patient information and as such, it is protected under the Data Protection Act 1998 and GDPR 2018 and cannot be made available as open data. Formal requests for release of cancer registration data can be made to the data custodian Public Health England (PHE), Office for Data Release (ODR) at odr@phe.gov.uk. The researchers will have beforehand obtained all the ethical and statutory approvals required for accessing sensitive data. Detailed information on the application process can be found at https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data.

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AUTHOR CONTRIBUTIONS

BR, DKK, AB and AE designed the study. AE and DKK conducted data analysis and created figures and tables. DKK designed the web-tool. AE and BR drafted the manuscript. All authors contributed to the interpretation of the results, revised and critically reviewed the manuscript and approved the submitted version.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The authors have obtained the ethical and statutory approvals required for this research (PIAG 1-05(c)/2007); ethical approval updated 6 April 2017 (REC 13/LO/0610).

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Research Paper 3 - Supplementary Materials

Appendix for the paper entitled:

Socio-economic inequalities in cancer survival: how do they translate into Number of Life-Years Lost?

Authors

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Non-parametric estimation of Number of Life-Years Lost due to cancer

It has been shown that the integral of the cause-specific cumulative probability function until time *t* can be interpreted as the expected number of life-years lost due to that cause before time *t*. [1, 2]

In a cohort of cancer patients, the Number of Life-Years Lost (NLYL) can be split into NLYL due to cancer and NLYL due to other causes. NLYL due to cancer at time *t* can be estimated as a function of the cancer-specific cumulative incidence function F_C from time *0* to time *t* (*aka* the crude probability of death due to cancer):

$$L_C(0,t) = \int_0^t F_C(u)du \quad (1)$$

F_C is a continuous function which reflects the probability of dying from cancer before or at time *t*, in the presence of competing causes of death. NLYLs are estimated within a pre-specified time window [0,*t*] to avoid extrapolation in the estimation of the cancer-specific cumulative incidence function F_C beyond the maximum time when all patients of the cohort have been followed up.[3]

On a group level, F_C can be defined as:

$$F_C(t) = \int_0^t S(u)\, \mathrm{d}\Lambda_C\,(u) \quad (2)$$

where $S(u)$ is the all-cause survival at time u and $d\Lambda_C(u)$ is the increase in the cancer-specific cumulative hazard from time *0* to time *t* on the whole population ("marginal").

In the relative survival framework of methods, F_C is often referred to as Crude Probability of Death (CPr) and its estimation is based on the main assumption of this framework[3], that the overall mortality hazard $\lambda_{O_i}(t)$ of an individual can be expressed as the sum of the excess (i.e. cancer-specific) hazard $\lambda_{C_i}(t)$ and the hazard of death from other causes (i.e. population hazard)[4] $\lambda_{P_i}(t)$:

$$\lambda_{O_i}(t) = \lambda_{C_i}(t) + \lambda_{P_i}(t) \quad (3)$$

After combining these individual hazards, the estimation of the marginal $\mathrm{d}\Lambda_c(u)$ in **(2)** can be based on the difference between the marginal overall cumulative hazard and the marginal population (or expected) cumulative hazard:

$$\mathrm{d}\Lambda_C(u) = \mathrm{d}\Lambda_O(u) - \mathrm{d}\Lambda_P(u) \quad (4)$$

More details can be found in Perme *et al*[2, 4] and in section 2.3.1 from Kipourou *et al*.[5]

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Supplementary material

Socio-economic inequalities in cancer survival: how do they translate into Number of Life-Years Lost?

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Figure 1 Probability of death up to 3 years since diagnosis for all cancer sites in male and female patients diagnosed in 2010-2014; NHL=Non-Hodgkin Lymphoma

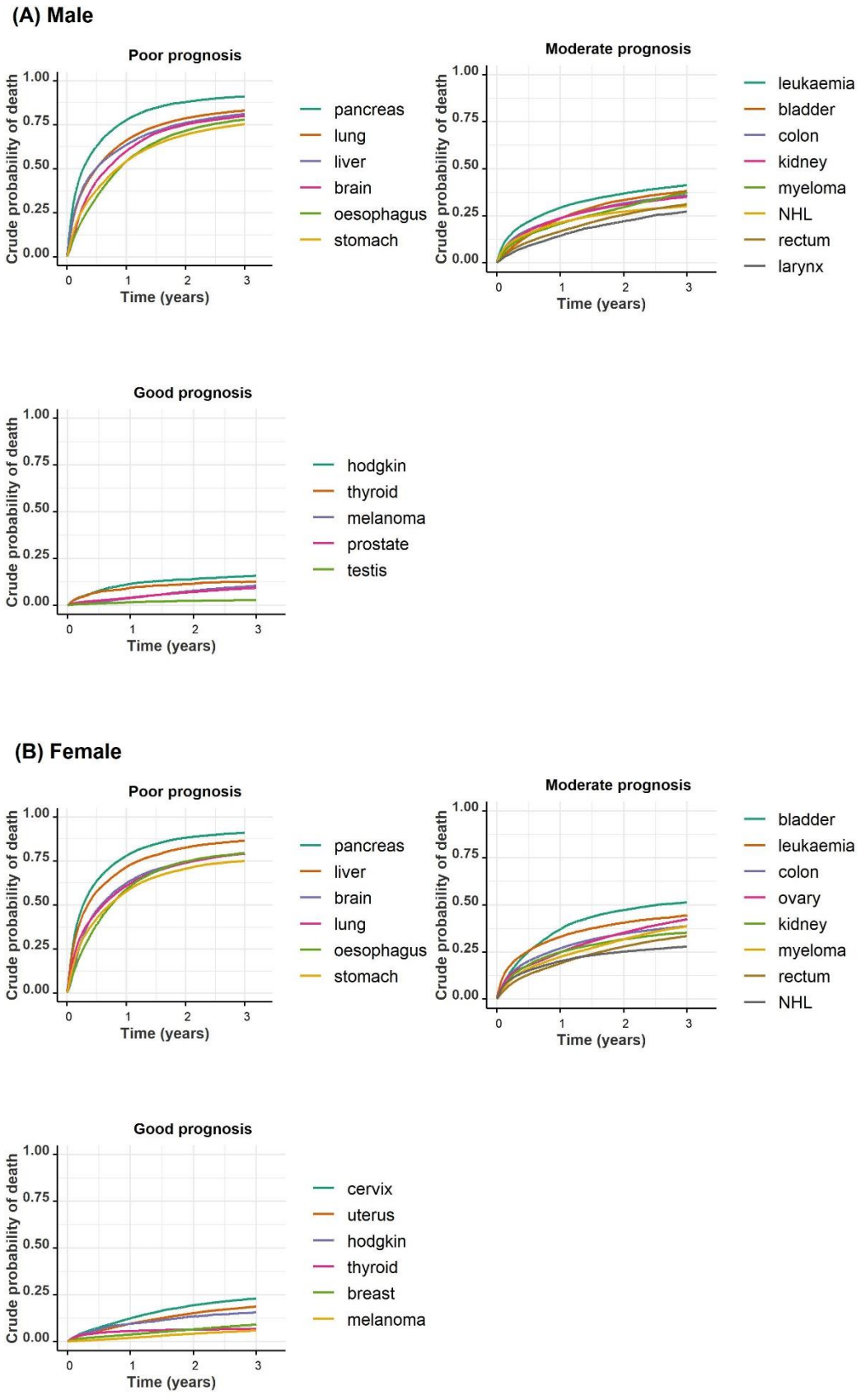

Table 1 Poor prognosis cancers: Number of Life-Years Lost within 3 years since cancer diagnosis in the least and most deprived patients

		Male				Female			
		Least deprived		Most deprived		Least deprived		Most deprived	
Cancer	**Age**	**Life-Years Lost**	**95% CI**	**Life-Years Lost**	**95% CI**	**Life-Years Lost**	**95%CI**	**Life-Years Lost**	**95% CI**
brain	**<45**	**0.68**	0.57 - 0.8	**0.78**	0.77 - 0.87	**0.47**	0.36 - 0.59	**0.66**	0.52 - 0.79
	45-54	**1.41**	1.29 - 1.52	**1.45**	1.39 - 1.61	**1.24**	1.08 - 1.38	**1.42**	1.24 - 1.6
	55-64	**1.83**	1.76 - 1.91	**1.98**	1.93 - 2.08	**1.82**	1.73 - 1.93	**1.88**	1.73 - 2.02
	65plus	**2.43**	2.39 - 2.47	**2.42**	2.38 - 2.47	**2.42**	2.38 - 2.47	**2.48**	2.42 - 2.54
liver	**<45**	**1.58**	1.19 - 1.96	**1.65**	1.53 - 1.84	**0.95**	0.58 - 1.38	**1.30**	0.95 - 1.68
	45-54	**1.33**	1.08 - 1.57	**1.73**	1.72 - 1.81	**1.45**	1.14 - 1.75	**1.59**	1.36 - 1.8
	55-64	**1.60**	1.49 - 1.73	**1.73**	1.69 - 1.8	**1.73**	1.55 - 1.89	**1.91**	1.76 - 2.04
	65plus	**2.07**	2.02 - 2.12	**2.11**	2.06 - 2.13	**2.21**	2.15 - 2.27	**2.28**	2.22 - 2.34
lung	**<45**	**1.41**	1.2 - 1.62	**1.72**	1.6 - 1.85	**0.95**	0.77 - 1.16	**1.49**	1.34 - 1.63
	45-54	**1.66**	1.55 - 1.76	**1.86**	1.8 - 1.92	**1.57**	1.47 - 1.67	**1.76**	1.7 - 1.82
	55-64	**1.84**	1.79 - 1.89	**1.94**	1.91 - 1.97	**1.61**	1.56 - 1.66	**1.73**	1.69 - 1.77
	65plus	**2.00**	1.98 - 2.02	**2.06**	2.04 - 2.07	**1.89**	1.86 - 1.91	**1.97**	1.95 - 1.99
oesophagus	**<45**	**1.41**	1.16 - 1.69	**1.64**	1.43 - 1.87	**1.12**	0.43 - 1.73	**1.72**	1.28 - 1.98
	45-54	**1.47**	1.34 - 1.6	**1.65**	1.55 - 1.75	**1.16**	0.94 - 1.36	**1.49**	1.3 - 1.66
	55-64	**1.48**	1.4 - 1.56	**1.64**	1.58 - 1.71	**1.34**	1.21 - 1.48	**1.56**	1.43 - 1.69
	65plus	**1.70**	1.66 - 1.74	**1.89**	1.85 - 1.93	**1.85**	1.8 - 1.9	**1.97**	1.91 - 2.02
pancreas	**<45**	**1.38**	1.05 - 1.71	**1.81**	1.56 - 2.07	**1.11**	0.77 - 1.43	**1.26**	1.02 - 1.51
	45-54	**1.93**	1.79 - 2.08	**2.04**	1.92 - 2.16	**1.62**	1.44 - 1.8	**1.86**	1.69 - 1.99
	55-64	**2.07**	2 - 2.15	**2.23**	2.16 - 2.3	**2.08**	2 - 2.16	**2.24**	2.15 - 2.32
	65plus	**2.37**	2.34 - 2.4	**2.46**	2.43 - 2.5	**2.36**	2.33 - 2.39	**2.44**	2.41 - 2.47
stomach	**<45**	**1.43**	1.17 - 1.69	**1.53**	1.33 - 1.74	**1.51**	1.2 - 1.82	**1.62**	1.4 - 1.85
	45-54	**1.37**	1.19 - 1.53	**1.37**	1.23 - 1.52	**1.49**	1.27 - 1.7	**1.46**	1.29 - 1.64
	55-64	**1.47**	1.36 - 1.59	**1.47**	1.36 - 1.57	**1.43**	1.25 - 1.61	**1.42**	1.28 - 1.58
	65plus	**1.72**	1.67 - 1.77	**1.83**	1.79 - 1.88	**1.77**	1.7 - 1.83	**1.84**	1.77 - 1.9

Table 2 Moderate prognosis cancers: Number of Life-Years Lost within 3 years since cancer diagnosis in the least and most deprived patients

		Male				Female			
		Least deprived		Most deprived		Least deprived		Most deprived	
Cancer	**Age**	**Life-Years Lost**	**95% CI**	**Life-Years Lost**	**95% CI**	**Life-Years Lost**	**95%CI**	**Life-Years Lost**	**95% CI**
bladder	**<45**	**0.35**	0.12 - 0.62	**0.51**	0.3 - 0.72	**0.63**	0.16 - 1.15	**1.26**	0.89 - 1.65
	45-54	**0.44**	0.32 - 0.56	**0.44**	0.34 - 0.56	**0.73**	0.51 - 0.98	**1.08**	0.85 - 1.33
	55-64	**0.52**	0.45 - 0.59	**0.62**	0.55 - 0.7	**0.73**	0.59 - 0.9	**0.94**	0.79 - 1.08
	65plus	**0.76**	0.73 - 0.79	**0.93**	0.89 - 0.97	**1.10**	1.04 - 1.16	**1.35**	1.28 - 1.41
colon	**<45**	**0.48**	0.38 - 0.58	**0.55**	0.44 - 0.64	**0.43**	0.35 - 0.52	**0.44**	0.35 - 0.52
	45-54	**0.58**	0.51 - 0.65	**0.70**	0.61 - 0.79	**0.44**	0.37 - 0.51	**0.65**	0.56 - 0.74
	55-64	**0.49**	0.45 - 0.53	**0.69**	0.64 - 0.75	**0.47**	0.43 - 0.52	**0.70**	0.63 - 0.76
	65plus	**0.79**	0.76 - 0.82	**0.97**	0.94 - 1	**0.87**	0.84 - 0.89	**1.09**	1.05 - 1.13
kidney	**<45**	**0.34**	0.22 - 0.47	**0.43**	0.33 - 0.53	**0.33**	0.17 - 0.51	**0.33**	0.21 - 0.45
	45-54	**0.42**	0.35 - 0.5	**0.58**	0.5 - 0.65	**0.44**	0.34 - 0.56	**0.44**	0.34 - 0.53
	55-64	**0.55**	0.49 - 0.61	**0.68**	0.61 - 0.74	**0.48**	0.4 - 0.56	**0.54**	0.47 - 0.63
	65plus	**0.83**	0.79 - 0.87	**1.01**	0.95 - 1.06	**0.87**	0.81 - 0.92	**1.02**	0.96 - 1.08
leukaemia	**<45**	**0.39**	0.29 - 0.48	**0.52**	0.43 - 0.61	**0.42**	0.31 - 0.53	**0.58**	0.46 - 0.7
	45-54	**0.42**	0.33 - 0.52	**0.55**	0.43 - 0.65	**0.46**	0.35 - 0.57	**0.62**	0.49 - 0.76
	55-64	**0.49**	0.42 - 0.56	**0.62**	0.53 - 0.7	**0.54**	0.46 - 0.64	**0.86**	0.74 - 0.99
	65plus	**1.12**	1.08 - 1.17	**1.16**	1.1 - 1.23	**1.23**	1.17 - 1.29	**1.34**	1.26 - 1.41
larynx	**<45**	**0.14**	0 - 0.48	**0.43**	0.21 - 0.66				
	45-54	**0.27**	0.12 - 0.46	**0.42**	0.31 - 0.54				
	55-64	**0.38**	0.27 - 0.5	**0.52**	0.44 - 0.59				
	65plus	**0.51**	0.43 - 0.59	**0.66**	0.59 - 0.74				
myeloma	**<45**	**0.36**	0.14 - 0.61	**0.29**	0.13 - 0.49	**0.18**	0 - 0.42	**0.32**	0.14 - 0.51
	45-54	**0.22**	0.12 - 0.32	**0.36**	0.25 - 0.47	**0.31**	0.17 - 0.44	**0.37**	0.23 - 0.54
	55-64	**0.32**	0.26 - 0.4	**0.55**	0.45 - 0.66	**0.30**	0.22 - 0.38	**0.45**	0.33 - 0.58
	65plus	**0.79**	0.74 - 0.85	**0.92**	0.85 - 0.99	**0.85**	0.8 - 0.91	**0.96**	0.89 - 1.04
Non-Hodgkin Lymphoma	**<45**	**0.26**	0.19 - 0.34	**0.37**	0.3 - 0.44	**0.17**	0.11 - 0.24	**0.32**	0.25 - 0.41
	45-54	**0.23**	0.17 - 0.29	**0.45**	0.37 - 0.52	**0.24**	0.18 - 0.31	**0.37**	0.29 - 0.46
	55-64	**0.41**	0.36 - 0.46	**0.61**	0.53 - 0.68	**0.29**	0.24 - 0.34	**0.47**	0.4 - 0.54
	65plus	**0.78**	0.74 - 0.81	**1.02**	0.96 - 1.07	**0.72**	0.68 - 0.76	**0.94**	0.88 - 0.99
rectum	**<45**	**0.45**	0.32 - 0.58	**0.51**	0.39 - 0.63	**0.45**	0.31 - 0.58	**0.59**	0.45 - 0.73
	45-54	**0.36**	0.3 - 0.43	**0.56**	0.49 - 0.64	**0.28**	0.21 - 0.35	**0.45**	0.36 - 0.55
	55-64	**0.38**	0.34 - 0.42	**0.57**	0.52 - 0.62	**0.27**	0.23 - 0.32	**0.57**	0.49 - 0.66
	65plus	**0.59**	0.56 - 0.62	**0.84**	0.8 - 0.88	**0.71**	0.67 - 0.75	**0.93**	0.87 - 0.98

Table 3 Good prognosis cancers: Number of Life-Years Lost within 3 years since cancer diagnosis in the least and most deprived patients

		Male				Female			
		Least deprived		Most deprived		Least deprived		Most deprived	
Cancer	**Age**	**Life-Years Lost**	**95% CI**	**Life-Years Lost**	**95% CI**	**Life-Years Lost**	**95%CI**	**Life-Years Lost**	**95% CI**
Hodgkin Lymphoma	**<45**	**0.04**	0.01 - 0.07	**0.06**	0.03 - 0.1	**0.05**	0.02 - 0.09	**0.07**	0.04 - 0.11
	45-54	**0.10**	0.01 - 0.19	**0.36**	0.21 - 0.51	**0.05**	0.01 - 0.13	**0.17**	0.05 - 0.33
	55-64	**0.21**	0.08 - 0.36	**0.60**	0.43 - 0.79	**0.24**	0.07 - 0.44	**0.60**	0.35 - 0.85
	65plus	**1.05**	0.87 - 1.22	**1.07**	0.86 - 1.3	**0.95**	0.76 - 1.14	**0.90**	0.68 - 1.11
thyroid	**<45**	**0.04**	0 - 0.09	**0.04**	0 - 0.08	**0.00**	0 - 0.01	**0.00**	0 - 0.01
	45-54	**0.15**	0.06 - 0.24	**0.06**	0.01 - 0.14	**0.04**	0.01 - 0.07	**0.02**	0.01 - 0.06
	55-64	**0.19**	0.09 - 0.3	**0.19**	0.08 - 0.33	**0.11**	0.07 - 0.17	**0.11**	0.04 - 0.2
	65plus	**0.58**	0.45 - 0.7	**1.01**	0.78 - 1.26	**0.53**	0.43 - 0.63	**0.62**	0.48 - 0.76
skin melanoma	**<45**	**0.06**	0.04 - 0.09	**0.14**	0.09 - 0.19	**0.04**	0.02 - 0.05	**0.04**	0.03 - 0.06
	45-54	**0.08**	0.05 - 0.1	**0.16**	0.1 - 0.21	**0.04**	0.02 - 0.05	**0.08**	0.05 - 0.12
	55-64	**0.10**	0.08 - 0.13	**0.26**	0.19 - 0.32	**0.05**	0.03 - 0.07	**0.07**	0.03 - 0.11
	65plus	**0.17**	0.15 - 0.19	**0.28**	0.23 - 0.34	**0.10**	0.08 - 0.12	**0.20**	0.14 - 0.25
prostate	**<45**	**0.03**	0 - 0.1	**0.08**	0.01 - 0.18				
	45-54	**0.05**	0.03 - 0.06	**0.10**	0.07 - 0.13				
	55-64	**0.05**	0.04 - 0.05	**0.09**	0.07 - 0.1				
	65plus	**0.18**	0.17 - 0.19	**0.22**	0.21 - 0.24				
testis	**<45**	**0.03**	0.02 - 0.05	**0.05**	0.04 - 0.07				
	45-54	**0.02**	0 - 0.04	**0.11**	0.04 - 0.18				
	55-64	**0.08**	0 - 0.17	**0.23**	0.08 - 0.42				
	65plus	**0.24**	0.07 - 0.44	**0.60**	0.25 - 1				
breast	**<45**					**0.08**	0.07 - 0.09	**0.12**	0.11 - 0.14
	45-54					**0.05**	0.04 - 0.06	**0.10**	0.09 - 0.12
	55-64					**0.05**	0.05 - 0.06	**0.11**	0.09 - 0.12
	65plus					**0.19**	0.18 - 0.2	**0.31**	0.29 - 0.33
cervix	**<45**					**0.12**	0.09 - 0.15	**0.22**	0.19 - 0.25
	45-54					**0.27**	0.19 - 0.35	**0.49**	0.41 - 0.56
	55-64					**0.52**	0.39 - 0.64	**0.50**	0.4 - 0.6
	65plus					**1.19**	1.07 - 1.32	**1.19**	1.08 - 1.3
ovary	**<45**					**0.22**	0.17 - 0.29	**0.17**	0.13 - 0.2
	45-54					**0.32**	0.27 - 0.37	**0.43**	0.37 - 0.5
	55-64					**0.54**	0.49 - 0.6	**0.66**	0.6 - 0.73
	65plus					**1.16**	1.12 - 1.2	**1.36**	1.3 - 1.42
uterus	**<45**					**0.23**	0.13 - 0.35	**0.25**	0.16 - 0.33
	45-54					**0.18**	0.14 - 0.22	**0.23**	0.18 - 0.28
	55-64					**0.17**	0.14 - 0.2	**0.23**	0.19 - 0.27
	65plus					**0.40**	0.37 - 0.43	**0.53**	0.49 - 0.58

Research Paper 4

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Epidemiology

What can hospital emergency admissions prior to cancer diagnosis tell us about socio-economic inequalities in cancer diagnosis? Evidence from population-based data in England

Aimilia Exarchakou[1]✉, Bernard Rachet[1], Georgios Lyratzopoulos[2], Camille Maringe[1] and Francisco Javier Rubio[3]

BACKGROUND: More deprived cancer patients are at higher risk of Emergency Presentation (EP) with most studies pointing to lower symptom awareness and increased comorbidities to explain those patterns. With the example of colon cancer, we examine patterns of hospital emergency admissions (HEAs) history in the most and least deprived patients as a potential precursor of EP.
METHODS: We analysed the rates of hospital admissions and their admission codes (retrieved from Hospital Episode Statistics) in the two years preceding cancer diagnosis by sex, deprivation and route to diagnosis (EP, non-EP). To select the conditions (grouped admission codes) that best predict emergency admission, we adapted the purposeful variable selection to mixed-effects logistic regression.
RESULTS: Colon cancer patients diagnosed through EP had the highest number of HEAs than all the other routes to diagnosis, especially in the last 7 months before diagnosis. Most deprived patients had an overall higher rate and higher probability of HEA but fewer conditions associated with it.
CONCLUSIONS: Our findings point to higher use of emergency services for non-specific symptoms and conditions in the most deprived patients, preceding colon cancer diagnosis. Health system barriers may be a shared factor of socio-economic inequalities in EP and HEAs.

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INTRODUCTION

Emergency Presentation (EP) is one of the broad routes to cancer diagnosis in England and represents the diagnosis following an unplanned hospitalisation in the National Health Service (NHS).

Despite some improvement in recent years, colorectal cancer has one of the highest proportions of patients diagnosed through EP among all cancers diagnosed in England, at around 22%. Patients diagnosed through this route experience significantly lower survival than those diagnosed through the two-week wait or other referral routes [1, 2] and report worse patient experience [3–5]. While most relevant evidence relates to English patients, a recent international study indicated that diagnosis of colon cancer as an emergency is a global phenomenon [6].

EP is an indicator of delays in diagnosis and can be a manifestation of both patient-specific behavioural patterns such as recognition of symptoms or cancer awareness as well as problems in access to and delivery of health care services [7]. The importance of monitoring EP proportions in England, has been recognised and Routes to Diagnosis are now regularly reported as Official Statistics by the National Disease Registration Service at NHS Digital [1].

Wide inequalities in EP with colorectal cancer are observed, with older, more deprived, female patients, patients of non-white ethnicity background and patients with comorbidities at a higher risk for an emergency diagnosis [8–12]. The large proportion of EP, especially in the more socio-economically deprived groups, may reflect the overall increased relative use of emergency to elective hospital care in more deprived areas of England [13, 14]. The excess number of emergency hospitalisations in the more deprived patients can be only partly attributed to the severity of comorbidity prevalent in the more deprived areas, pointing to other systemic factors of care delivery [13].

In this study, we hypothesise that whether patients use elective or emergency route to be admitted in hospital in the years preceding their cancer diagnosis, is linked to EP. The conditions for which patients get hospitalised for and the admission route for those conditions, even if unrelated to the cancer, can help understand the use of healthcare services and problems of access in cancer patients. Benchmarking the disease-mix and the risk of emergency hospitalisation in most deprived patients against the least deprived cancer patients, can further highlight the inequalities component. For example, we know that patients with specific

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comorbidities are at a higher risk for EP [10] but it still remains unclear whether the type of admission for these conditions varies by socio-demographic characteristics.

Our study aims to understand the mechanism associated to HEAs, which in turn may help devise strategies to improve outcomes for the most affected population groups and reduce the overall burden of emergency presentation. With the example of colon cancer, we aim to tackle this by 1) examining whether more deprived patients and patients diagnosed through EP experience higher proportion of HEAs up to two years prior to colon cancer diagnosis and 2) identifying the combination of conditions or diseases that most commonly trigger the HEAs.

METHODS

Data

We included all patients diagnosed with colon cancer (C18.0-C18.9) in England in 2013. Information on patient and tumour characteristics was retrieved from the English Cancer Registry Data. Whilst the Routes to Diagnosis is part of this dataset, the original information is derived through an algorithm developed by Public Health England using hospital records. With this algorithm, a cancer case is assigned to a route to diagnosis by examining the type of hospital admission on the date closest to the date of the cancer diagnosis, typically up to 28 days before the cancer diagnosis [2].

Patient history of hospitalisations was derived from the Admitted Patient Care (APC) records of the Hospital Episode Statistics (HES) in the two years preceding the cancer diagnosis [15, 16]. Patient admissions comprise of spells - periods of continuous care in one provider institution and each spell may comprise of more than one episode, i.e., a period of continuous care under the responsibility of a single consultant, although this is only a small proportion of hospital admissions (around 20%) [16].

The linkage of the cancer registry and HES datasets was deterministic, based on patient and tumour pseudo-identifiers and has been described in previous studies [12, 17]. We excluded 2,522 patients for whom there was no record in HES. We analysed the primary diagnostic codes, recorded in the first of 20 diagnostic fields, using the International Statistical Classification of Diseases, Injuries and Causes of Death, tenth revision (ICD-10) coding system [18]. The primary diagnostic codes are more likely to accurately represent the trigger cause for hospital admission and more likely to be linked to the mode of admission (emergency or non-emergency).

For the purpose of this study, we used the first diagnostic field of the discharge episode of the spell to define the reason for hospital admission. For the majority (> 95%) of the multi-episode spells, the main diagnosis in the admission episode was identical to the main diagnosis in the discharge episode. The data selected for this study contained 5,118 distinct ICD-10 codes. As many individual diagnostic codes presented strong clinical or symptom similarities, we a priori grouped the codes into 58 aggregate condition groups. Furthermore, several grouped admission codes had low or zero incidence in certain combinations of sex and deprivation population groups and were excluded. The total number of aggregate condition groups initially considered for analysis was therefore 42.

Socioeconomic deprivation of patients was based on the income domain score of the English Index of Multiple Deprivation of the lower-layer super output area (LSOA) of patient residence at the time of cancer diagnosis [19]. Deprivation of cancer patients was then categorised according to the quintiles (from 1 indicating "least deprived" to 5 indicating "most deprived") of the national distribution of scores for all LSOAs in England.

We only used the income domain as the IMD contains components about health deprivation and access to public services which are strongly related to inequalities in cancer outcomes, and therefore may lead to erroneous results and misinterpretation [20, 21]. Additionally, the income and employment domains have the highest degree of agreement with the overall composite IMD measure, as they carry the highest contributing weights (22.5%) [19].

Data analysis

To describe trends in hospital admissions we present two main measures: the monthly rate of hospital admissions per patient and the monthly proportion of patients with at least one emergency admission. The latter represents unique patients, meaning that each patient can only be part of the monthly proportion once. These measures are useful to interpret trends in HEA over the 2-year pre-diagnostic interval and visualise differences between deprivation levels and routes to diagnosis (EP and non-EP). As most patients had a hospital admission on the date of colon cancer diagnosis, we excluded that hospitalisation from the visualization and analysis of hospital admissions (not from the descriptive table), to avoid the impact imbalanced data may have on the results. This led to the exclusion of 2,596 patients who had only one hospital admission during which the cancer diagnosis was made.

For the second study aim, i.e. identifying the combinations of conditions associated with HEAs, we developed a multi-step approach in order to select the relevant conditions among the very high number of admission codes recorded. The outcome was HEA (binary format) and the main predictors were the distinct grouped conditions and age at diagnosis. We fitted a generalized mixed-effects logistic model to account for the cluster structure of the observations at patient level. We specified a random intercept model with a logit link function implemented with the "glmer" function in R [22].

Multi-step approach to select the admission codes. For the selection of the most relevant groups of conditions, we adapted the Purposeful Variable Selection (PVS) for fixed effects logistic regression as described by Hosmer et al. (2013) [23], to mixed-effects logistic regression.

PVS represents a selection decision process in which, at each step, variables that are not significant and not a confounder are removed. At each step, the full model is compared to the nested model with a likelihood-ratio test (LRT) to determine the statistically significant covariates.

In Step 1, The PVS process began with a univariable analysis of each independent variable compared to the model with just the intercept. At the end of this step, all covariates that yielded a statistically significant p value were included to build the multivariable model M1.

In Step 2, M1 was compared to the nested model which included all but one of the M1 covariates. This was iteratively repeated for all covariates to determine the ones that could be eliminated, so that, at the end of Step 2, the reduced model M2 included only the covariates which were not eliminated.

In Step 3, any covariates eliminated in Step 2 were examined for confounding. Confounding was determined when a change in the remaining parameter estimates of model M2 compared to the parameter estimates of model M1 was greater than 10%. These confounders were added back to form the multivariable model M3.

In Step 4, each variable not selected in Step 1 was added one at a time to model M3 and its significance checked. At the end of this step, the final main effects model was obtained.

Due to large number of observations, we defined statistical significance based on p values less than 0.01 for LRT throughout the analysis. A few of the covariates (appendicitis, cognition and speech symptoms, musculoskeletal symptoms) created complete separation in specific combinations of sex and deprivation, because they perfectly predicted HEA or non-HEA. These were eventually removed from the mixed-effects model as they would otherwise create convergence issues in the Maximum Likelihood Estimation (MLE) and yield extremely large Wald standard errors (Hauck-Donner effect, i.e. the Wald test statistic is not monotonically increasing as a function of increasing distance between the parameter estimate and the null value) [24]. To detect complete separation we used the "brglm2" package in R only on the fixed effects [25]. All the analytic steps were stratified by sex and deprivation.

The marginal effect of each condition group retrieved from the final main effects model in Step 4 of the approach, using the R package "ggeffects" [26]. In the Supplementary material, we also present the average change in the probability of HEA that each covariate contributes at population level, alongside 95% approximate confidence intervals for the difference of two probabilities.

In the figures, a further clinical grouping of the conditions was done to facilitate the interpretation. The classification to "Potentially related", "Indirect/non-specific" and "Unrelated" was done after the analysis, based on the similarity of colon cancer symptoms to the presenting symptoms of these conditions.

RESULTS

Patient characteristics

The analysis included 15,263 patients diagnosed with a colon cancer in 2013 and who experienced at least one NHS hospital

admission (HA) in the two-year window prior to colon cancer diagnosis (74% of all colon cancer cases). Approximately 15% of those patients lived in the most deprived and 21% in the least deprived neighbourhoods in England, at diagnosis. Although the majority of patients were aged over 65 years old at diagnosis in all deprivation groups, the distribution of age slightly shifted to younger ages with increasing deprivation (Table 1).

Number of hospitalisations by route to diagnosis and deprivation

Excluding the hospitalisation during which the cancer diagnosis was made, patients had a total of 38,859 inpatient hospitalisations, 37% of which were emergency admissions. Approximately 80% of patients had at least one HEA and 20% had two or more HEAs.

Patients whose colon cancer was diagnosed through emergency presentation (EP) had an excess of HEAs compared to those diagnosed through other routes (Non-EP) (Fig. 1). The difference in the rate of HEAs between the EP and Non-EP group of patients was relatively constant up to 7 months before diagnosis at around 0.01 difference. From 7 months onwards, the number of emergency admissions increased disproportionately for the EP group of patients, reaching a difference of 0.18 in the rate with the Non-EP group in the last month before diagnosis (0.29 emergency admissions per patient in EP group *vs.* 0.11 emergency admissions per patient in Non-EP group). The increase in hospital admissions (HA) occurred at the same time, around 7 months before colon cancer diagnosis, regardless the type (elective or emergency) of admission.

The proportion of patients with multiple HAs or multiple HEAs, increased with deprivation. Among male patients, 17% of the least deprived had more than three hospitalisations and 7% had more than two HEAs within two years prior to diagnosis (Table 1). In the most deprived, the proportions increased to 21% and 11%, respectively. Among female patients, 16% of the least deprived patients had more than three hospitalisations and 7% more than two HEAs, and these proportions rose to 21% and 14%, respectively, among the most deprived.

Deprivation-related differences were more marked for HEAs, where the rate was consistently higher in the most deprived than the least deprived patients (Fig. 2). These differences increased

Table 1. Characteristics of male and female patients diagnosed with colon cancer in 2013, during the two years prior to diagnosis, by deprivation quintile[a].

Male						
	Least deprived (*N* = 1722)	**2 (*N* = 1725)**	**3 (*N* = 1687)**	**4 (*N* = 1611)**	**Most deprived (*N* = 1252)**	**Total (*N* = 7997)**
Age in years (N (%))						
<45	51 (3.0%)	50 (2.9%)	45 (2.7%)	65 (4.0%)	56 (4.5%)	267 (3.3%)
(45–55]	69 (4.0%)	72 (4.2%)	86 (5.1%)	107 (6.6%)	92 (7.3%)	426 (5.3%)
(55–65]	242 (14.1%)	215 (12.5%)	248 (14.7%)	226 (14.0%)	232 (18.5%)	1163 (14.5%)
>65	1360 (79.0%)	1388 (80.5%)	1308 (77.5%)	1213 (75.3%)	872 (69.6%)	6141 (76.8%)
Patients with:						
1–2 HA[b]	1205 (70.0%)	1180 (68.4%)	1176 (69.7%)	1,094 (67.9%)	812 (64.9%)	5467 (68.4%)
3 HA	226 (13.1%)	228 (13.2%)	221 (13.1%)	225 (14.0%)	182 (14.5%)	1082 (13.5%)
>3 HA	291 (16.9%)	317 (18.4%)	290 (17.2%)	292 (18.1%)	258 (20.6%)	1448 (18.1%)
Patients with:						
1 HEA[c]	1433 (83.2%)	1432 (83.0%)	1375 (81.5%)	1302 (80.8%)	943 (75.3%)	6485 (81.1%)
2 HEA	173 (10.0%)	181 (10.5%)	168 (10.0%)	181 (11.2%)	166 (13.3%)	869 (10.9%)
>2 HEA	116 (6.7%)	112 (6.5%)	144 (8.5%)	128 (7.9%)	143 (11.4%)	643 (8.0%)
Female						
	Least deprived (*N* = 1500)	**2 (*N* = 1642)**	**3 (*N* = 1516)**	**4 (*N* = 1467)**	**Most deprived (*N* = 1141)**	**Total (*N* = 7266)**
Age in years						
(15–45]	56 (3.7%)	71 (4.3%)	74 (4.9%)	79 (5.4%)	77 (6.7%)	357 (4.9%)
(45–55]	71 (4.7%)	87 (5.3%)	87 (5.7%)	100 (6.8%)	74 (6.5%)	419 (5.8%)
(55–65]	186 (12.4%)	192 (11.7%)	190 (12.5%)	184 (12.5%)	186 (16.3%)	938 (12.9%)
>65	1187 (79.1%)	1292 (78.7%)	1165 (76.8%)	1104 (75.3%)	804 (70.5%)	5552 (76.4%)
Patients with:						
1–2 HA	1070 (71.3%)	1162 (70.8%)	1037 (68.4%)	1008 (68.7%)	733 (64.2%)	5010 (69.0%)
3 HA	196 (13.1%)	206 (12.5%)	195 (12.9%)	216 (14.7%)	169 (14.8%)	982 (13.5%)
>3 HA	234 (15.6%)	274 (16.7%)	284 (18.7%)	243 (16.6%)	239 (20.9%)	1274 (17.5%)
Patients with:						
1 HEA	1237 (82.5%)	1338 (81.5%)	1185 (78.2%)	1129 (77.0%)	851 (74.6%)	5740 (79.0%)
2 HEA	161 (10.7%)	173 (10.5%)	192 (12.7%)	206 (14.0%)	159 (13.9%)	891 (12.3%)
>2 HEA	102 (6.8%)	131 (8.0%)	139 (9.2%)	132 (9.0%)	131 (11.5%)	635 (8.7%)

[a]Based on the income domain score of the English Index of Multiple Deprivation.
[b]HA = Hospital Admissions.
[c]HEA = Hospital Emergency Admissions.

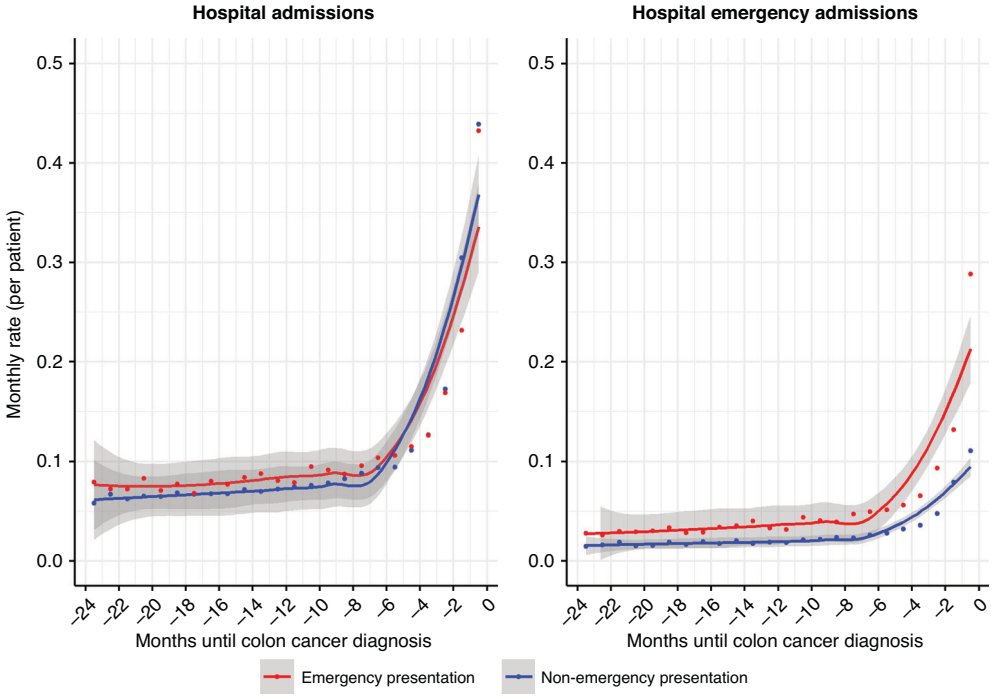

Fig. 1 Monthly rate of hospitalisations in the two years prior to colon cancer diagnosis in patients diagnosed through emergency ($N = 3671$) and non-emergency presentation ($N = 8996$). Left panel: monthly rate of hospital admissions, right panel: monthly rate of hospital emergency admissions.

notably from 7 months before diagnosis, reaching a gap in monthly HEA rates of around 20% in the last month prior to diagnosis. Similar turning point is seen across the elective and non-elective hospitalisations, as in Fig. 1.

The proportion of patients with at least one HEA, by contrast, was minimally higher in the most deprived than in the least deprived patients (< 5% difference) (Fig. 3).

Conditions predictive of emergency admission

From the total of 42 clinical conditions initially included in each model, only 22–26 (varying by specific combinations of sex and deprivation) were retained in the final model as most predictive of the mode of hospital admission among colon cancer patients (Fig. 4 & Supplementary Table 2 & Supplementary Fig. 1).

Overall, some of the conditions with similar or potentially related symptoms with colon cancer such as abdominal and pelvic pain, appendicitis, digestive disorders and disorders of the peritoneum increased the probability of HEA above the baseline. In particular, appendicitis was highly predictive of HEA in both sexes and deprivation groups. In contrast, upper GI diseases and inflammatory bowel diseases decreased the probability of HEA below the baseline.

Urinary tract disorders and general symptoms also increased the probability of HEA. Patients with hospital admissions may present with non-specific symptoms that may be indirectly related to colon cancer.

From the group of conditions that are unlikely to be related to colon cancer, some acute conditions (e.g., infectious and parasitic diseases, injury and poisoning), some conditions affecting the cardiovascular and respiratory system (COPD, heart diseases) and mental and behavioural disorders increased the probability of HEA to higher than 0.6 in both male and female patients.

Cancer (malignant neoplasm, in situ/benign/other neoplasm) and some general conditions reduced the probability of HEA.

Discrepancies by sex and deprivation. The overall baseline probability of HEA for male patients, when age was set at its mean value (72.7 and 74.9 in the most and least deprived, respectively) and all grouped conditions were set to zero (reference values), was 0.62 (95%CI: 0.57–0.66) in the most deprived, almost double than in the least deprived (0.33; 95%CI: 0.3–0.37), despite their younger mean age (Fig. 4 & Suppl. Table 2 & Suppl. Fig. 1). In female patients (mean age at 72.8 and 75.2 in the most and least deprived, respectively), the baseline probabilities of HEA were similar in the two deprivation groups: 0.50 (95%CI: 0.45–0.55) in the most deprived and 0.45 (95%CI: 0.40–0.51) in the least deprived.

The marginal probabilities of HEA for individual conditions were similar across deprivation groups or sex. However, since the baseline probability varied widely between the most and the least deprived male patients, and between male and female patients, the average change in the marginal probabilities of HEA also appeared to vary.

Due to the higher baseline probability of HEA in the most deprived male patients, the specific conditions explained little of the HEA probabilities, as demonstrated by their smaller marginal effect than in the least deprived. In female patients, the marginal effect of individual conditions was similar between the least and most deprived patients, as their baseline probabilities were also very close.

Among male patients, the number of conditions that predicted type of admission was only 22 in the most deprived but 26 in the least deprived. There were very few discrepancies in which conditions predicted HEA between the two deprivation groups. Except for cardiovascular and respiratory conditions that were common, mental and behavioural disorders and some digestive conditions such as digestive disorders and disorders of the peritoneum, and urinary tract disorders all increased the probability of HEA above the baseline in the least but not in the most deprived.

In female patients, urinary diseases and general symptoms increased the probability of HEA in the least but not the most deprived patients. In contrast, gynaecological conditions such as

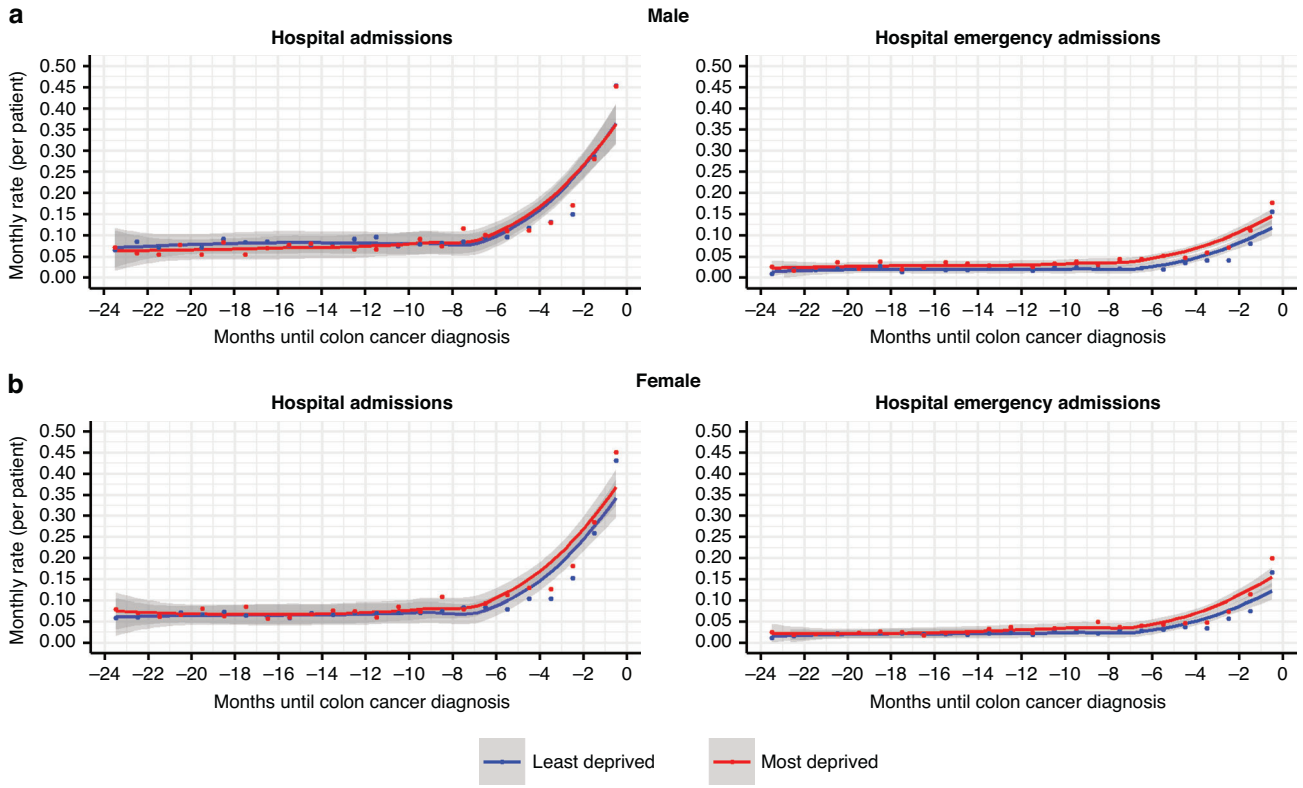

Fig. 2 Monthly rate of hospitalisations in the two years prior to diagnosis in the most and the least deprived colon cancer patients. **a** Male. Left panel: monthly rate of hospital admissions; right panel: monthly rate of hospital emergency admissions. Most deprived $N = 1040$, least deprived $N = 1407$. **b** Female. Left panel: monthly rate of hospital admissions; right panel: monthly rate of hospital emergency admissions. Most deprived $N = 956$, least deprived $N = 1234$.

pregnancy and perinatal related disorders, and female genital organs disorders increased the probability of HEA in the most but not the least deprived female patients.

Interestingly, anaemia was associated with a decrease in the probability of HEA only in the most deprived male patients, whilst among females the decrease was only in the least deprived patients.

DISCUSSION

While hospital admissions for any cause were very similar between the most and the least deprived colon cancer patients, emergency admissions preceding the diagnosis of colon cancer, clearly differed between socio-economic groups. This has been found internationally [27–29] as well as in the UK [30, 31].

The most deprived patients had an overall higher rate of HEAs and this was more marked in the last 7 months prior to cancer diagnosis. By contrast, the proportions of patients using the emergency services were fairly comparable between the most and the least deprived, at around 1.5% every month until 7 months before diagnosis.

Further, the patterns of grouped conditions as well as the level of their associated HEA probability were very comparable between most and least deprived patients, which suggests that there are similar conditions driving HEAs in both groups. Individual disease-specific aspects of care do not seem to explain the excess of emergency admissions in the most deprived patients, it may rather suggest an overall higher use of the emergency services as the privileged path. In other words, given the contrast between the proportion of patients (Fig. 3) and rate of HEA (Fig. 2) by deprivation, it seems that the higher HEA rate in the most deprived was mostly due to some patients using repeatedly the emergency services for conditions which were not well established.

Some digestive conditions such as appendicitis and to a lesser extent, abdominal and pelvic pain, represent a high proportion of HEA in colon cancer patients (Suppl. Table 1) and could be related to colorectal cancer. Appendicitis in older age groups could be a direct consequence of colorectal cancer potentially due to blockage of the appendix or stool obstruction. Abdominal and pelvic pain is another colorectal cancer symptom [32], often indicating late-stage tumour. Whilst appendicitis had similar effect on HEA probabilities in both the least and the most deprived patients, abdominal and pelvic pain represented higher proportion of HEA in the most than the least deprived.

Repeated use of emergency services by most deprived patients with abdominal/pelvic pain two years prior to definitive cancer diagnosis, suggests delays on the pathway to cancer diagnosis. Often, delays in cancer diagnosis are attributed to delays in seeking help due to lack of symptom awareness, limiting beliefs [33], underestimation of the seriousness of symptoms or increased comorbidities [34–37]. Whilst not minimising the impact of those factors, our study showed that there may be system-level factors that contribute to delays in diagnosis [38]. The extent to which the patient-related or the system-related factors account for EP with colorectal cancer is debatable and may vary by socio-demographic characteristics.

Against the cancer awareness hypothesis is the higher risk of EP for colon cancer in women [39]. Women generally have higher symptom awareness than men [40]. Nevertheless, our study showed that they had a higher baseline probability of HEA than men but similar marginal probabilities for the symptoms or conditions potentially related to colon cancer. Women also experience less specific symptoms which are more often attributed to benign diagnoses, which may explain some of their increased risk of EP for colon cancer. Abdominal symptoms such

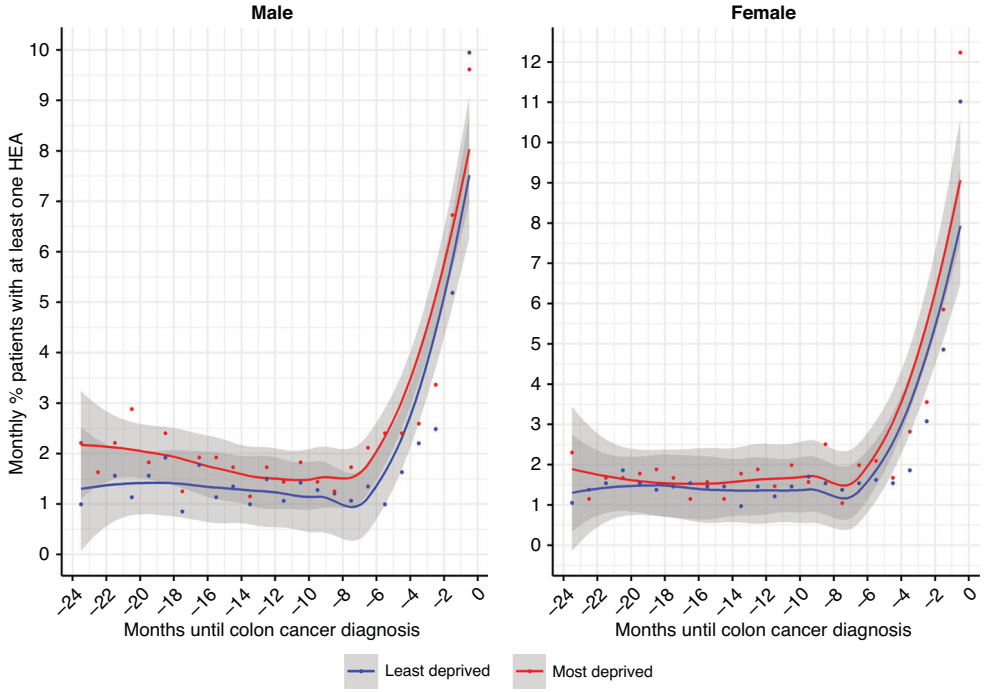

Fig. 3 Proportion of colon cancer patients with at least one hospital emergency admission (HEA) in the two years prior to colon cancer diagnosis. Left panel: male; right panel: female.

as changes in bowel habits are more likely to receive a benign diagnosis of IBS or diverticular disease than men, one year prior to emergency presentation with colon cancer [39].

Another example of sex and deprivation contrast, is anaemia, which was associated with HEA only in male patients and the least deprived female patients. This suggests that iron deficiency may be less promptly recognised or managed in more deprived female patients because any concurrent symptoms such as fatigue/lack of energy, pale skin, shortness of breath and headaches can be overlooked by the patient or the physician [41].

The conditions that increased the probability of HEA in the most and the least deprived colon cancer patients were a combination of acute and long-term conditions. Injury, poisoning, infectious and parasitic diseases and acute respiratory symptoms such as troubled breathing, persistent chesty cough and frequent chest infections, are all urgent care conditions and most likely require an emergency admission to the hospital. In contrast, long-term conditions or comorbidities such as malignant or benign neoplasm, COPD, heart diseases, renal disease and mental and behavioural disorders can be considered Ambulatory Care Sensitive Conditions (ACSC) for which HEA can be prevented [42–44].

In particular, among the more deprived colon cancer patients, a few of those ACSCs such as COPD, respiratory and heart diseases, were associated with a higher probability of HEA than in the less deprived. Also, conditions such as mental and behavioural disorders were only associated with HEA in the least deprived. Those discrepancies highlight the different disease burdens and severity of these conditions between deprivation groups and represent opportunities for preventing HEA, through the identification of vulnerable groups of patients [45].

Conditions such as malignant or benign neoplasm and upper GI related conditions were associated with decreased effect on the probability of HEA, i.e. they generally do not require HEA. For neoplasms, this may be because the majority of patients may return to the hospital for scheduled diagnostic or treatment appointments. Similarly, nearly 90% of the upper GI related conditions corresponded to inflammatory conditions or ulcer of the upper GI, with fairly specific symptoms and which are generally treatable in ambulatory setting. Most urinary disorders or infections increased the probability of HEA which aligns with the ACSCs statistics for England, reported as a quality indicator [46]. In recent years, a drop in the number of emergency admissions due to urinary tract infections was observed due to improved coding for sepsis [46].

EP flags challenges in early detection of cancer partly due to the disease itself e.g. rapidly progressing tumour, irregular or non-specific symptoms and complications that require emergency hospitalisation, but also due to patient help-seeking behaviours or other health-system factors related to the patient pathway [6]. Our findings add to the evidence that colon cancer EP and higher use of emergency services share similar drivers, particularly among the most deprived patients and those with more comorbidities [10, 13]. The groups of conditions in our study, do not seem to explain much of the HEAs among the most deprived, and they do not explain much of the inequalities in referral pathway either [47–49]. More deprived patients are less likely to be diagnosed with, and hospitalised for, symptoms and conditions related to colon cancer. In contrast, less deprived patients may opt to refer themselves to the Emergency Department for symptomatic but not critical conditions, bypassing the elective care system.

Strengths and limitations

These analyses used population-based national cancer registrations known for their high level of completeness and quality [50]. These were successfully linked to secondary care records, as only 2,522 cancer patients (12%) did not have any HES record, most likely because they received care outside the NHS, such as privately or abroad.

The Purposeful Variable Selection method for confounding and covariate selection performs better than more automated methods when the analyst is interested in risk factor modelling rather than prediction, and this is especially true in smaller sample sizes [51]. However, one possible limitation is that the variables that were not selected initially for the multivariable model are only tested with the selected set of covariates one at a time and not jointly.

To assess the robustness of the method, we performed a sensitivity analysis using the "glmmmixedlasso" package in R, an $\ell 1$-

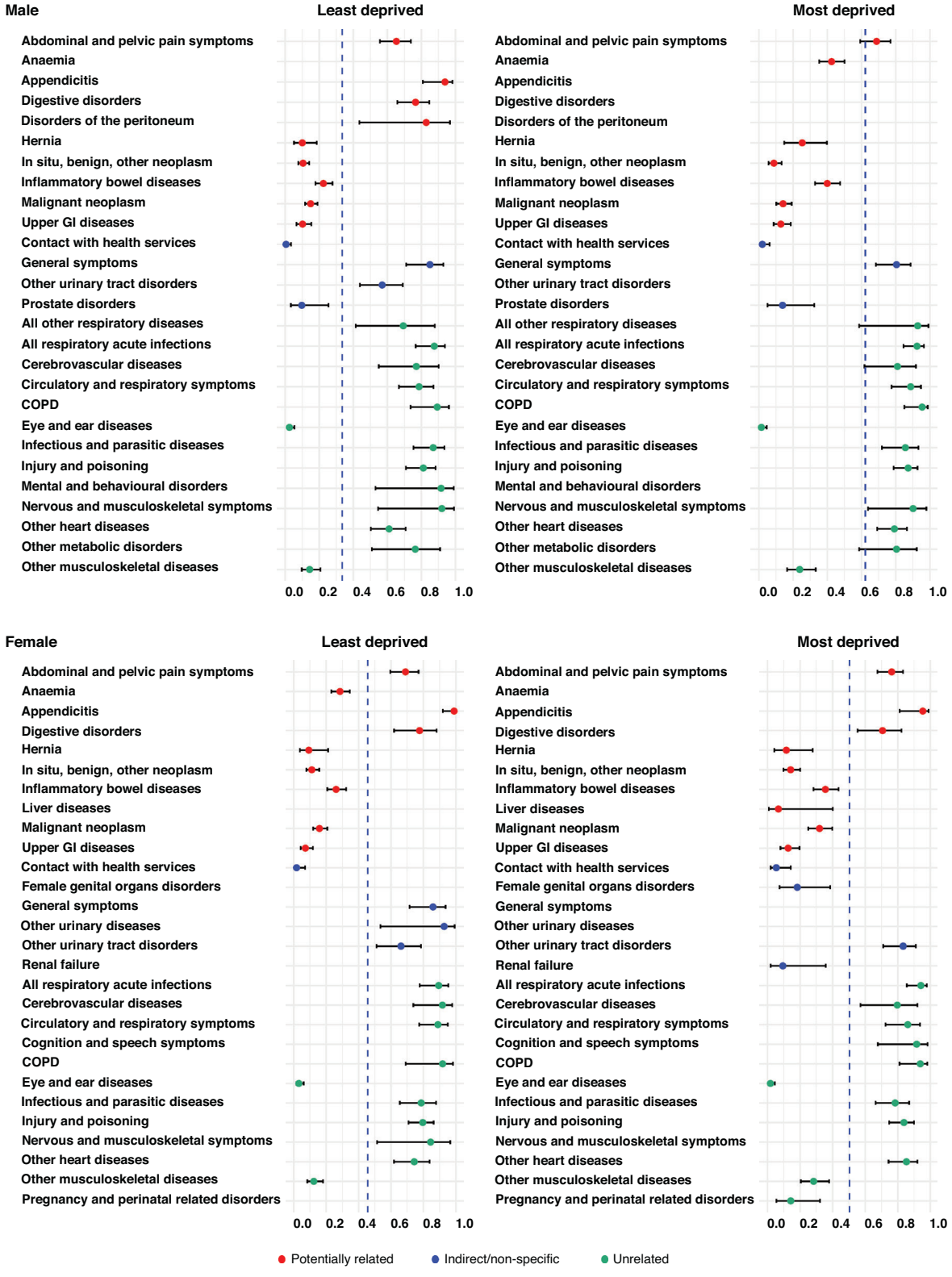

Fig. 4 Marginal effects of the selected grouped conditions on the probability of Hospital Emergency Admission (HEA) in the two years prior to colon cancer diagnosis, by sex and deprivation level. The estimates are derived from mixed effect models specific to each of the four panels. Each of the four final models includes the set of covariates listed in each panel, as well as age. The vertical hyphenated blue line represents the average probability of HEA in the population, with all listed covariates set to zero and age at its mean value.

penalized algorithm for fitting high-dimensional generalized linear mixed models [52]. The algorithm was applied to female patients of the least deprived group, testing a wide range of lambda values and evaluating them based on the acquired BIC values of each model. There was agreement with PVS in 24 out of the 29 variables retained except for "nervous system diseases", "functional intestinal disorders", "gallbladder and pancreatic diseases", "abnormal and diagnostic imaging" and "skin disorders." In contrast, "renal failure," "other urinary diseases" and "liver diseases" retained with the PVS method were not retained in the sensitivity analysis. This result is potentially related to the false discovery problems associated to LASSO under highly correlated covariates.

To identify the combination of grouped conditions associated with higher probabilities of emergency admission, we further fitted a regression tree on the probabilities predicted from the final model. We used the "rpart" package in R [53]; The regression trees confirmed the absence of outstanding conditions or combinations of conditions that could be driving high probabilities of HEA. The overall patterns were again similar across deprivation and sex categories, only with fewer selected conditions among the most deprived male patients.

CONCLUSION

To address inequalities in delays in cancer diagnosis, academic community and stakeholders have often focused on the lower cancer awareness and higher comorbidity prevalence observed in more deprived populations. Without ignoring these factors, our findings add evidence on an additional explanation. More disadvantaged populations may experience successive services-related barriers [54] in seeking help for any reason, causing delays in tests and diagnosis, and leading them to use emergency services [55]. For example, the current consultation conditions in primary care (e.g. short duration of consultation) [56] penalise the patients with poor health literacy, even more in the presence of multiple comorbidities [54]. Since the COVID-19 pandemic, patients with poor digital literacy may experience additional barriers due to the increased use of e-consultation. Delays may also occur in accessing diagnostic tests and specialised consultations [55]. Researchers and policymakers should shift their priorities toward the healthcare system factors that can influence these inequalities.

DATA AVAILABILITY

The data used for this study are the English National Cancer Registry data and the Hospital Episode Statistics (HES). This data consists of patient information and as such, it is protected under the Data Protection Act 1998 and GDPR 2018 and cannot be made available as open data. Formal requests for release of the data can be made to the data custodian NHS Digital. The researchers will have beforehand obtained all the ethical and statutory approvals required for accessing sensitive data.

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AUTHOR CONTRIBUTIONS

FJR, BR, CM and AE designed the study. FJR and CM provided guidance and advice on statistics and data analysis. GL and BR provided expert clinical and content advice. AE conducted data analysis, created figures and tables and drafted the first version of the manuscript. All authors contributed to the interpretation of the results, revised and critically reviewed the manuscript and approved the submitted version.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The authors have obtained the ethical and statutory approvals required for this research (PIAG 1-05(c)/2007); ethical approval updated 6 April 2017 (REC 13/LO/0610).

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41416-024-02688-6.

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Research Paper 4 - Supplementary Material

Supplementary material

What can hospital emergency admissions prior to cancer diagnosis tell us about socio-economic inequalities in cancer diagnosis? Evidence from population-based data in England.

Authors

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Table 1. Number and proportion of Hospital Admissions (HA) and Hospital Emergency Admissions (HEA) due to individual conditions, and proportions of HEA to HA due to individual conditions in the most and the least deprived colon cancer patients diagnosed in 2013.

ICD-10 DISEASE GROUP	**ICD-10 DIAGNOSTIC CODES**	**Least deprived**			**Most deprived**		
		Number of **Hospital** Admissions **(N=6,750)**	Number of **Emergency** Admissions **(N=2,051)**	**%**	Number of **Hospital** Admissions **(N=5,247)**	Number of **Emergency** Admissions **(N=2,123)**	**%**
abdominal and pelvic pain symptoms	R1	246 (3.6%)	143 (7%)	58.1	224 (4.3%)	145 (6.8%)	64.7
abnormal blood and urine findings	R7, R8	23 (0.3%)	7 (0.3%)	30.4	16 (0.3%)	6 (0.3%)	37.5
abnormal diagnostic imaging	R9	53 (0.8%)	6 (0.3%)	11.3	47 (0.9%)	13 (0.6%)	27.7
all other respiratory diseases	J (except other J)	22 (0.3%)	18 (0.9%)	81.8	13 (0.2%)	7 (0.3%)	53.8
all respiratory acute infections	J0-J3, J85-J86	102 (1.5%)	89 (4.3%)	87.3	127 (2.4%)	114 (5.4%)	89.8
anaemia	D50-D64	645 (9.6%)	213 (10.4%)	33.0	519 (9.9%)	190 (8.9%)	36.6
appendicitis	K35-K38	25 (0.4%)	25 (1.2%)	100	17 (0.3%)	16 (0.8%)	94.1
cerebrovascular diseases	I60-I69	50 (0.7%)	41 (2%)	82.0	53 (1%)	40 (1.9%)	75.5
chronic rheumatic heart diseases	I05-I09	6 (0.1%)	2 (0.1%)	33.3	1 (0%)	0 (0%)	0
circulatory and respiratory symptoms	R0	131 (1.9%)	105 (5.1%)	80.2	109 (2.1%)	94 (4.4%)	86.2
circulatory system diseases	I70-I99	129 (1.9%)	55 (2.7%)	42.6	119 (2.3%)	58 (2.7%)	48.7
coagulatory defects	D65-D69, D7, D8	46 (0.7%)	5 (0.2%)	10.9	12 (0.2%)	3 (0.1%)	25.0
cognition and speech symptoms	R4	19 (0.3%)	19 (0.9%)	100	26 (0.5%)	24 (1.1%)	92.3
congenital malformations	Q	8 (0.1%)	2 (0.1%)	25.0	7 (0.1%)	1 (0%)	14.3
contact with health services	Z	228 (3.4%)	2 (0.1%)	0.9	170 (3.2%)	7 (0.3%)	4.1
COPD	J40-J47	54 (0.8%)	47 (2.3%)	87.0	86 (1.6%)	80 (3.8%)	93.0
diabetes mellitus	E10-E14	11 (0.2%)	7 (0.3%)	63.6	19 (0.4%)	12 (0.6%)	63.2
digestive disorders	K91-K93	125 (1.9%)	94 (4.6%)	75.2	91 (1.7%)	58 (2.7%)	63.7
disorders of the peritoneum	K65-K67	7 (0.1%)	5 (0.2%)	71.4	7 (0.1%)	5 (0.2%)	71.4
external causes of morbidity	V, W, X, Y,						
eye and ear diseases	H	388 (5.7%)	16 (0.8%)	4.1	311 (5.9%)	8 (0.4%)	2.6
female breast disorders	N60-N64	1 (0%)	0 (0%)	0			
female genital organs disorders	N70-N74, N75-N98	41 (0.6%)	9 (0.4%)	22.0	28 (0.5%)	4 (0.2%)	14.3
functional intestinal disorders	K57-K59	189 (2.8%)	78 (3.8%)	41.3	153 (2.9%)	84 (4%)	54.9
gallbladder and pancreatic diseases	K80-K87	59 (0.9%)	24 (1.2%)	40.7	62 (1.2%)	39 (1.8%)	62.9

general symptoms	R5, R6	80 (1.2%)	65 (3.2%)	81.3	118 (2.2%)	81 (3.8%)	68.6
hernia	K40-K46	113 (1.7%)	11 (0.5%)	9.7	87 (1.7%)	19 (0.9%)	21.8
hypertension	I10-I15	166 (2.5%)	1 (0%)	0.6	3 (0.1%)	3 (0.1%)	100
hyperthyroidism	E05						
hypothyroidism	E02,E03						
in situ, benign, other neoplasm	D0-D4, D10-D36, D37-D48	446 (6.6%)	32 (1.6%)	7.2	304 (5.8%)	20 (0.9%)	6.6
infectious and parasitic diseases	A, B	97 (1.4%)	76 (3.7%)	78.4	95 (1.8%)	73 (3.4%)	76.8
inflammatory bowel diseases	K50-K51	449 (6.7%)	84 (4.1%)	18.7	315 (6%)	93 (4.4%)	29.5
injury and poisoning	S, T	224 (3.3%)	176 (8.6%)	78.6	201 (3.8%)	166 (7.8%)	82.6
ischaemic heart diseases	I20-I25	148 (2.2%)	72 (3.5%)	48.6	123 (2.3%)	67 (3.2%)	54.5
liver diseases	K70-K77	36 (0.5%)	11 (0.5%)	30.6	24 (0.5%)	8 (0.4%)	33.3
male genital organs disorders	N43-N51	11 (0.2%)	3 (0.1%)	27.3	7 (0.1%)	3 (0.1%)	42.9
malignant neoplasm	C	773 (11.5%)	43 (2.1%)	5.6	413 (7.9%)	38 (1.8%)	9.2
mental and behavioural disorders	F	14 (0.2%)	12 (0.6%)	85.7	24 (0.5%)	17 (0.8%)	70.8
nervous and musculoskeletal symptoms	R25-R29	19 (0.3%)	17 (0.8%)	89.5	32 (0.6%)	30 (1.4%)	93.8
nervous system diseases	G	59 (0.9%)	22 (1.1%)	37.3	62 (1.2%)	37 (1.7%)	59.7
obesity	E65-E68				1	0	0
other heart diseases	I (except I05-I15, I20-I25, I60-I99)	197 (2.9%)	124 (6%)	62.9	163 (3.1%)	122 (5.7%)	74.8
other intestinal disorders	K52-K56, K60-K63						
other metabolic disorders	E0-E9 (except all other E)	41 (0.6%)	28 (1.4%)	68.3	44 (0.8%)	26 (1.2%)	59.1
other musculoskeletal diseases	M (except M30-M36)	390 (5.8%)	62 (3%)	15.9	286 (5.5%)	77 (3.6%)	26.9
other urinary diseases	N (except other N)	11 (0.2%)	6 (0.3%)	54.5	21 (0.4%)	14 (0.7%)	66.7
other urinary tract disorders	N20-N39	156 (2.3%)	81 (3.9%)	51.9	145 (2.8%)	94 (4.4%)	64.8
pregnancy and perinatal related disorders	0, P	15 (0.2%)	1 (0%)	6.7	49 (0.9%)	8 (0.4%)	16.3
prostate disorders	N40-N42	34 (0.5%)	4 (0.2%)	11.8	26 (0.5%)	5 (0.2%)	19.2
renal failure	N17-N19	167 (2.5%)	15 (0.7%)	9.0	55 (1%)	16 (0.8%)	29.1
skin disorders	L	77 (1.1%)	26 (1.3%)	33.8	57 (1.1%)	30 (1.4%)	52.6
skin symptoms	R20-R23	8 (0.1%)	7 (0.3%)	87.5	6 (0.1%)	3 (0.1%)	50.0
special codes	U						
systemic connective tissue disorders	M30-M36	1 (0%)	0 (0%)	0	1 (0%)	1 (0%)	100
thyroid disorders	E04, E07						
thyroiditis	E06						
upper GI diseases	K0-K3	340 (5%)	36 (1.8%)	10.6	323 (6.2%)	45 (2.1%)	13.9
urinary system symptoms	R3	70 (1%)	24 (1.2%)	34.3	45 (0.9%)	19 (0.9%)	42.2

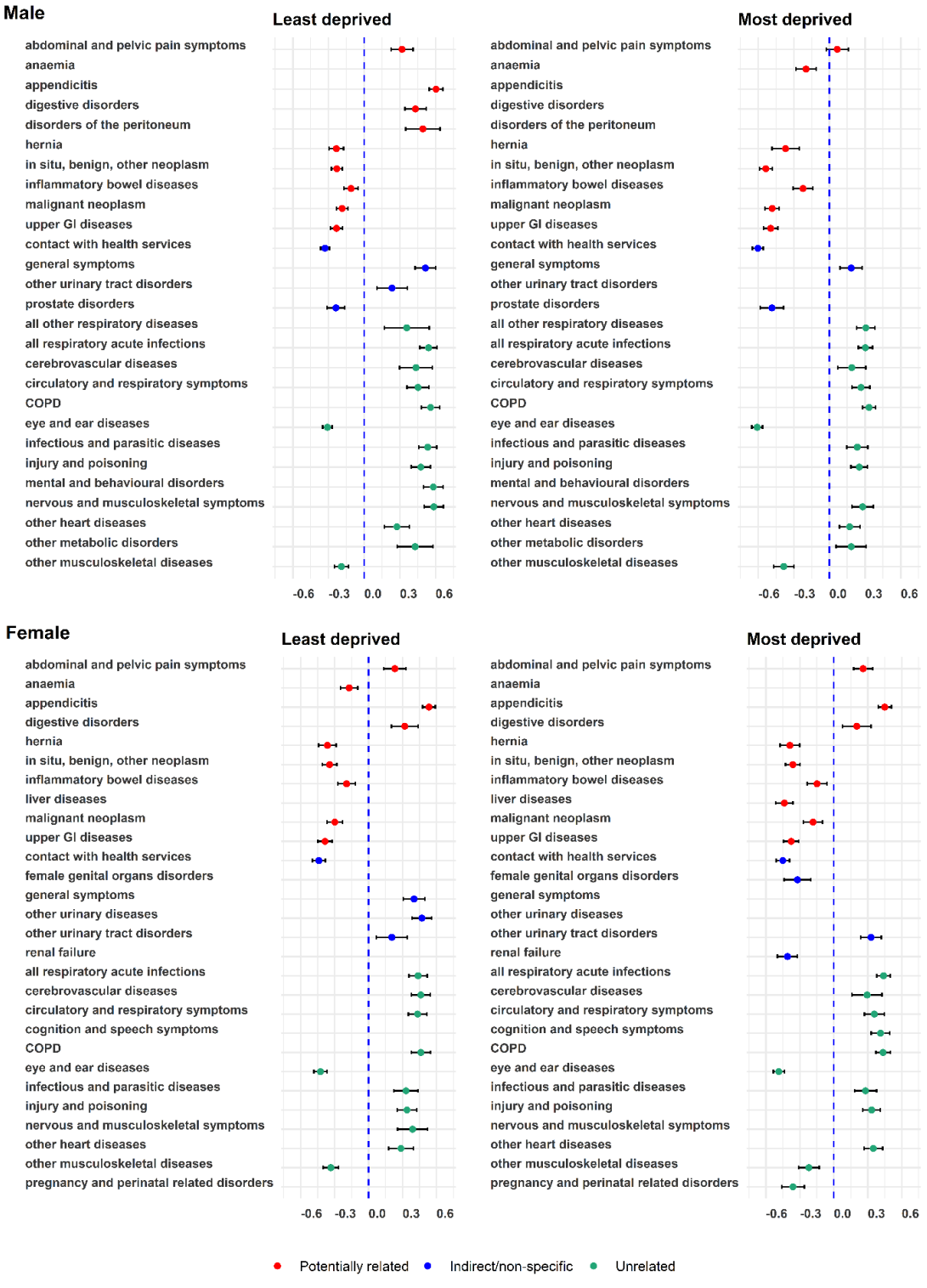
Table 2. Marginal effects of the selected grouped conditions on the probability of HEA in the two years prior to colon cancer diagnosis

	Male		**Female**	
ICD-10 Disease Group	**Least deprived** Baseline prob: 0.33 (95%CI: 0.3-0.37)	**Most deprived** Baseline prob: 0.62 (95%CI: 0.57-0.66)	**Least deprived** Baseline prob: 0.45 (95%CI: 0.4-0.51)	**Most deprived** Baseline prob: 0.50 (95%CI: 0.45-0.55)
abdominal and pelvic pain symptoms	0.653 (0.557-0.738)	0.688 (0.593-0.770)	0.689 (0.596-0.77)	0.763 (0.676-0.833)
all other respiratory diseases	0.693 (0.415-0.878)	0.929 (0.587-0.992)	0.894 (0.777-0.953)	0.942 (0.856-0.978)
all respiratory acute infections	0.876 (0.766-0.938)	0.925 (0.847-0.965)		
anaemia		0.425 (0.353-0.500)	0.285 (0.232-0.345)	
appendicitis	0.939 (0.809-0.982)		0.989 (0.92-0.999)	0.954 (0.811-0.99)
cerebrovascular diseases	0.77 (0.549-0.902)	0.810 (0.617-0.919)	0.917 (0.738-0.978)	0.797 (0.571-0.921)
circulatory and respiratory symptoms	0.787 (0.668-0.871)	0.888 (0.776-0.947)	0.890 (0.774-0.95)	0.862 (0.726-0.936)
contact with health services	0.005 (0.001-0.034)	0.020 (0.006-0.063)	0.017 (0.004-0.07)	0.054 (0.019-0.144)
COPD	0.893 (0.736-0.961)	0.955 (0.851-0.987)	0.918 (0.691-0.983)	0.938 (0.811-0.982)
digestive disorders	0.766 (0.659-0.847)		0.776 (0.619-0.881)	0.706 (0.554-0.823)
disorders of the peritoneum	0.828 (0.435-0.968)			
eye and ear diseases	0.025 (0.011-0.053)	0.014 (0.004-0.045)	0.031 (0.016-0.061)	0.018 (0.007-0.045)
female genital organs disorders				0.183 (0.074-0.385)
general symptoms	0.850 (0.711-0.929)	0.805 (0.684-0.887)	0.859 (0.715-0.937)	
hernia	0.100 (0.052-0.185)	0.253 (0.148-0.398)	0.092 (0.037-0.212)	0.116 (0.042-0.278)
in situ, benign, other neoplasm	0.104 (0.076-0.141)	0.087 (0.057-0.133)	0.111 (0.077-0.157)	0.142 (0.098-0.201)
infectious and parasitic diseases	0.869 (0.753-0.935)	0.857 (0.719-0.933)	0.786 (0.654-0.877)	0.784 (0.664-0.87)
inflammatory bowel diseases	0.224 (0.178-0.278)	0.400 (0.329-0.475)	0.261 (0.207-0.324)	0.356 (0.283-0.436)
injury and poisoning	0.811 (0.71-0.883)	0.873 (0.788-0.927)	0.796 (0.708-0.863)	0.838 (0.748-0.9)
liver diseases				0.067 (0.008-0.401)
malignant neoplasm	0.149 (0.116-0.19)	0.141 (0.102-0.192)	0.158 (0.119-0.207)	0.32 (0.251-0.398)
mental and behavioural disorders	0.916 (0.530-0.991)			
nervous and musculoskeletal symptoms	0.92 (0.546-0.991)	0.902 (0.639-0.979)	0.844 (0.514-0.965)	
other heart diseases	0.610 (0.502-0.708)	0.792 (0.692-0.866)	0.743 (0.618-0.838)	0.853 (0.743-0.921)
other metabolic disorders	0.764 (0.509-0.91)	0.805 (0.586-0.923)		
other musculoskeletal diseases	0.143 (0.097-0.206)	0.239 (0.165-0.332)	0.124 (0.083-0.18)	0.284 (0.205-0.378)
other urinary diseases			0.928 (0.534-0.993)	
other urinary tract disorders	0.569 (0.438-0.691)		0.661 (0.511-0.785)	0.833 (0.71-0.911)
pregnancy and perinatal related disorders				0.143 (0.055-0.322)
prostate disorders	0.097 (0.033-0.254)	0.138 (0.051-0.323)		

renal failure				0.094 (0.019-0.358)
upper GI diseases	0.102 (0.066-0.154)	0.128 (0.086-0.186)	0.071 (0.042-0.118)	0.127 (0.08-0.196)

The estimated probabilities are derived from mixed effect models specific to each of the four combinations of sex and deprivation. Each of the four final models includes the set of covariates listed in the relevant column, as well as age.

Fig. 1 Average change in the probability of Hospital Emergency Admission in the two years prior to colon cancer diagnosis in the presence of each of the selected risk factors, by sex and deprivation



The values on the figure represent the linear transformation of the probabilities retrieved from the mixed effect models specific to each of the four panels. Each of the four final models includes the set of covariates listed in each panel as well as age. The vertical hyphenated blue line represents zero effect.

Research Paper 5

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Student ID Number	1604651	**Title**	Ms
First Name(s)	Aimilia		
Surname/Family Name	Exarchakou		
Thesis Title	Inequalities in cancer care in England: from diagnosis to treatment		
Primary Supervisor	Professor Bernard Rachet		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Pancreatology journal		
When was the work published?	April 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	PhD by Prior Publication		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the lead author of this publication. I was involved in the design of the study and the mapping of NHS Trust hospitals, hospices and Primary Care Units to the areas covered by the 23 HPB centres. I conducted the data analysis, drafted the first version of the manuscript with tables and figures.

SECTION E

Student Signature	[redacted]
Date	20/10/2023

Supervisor Signature	[redacted]
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Pancreatic cancer incidence and survival and the role of specialist centres in resection rates in England, 2000 to 2014: A population-based study

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ABSTRACT

Background: The aim was to compare population-based survival for exocrine pancreatic cancer in England in the 23 regions covered by specialist centres. The centres were initiated in 2001, covering populations of 2–4 million.
Methods: We examined incidence for adults diagnosed with a pancreatic exocrine cancer during 1995–2014 and age-standardised net survival up to five years after diagnosis for patients diagnosed during 2000–2013. We examined variation in regional resection rates and survival for patients diagnosed during 2010–2013. The data were extracted from the National Cancer Registration and Analysis Service.
Results: Age-standardised annual incidence rates of exocrine pancreatic cancer increased from 17.1 per 100,000 during 1995–1999 to 18.7 during 2010–2014. Age-standardised one-year and five-year net survival increased from 17.9% and 3.6%, respectively, for 2000–2009, to 21.6% and 4.2% during 2010–2013. There were 2086 (8.9%) resections among 23,415 patients diagnosed with an exocrine tumour in 2010–2013. The proportion ranged from 5.1% to 19.6% between centres. Among resected patients, survival was 73.0% at one year and 20.2% at five years. Of the total 2118 resected patients, 18 (0.9%) were at stage 1; 34 (1.6%) at stage 2; 791 (37.3%) at stage 3 and 140 (6.6%) at stage 4, although 53.6% of stage information was missing. Five-year survival was 2.1% for those who were not resected. The number of resections performed in each centre was not correlated with one-year survival.
Conclusions: Despite improvements in the management of pancreatic cancer in England with the introduction of specialist centres, resection rates remain relatively low, and survival remains lower than in comparably wealthy countries.

Introduction

Pancreatic cancer is one of the most lethal cancers in adults. It is estimated that almost 460,000 cases occurred world-wide in 2018, with 430,000 deaths [1]. In England, survival is the lowest among the 10 most common cancers [2]. Unfortunately, there is currently no viable screening test for pancreatic cancer [3], but there has been some improvement in outcome in recent years, especially among the 15–20% of patients who can have removal of the cancer by surgery, followed by adjuvant chemotherapy [4–6]. Trials have shown a small to modest improvement in the 30% of patients with locally advanced disease, and for patients with metastatic disease who have good performance status [7,8].

Cancer incidence and mortality rates vary widely [9], but five-year survival from cancer in Europe has improved over the past 20 years [10]. Disparities in cancer survival persist, even between

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high-income countries [11]. Stage of disease at diagnosis, timely access to effective treatment, and the extent of comorbidity are probably the main determinants of patient outcomes [12].

In the UK, wide disparities in surgical outcomes for pancreatic cancer between District General Hospitals and specialist tertiary centres led to the introduction of centralised pancreatic centres between 2001 and 2006 [13–15]. Each centre covers a population of 2–4 million people, either as a stand-alone pancreas-specific centre or as part of a Hepato-Pancreato-Biliary (HPB) centre [16]. Patients referred to a pancreatic centre are given a diagnosis, and the specialist Multidisciplinary Team (sMDT) decides the best management. Surgical resection is carried out in the specialist centre, but oncological medical therapy and palliative care are undertaken either centrally or at the referring unit.

This is the first study to evaluate national incidence and survival trends for pancreatic cancer, and to assess variation in survival between areas covered by the 23 pancreatic cancer specialist centres for all patients in England, both for all patients and for those who had a resection.

Data and methods

Study design

We calculated age-standardised annual incidence rates for all adults (15–99 years) diagnosed with a primary, invasive, malignant neoplasm of the pancreas in England between January 1, 1995 and December 31, 2014. We also estimated age-standardised net survival up to five years after diagnosis. The cohort approach was used for patients diagnosed between January 1, 2000 and December 31, 2009, all of whom were followed up for at least five years by December 31, 2014. The period approach was used to obtain short-term predictions of five-year survival for patients diagnosed between January 1, 2010 and December 31, 2013 [17].

This study is part of the Cancer Survival Programme, approved by the Ethics Committee of the London School of Hygiene and Tropical Medicine (#11984, updated April 6, 2018).

Data

The main source of information was the National Cancer Registry database, which was maintained by the Office for National Statistics (ONS) at the time of data acquisition. Cancer records were linked to Hospital Episode Statistics (HES) records and the Cancer Analysis System (CAS) to derive data on treatment and stage. These databases are now maintained by the National Cancer Registration and Analysis Service (NCRAS) in Public Health England (PHE).

Extensive quality control of the data was performed. Details of the eligibility and exclusion criteria have been described [18]. Patients for whom a death certificate or autopsy report was the only information available, were excluded from survival analysis because their duration of survival was unknown, but these patients were included in the calculation of incidence rates for the year of their death. Patients whose vital status was unknown, those aged 100 years or over at diagnosis and those whose records contained invalid dates or date sequences were also excluded from survival analysis.

Tumour morphology was coded according to the World Health Organisation's International Classification of Diseases for Oncology (revision 3.1) [19]. Tumours were grouped into three broad morphologic categories for analysis: exocrine carcinomas, pancreatic neuroendocrine tumours (PNET), and other malignant cancers of the pancreas.

Pancreatic cancer specialist centres

For survival analysis, patients were allocated to one of the 23 areas covered by each pancreatic centre, by mapping all National Health Service (NHS) Trust hospitals, hospices and Primary Care Units, using treatment information from Hospital Episode Statistics. Each region represents one of the 23 pancreatic centres and its local providers. Patients were allocated to the hospital where they received surgery, or if not, chemotherapy or radiotherapy. If no treatment had been recorded, they were allocated to the hospital where they were diagnosed. Specialists in each centre agreed the mapping of hospitals to pancreatic centres, with the exception of Cambridge, Blackburn, Hull and North West London. This was a population-based analysis for residents of England, so patients resident in other UK nations (Wales, Northern Ireland, Scotland), or Ireland, but who were treated in a pancreatic centre in England, were not included in the analyses.

Treatment and stage

Information on surgical treatment was obtained from Hospital Episode Statistics data. We used codes for 17 major surgical procedures from the Office for Population Censuses and Surveys' Classification of Interventions and Procedures (fourth version) (OPCS-4) [20]. These procedures include all types of partial and total pancreatectomy (OPCS-4 codes J55.1–2, J55.8–9, J56.1–4, 8 and 9, and J57.1–5, 8 and 9) (S1 Table), which were designated as of curative intent by pancreatic cancer specialists. Patients who received major surgery between one month before and six months after diagnosis – regardless of any additional treatment – were assigned to the "resected" group, and patients who either received only minor surgery, chemotherapy, radiotherapy or no standard oncological treatment were assigned to the "non-resected" group.

Composite stage at diagnosis was derived from an algorithm that was designed to combine data on stage from various sources, prioritising information in the clinical audit data, then data from the Cancer Analysis System (CAS) and the National Cancer Registry database [21]. In this study, however, the only source of information on stage was the CAS database, because there is currently no clinical audit database for pancreatic cancer. Data on the individual tumour (T), nodes (N) and metastasis (M) components of stage were combined to derive a summary stage variable with four categories, with stage 1 representing localised cancer, stages 2 and 3 representing larger tumours, with nearby tissue or lymph nodes involved, and stage 4 indicating metastatic cancer [22].

Statistical analysis

Annual incidence rates per 100,000 persons were calculated for each year between 1995 and 2014, age-standardised to adjust for changes in the age profile of the population over time. We used the European Standard Population weights, modified to reflect only the adult population (15–99 years) [23].

We estimated net survival up to five years after diagnosis. Net survival is the probability of survival derived solely from the risk of death from cancer, correcting for the risk of death from other causes (background mortality) [24]. To enable comparison of survival estimates for all ages combined between geographical areas and over time, survival estimates were age-standardised with the International Cancer Survival Standard (ICSS) weights [25].

Variation in age-standardised net survival between the regions served by each pancreatic centre around the pooled estimate for England for patients diagnosed during 2010–2013 is shown in funnel plots [26], in which the survival estimates for each region are plotted on the y-axis against their precision (the inverse of the variance) on the x-axis. The control limits, in the shape of a funnel,

represent the theoretical distribution of survival around the overall mean value for England across the observed range of precision of the regional survival estimates, at 95% and 99.8% significance. Survival estimates outside the control limits represent regional variation that is wider than would be expected from simple random variation, after controlling for differences in the precision of the estimates. Linear regression was used to determine the association between the number of resections performed in each pancreatic centre during 2010–2013 and one-year net survival for patients who were resected. We used the number of patients who were resected, rather than the proportion of those referred who were resected, because some HPBs receive a larger number of patients whose tumours are not resected.

Results

Pancreatic cancer was diagnosed in 133,325 patients in the 20 years covered by the study (1995–2014 inclusive). Based on the study eligibility criteria, 132,693 (99.5%) patients were included in the incidence analyses, and 121,359 (91.0%) in the national survival analyses (S2 Table). For 81,610 (61%) patients, the morphology of the pancreatic cancer was registered as 'not otherwise specified', either because of poor tissue availability or based only on co-axial imaging. These tumours were included among the exocrine tumours, since the vast majority of tumours with known morphology were exocrine carcinomas.

For the regional survival analyses (patients diagnosed during 2010–2013), 1632 (6.2%) of 26,091 patients were excluded because of missing information on the hospital of treatment, including a small proportion of patients who were treated in private hospitals or cared for in hospices or nursing homes. In all, 24,459 patients were included in the survival comparisons between the 23 pancreatic cancer centre regions (Table 1).

National incidence and survival

Exocrine pancreatic tumours

Exocrine carcinomas comprised 97.6% of all pancreatic tumours diagnosed during 1995–2014 (S2 Table). Age-standardised incidence rates for exocrine tumours rose slightly but steadily from 17.1 per 100,000 per year during 1995–1999 to 17.3 during 2000–2004, 18.3 during 2005–2009 and 18.7 during 2010–2014 (Fig. 1).

Age-standardised one-year net survival for pancreatic exocrine cancers increased from 17.9% for patients diagnosed during 2000–2009 to 21.6% in 2010–2013. Five-year net survival increased

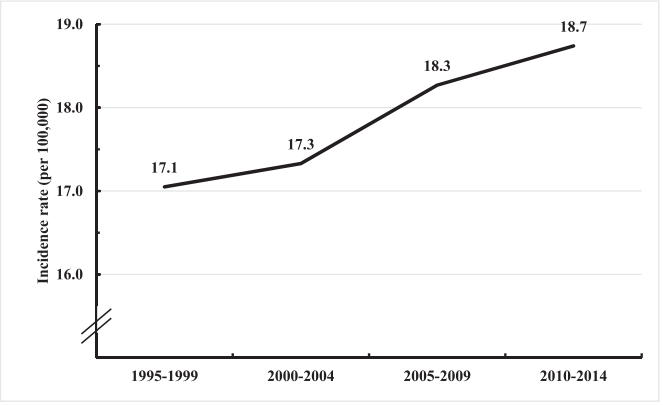


Fig. 1. Trends in the age-standardised annual incidence rate for pancreatic exocrine tumours in England, 1995–2014.

Table 1
Proportion of resected and non-resected pancreatic tumours in the 23 pancreatic cancer centre regions in England, 2010–2013.

HPB territory	Pancreatic Exocrine carcinomas					Pancreatic neuro-endocrine tumours					All Tumours[a]
	Resected		Not resected		Total	Resected		Not resected		Total	
	No.	%	No.	%		No.	%	No.	%		
London South East	149	**10.7**	1249	**89.3**	1398	20	**37.7**	33	**62.3**	53	1452
London South West	58	**10.5**	492	**89.5**	550	9	**28.1**	23	**71.9**	32	584
London North East	66	**6.7**	912	**93.3**	978	18	**42.9**	24	**57.1**	42	1020
London North West	76	**14.0**	465	**86.0**	541	10	**30.3**	23	**69.7**	33	574
London North	117	**8.1**	1330	**91.9**	1447	30	**40.0**	45	**60.0**	75	1525
Cambridge	139	**8.2**	1559	**91.8**	1698	32	**38.1**	52	**61.9**	84	1784
Leicester	50	**7.1**	651	**92.9**	701	10	**47.6**	11	**52.4**	21	722
Nottingham	54	**5.1**	1008	**94.9**	1062	9	**28.1**	23	**71.9**	32	1095
Guildford	73	**7.3**	923	**92.7**	996	6	**23.1**	20	**76.9**	26	1022
Oxford	132	**19.6**	542	**80.4**	674	15	**50.0**	15	**50.0**	30	704
Southampton	123	**7.8**	1454	**92.2**	1577	15	**30.6**	34	**69.4**	49	1628
Plymouth	110	**10.1**	982	**89.9**	1092	7	**25.9**	20	**74.1**	27	1119
Bristol	64	**8.9**	653	**91.1**	717	10	**26.3**	28	**73.7**	38	755
Birmingham	132	**7.4**	1658	**92.6**	1790	25	**25.5**	73	**74.5**	98	1888
Coventry	45	**12.0**	329	**88.0**	374	8	**47.1**	9	**52.9**	17	392
Stoke-on-Trent	51	**8.8**	531	**91.2**	582	13	**52.0**	12	**48.0**	25	607
Hull	51	**8.4**	553	**91.6**	604	9	**32.1**	19	**67.9**	28	633
Leeds	94	**6.5**	1363	**93.5**	1457	23	**29.1**	56	**70.9**	79	1538
Sheffield	79	**9.1**	789	**90.9**	868	14	**48.3**	15	**51.7**	29	897
Newcastle	96	**7.6**	1165	**92.4**	1261	27	**42.2**	37	**57.8**	64	1325
Blackburn	61	**7.1**	800	**92.9**	861	6	**21.4**	22	**78.6**	28	890
Liverpool	121	**11.4**	940	**88.6**	1061	22	**40.0**	33	**60.0**	55	1117
Manchester	145	**12.9**	981	**87.1**	1126	28	**45.9**	33	**54.1**	61	1188
All centres	*2086*	***8.9***	*21,329*	***91.1***	*23,415*	*366*	***35.7***	*660*	***64.3***	*1026*	*24,459*
Private hospitals	4	**1.6**	242	**98.4**	246	*1*	***25.0***	*3*	***75.0***	*4*	*251*
Other	28	**2.5**	1080	**97.5**	1108	*4*	***14.8***	*23*	***85.2***	*27*	*1136*
Total	*2118*	***8.6***	*22,651*	***91.4***	*24,769*	*371*	***35.1***	*686*	***64.9***	*1057*	*25,846*

[a] Total number of patients, including patients diagnosed with pancreatic tumours of rare morphologies.

slightly from 3.6% during 2000–2009 to 4.2% in 2010–2013 (S1 Figure).

Pancreatic neuroendocrine tumours

Pancreatic neuroendocrine tumours (PNET) comprised only 2.3% of all pancreatic tumours diagnosed during 1995–2014 (S2 Table). Age-standardised incidence rates also rose, but remained below 1.0 per 100,000 per year throughout the 20-year period 1995–2014 (data not shown).

For patients diagnosed with a PNET during 2000–2009, one-year net survival was 62.0%, rising to 71.3% for patients diagnosed during 2010–2013. Five-year net survival for patients diagnosed during 2000–2009 was 36.5%, rising to 42.9% during 2010–2013 (S1 Figure).

Variation of survival by pancreatic cancer centre region (exocrine tumours)

For exocrine tumours, age-standardised one-year net survival varied between centres from 16.1% to 36.4%, while 5-year survival ranged from 1.7% to 7.6% (Fig. 2a & b).

One-year net survival was within the control limits for 19 of the 23 regions (Fig. 2a). Survival estimates for Manchester and South West London were high outliers, whilst those for Leicester and North East London were low outliers. Five-year net survival was also within the control limits for 19 of the 23 regions (Fig. 2b). The estimates for Oxford, South West London, Liverpool and Manchester were above the 95% control limit but within the 99.8% limit. The estimates for Cambridge, Birmingham, Nottingham and Stoke-on-Trent were low outliers, outside the 99.8% limit.

Variation in stage, resection rates and survival after resection (exocrine tumours)

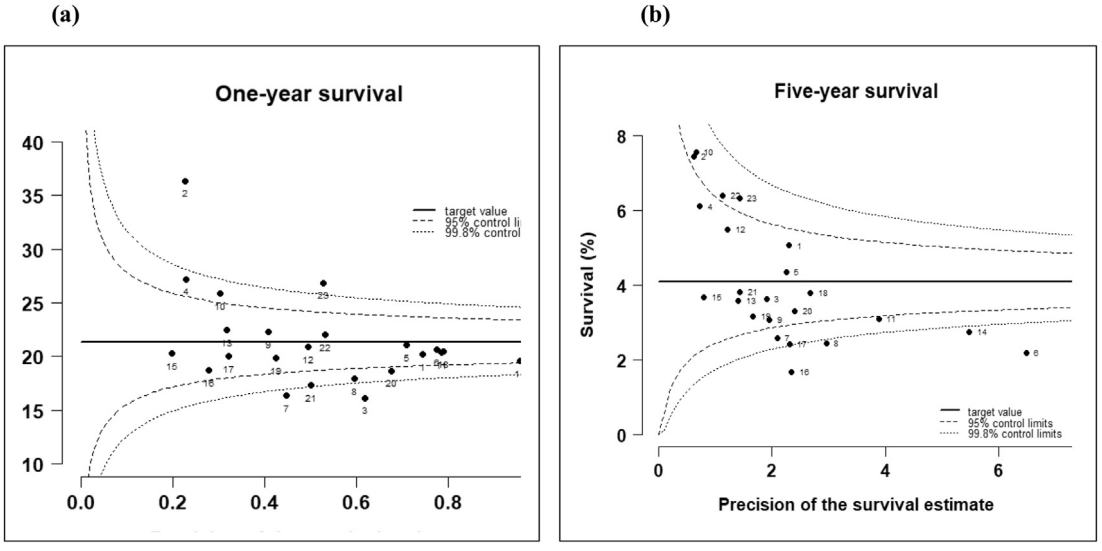
For all 24,769 pancreatic exocrine patients diagnosed in 2010–2013, including those treated in private hospitals, hospices or nursing homes, stage 1 was reported for 110 (0.4%), stage 2 in 288 (1.2%), stage 3 in 1838 (7.4%) and stage 4 in 7315 (29.5%), but information was missing for 15,218 patients (61.4%) (Table 2). Among 2118 resected patients, tumour stage 1 was returned in 18 (0.9%), stage 2 in 34 (1.6%), stage 3 in 791 (37.3%) and stage 4 in 140 (6.6%), while information was missing for 1135 (53.6%) (Table 2). Among the 398 patients with stage 1 or 2 exocrine cancer, 52 (13.2%) were resected. South West England (Plymouth and Bristol) and West Midlands (Birmingham, Coventry and Stoke-on-Trent) had the highest proportion of stage 4 tumours (data not shown).

Nationally, only 2086 (8.9%) of 23,415 patients with an exocrine tumour underwent resection (Table 1) in 2010–2013, 13,827 (59.1%) received minor surgery, 977 (4.2%) received only chemotherapy and 6173 (26.4%) underwent only a diagnostic procedure (results not shown). A small proportion of patients (1.5%) received other or unrelated procedures. Among resected patients, net survival was 73.0% at one year and 20.2% at five years (Fig. 3a). One- and five-year net survival was higher among resected patients than non-resected patients (Fig. 3a).

One-year survival for patients who were resected for an exocrine tumour diagnosed during 2010–2013 was within the 99.8% control limits for all 23 regions (Fig. 3b). Survival in South West London and Guildford territories was above the 95% control limit, and in Plymouth, below the 95% control limit. Five-year survival ranged between 6.6% and 29.9% for those who were resected and between 0.2% and 5.4% for those who were not, but most of these estimates were not statistically robust due to the sparseness of data (flagged in S3 Table). The proportion of resections for pancreatic exocrine cancers ranged from 5.1% in Nottingham to 19.6% in Oxford (Table 1), but the number of resections performed in each centre was not significantly correlated with one-year survival among resected patients ($r^2 = -1.2\%$).

Discussion

The incidence of pancreatic cancer in England has increased



*1 - London South East, 2 - London South West, 3 - London North East, 4 - London North West, 5 - London North, 6 - Cambridge, 7 - Leicester, 8 - Nottingham, 9 - Guildford, 10 - Oxford, 11 - Southampton, 12 - Plymouth, 13 - Bristol, 14 - Birmingham, 15 - Coventry, 16 - Stoke-on-Trent, 17- Hull, 18 - Leeds, 19 - Sheffield, 20 - Newcastle, 21 - Blackburn, 22 - Liverpool, 23 - Manchester.

Fig. 2. Funnel plot of age-standardised net survival at (a) one year and (b) five years, in the 23 pancreatic cancer centre regions*, for patients diagnosed with a pancreatic exocrine tumour in England during 2010–2013.

Table 2
Proportion of pancreatic exocrine tumours patients by stage and resection status: England, 2010–2013. Total = 24,7699.

Age group	Stage	No Resection		Resection		Total	
		No.	%	No.	%	No.	%
15–44	**Stage 1**	–	0.0	–	0.0	–	0
	Stage 2	2	40.0	3	60.0	5	100
	Stage 3	12	44.4	15	55.6	27	100
	Stage 4	115	95.8	5	4.2	120	100
	Missing	178	80.5	43	19.5	221	100
45–54	**Stage 1**	3	37.5	5	62.5	8	100
	Stage 2	16	84.2	3	15.8	19	100
	Stage 3	73	44.8	90	55.2	163	100
	Stage 4	502	98.0	10	2.0	512	100
	Missing	718	85.5	122	14.5	840	100
55–64	**Stage 1**	10	76.9	3	23.1	13	100
	Stage 2	28	77.8	8	22.2	36	100
	Stage 3	186	48.6	197	51.4	383	100
	Stage 4	1406	97.0	43	3.0	1449	100
	Missing	2158	87.4	312	12.6	2470	100
65–74	**Stage 1**	20	71.4	8	28.6	28	100
	Stage 2	54	78.3	15	21.7	69	100
	Stage 3	342	49.9	344	50.1	686	100
	Stage 4	2324	97.7	54	2.3	2378	100
	Missing	3832	90.0	426	10.0	4258	100
75–99	**Stage 1**	59	96.7	2	3.3	61	100
	Stage 2	154	96.9	5	3.1	159	100
	Stage 3	434	75.0	145	25.0	579	100
	Stage 4	2828	99.0	28	1.0	2856	100
	Missing	7197	96.9	232	3.1	7429	100
All ages	**Stage 1**	92	83.6	18	16.4	110	100
	Stage 2	254	88.2	34	11.8	288	100
	Stage 3	1047	57.0	791	43.0	1838	100
	Stage 4	7175	98.1	140	1.9	7315	100
	Missing	14,083	92.5	1135	7.5	15,218	100

slightly over the 20 years between 1995 and 2014. Similar increases have been reported in the USA and globally [27–29], suggesting change in the prevalence of risk factors. Whereas smoking has decreased, other risk factors, notably obesity and diabetes mellitus, have been increasing [30]. It has been estimated that lifestyle and environmental factors accounted for 31.5% of all pancreatic cancers in the UK in 2015 [31].

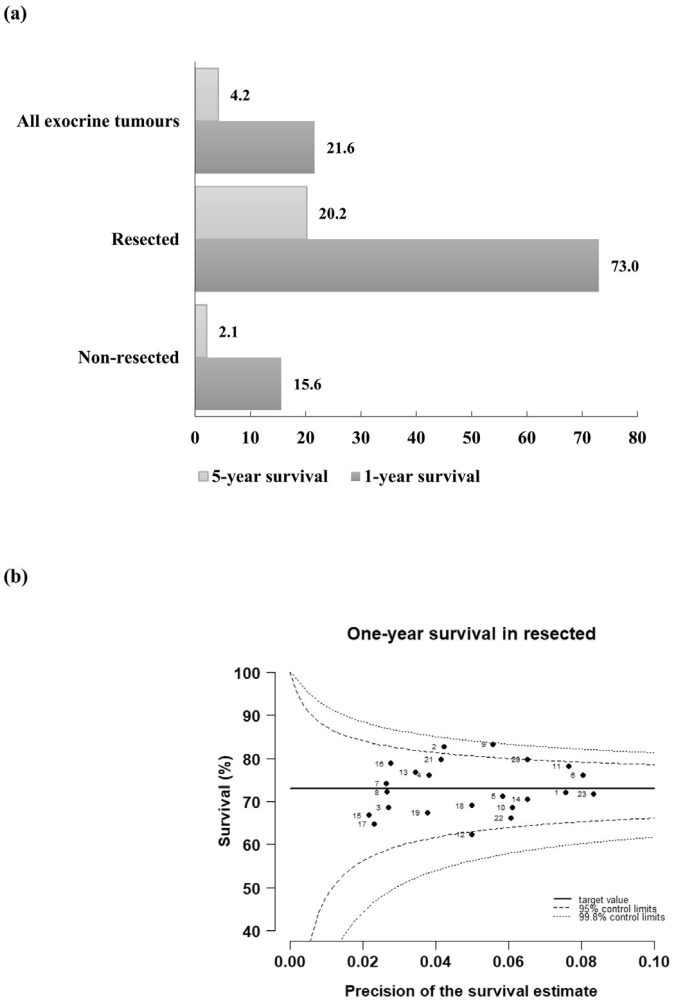
Despite small improvements in one-year and five-year survival between 2000 and 2013, pancreatic cancer patients continue to experience poor survival. Exocrine carcinomas, which comprise the vast majority of pancreatic tumours, have a particularly poor prognosis. Survival for patients who underwent resection was much higher than for those who did not. Short-term (one-year) survival varied between the regions served by the 23 specialist centres, but the number of resections performed at each centre did not explain this variation. At one year after diagnosis, net survival for patients diagnosed during 2010–2013 in South West London (36.4%) was much higher than in North East London (16.1%). At five years after diagnosis, net survival ranged from 7.6% in Oxford to 1.7% in Stoke-on-Trent. For most regions, geographic variation around the national average in one-year and five-year net survival was not wider than would be expected from chance. Only Leicester and North East London were low outliers in one-year survival, while Cambridge, Birmingham, Nottingham and Stoke-on-Trent were low outliers in five-year survival. Regional variation in short-term survival was smaller among patients who were resected.

Major obstacles in managing exocrine tumours include the lack of specific early symptoms, advanced stage at diagnosis, and rapid progression. Emergency presentation is still the most common route of diagnosis, and it is linked to lower one-year survival [32]. Patients diagnosed following urgent referral by their primary care physician under the “two-week wait” rule may have a better prognosis, but only 11% of patients with pancreatic cancer were diagnosed through this route, whilst 50% were diagnosed with an emergency presentation in 2006–2008 [33]. This has not changed much over the last 10 years, such that in 2016, emergency presentation still accounted for 46% of diagnoses [32]. In some regions, a large proportion of patients are diagnosed with advanced disease. In Birmingham and Stoke-on-Trent, 60% of patients were diagnosed with stage 3 or 4 cancers. These regions were also among the 20 most deprived Local Authority districts in England on the Index of Multiple Deprivation 2015 [34]. In 2016, emergency presentation was the route of diagnosis for 49% of patients living in the most deprived areas, compared with 40% in affluent areas [32]. At the same time, Liverpool, Knowsley (part of the Liverpool region) and Manchester Local Authorities are amongst the top five with the highest proportions of the most deprived neighbourhoods in England [34], yet Liverpool and Manchester have relatively good survival outcomes, so deprivation alone is unlikely to account for the generally poor outcome data.

This study shows that under-treatment of pancreatic cancer is an important barrier to improving outcomes. In the four-year period 2010–2013, only 8.9% of all patients with an exocrine cancer received a resection. The National Cancer Registration and Analysis Service reported 23,741 patients with an exocrine carcinoma between 2013 and 2015, of whom only 1917 (8.1%) received surgery: 1189 (62.0%) of these patients received both surgery and chemotherapy [35]. A study of 147,700 patients diagnosed with pancreatic cancer in the USA, the Netherlands, Belgium, Norway, Slovenia, Denmark and Estonia over different periods during 2003–2016, reported that 23,683 (16.0%) patients underwent a resection [36]. Resection rates varied from 13.1% in Norway and the Netherlands to 21.7% in Belgium, whilst adjuvant chemotherapy ranged from 12.0% in Estonia, 19.2% in Norway, 28.6% in Slovenia, 39.6% in the Netherlands, 55.0% in Belgium, and 55.7% in Denmark, whilst 29.5% had chemo-radiotherapy in the USA [36]. The relatively high proportion of patients receiving adjuvant chemotherapy in England compared to Europe and the USA is related to the longstanding leadership taken in England with the development of adjuvant chemotherapy through large randomised multicentre clinical trials [5,37,38].

In this study from England, resection was only undertaken in 52 (13.2%) of 398 patients known to have been diagnosed in stages 1–2 during the four years 2010–2013. The National Cancer Registration and Analysis Service reported that 1252 (39.3%) of 3186 patients with stage 1–2 tumours diagnosed during the three years 2013–2015 had a resection, of whom 847 (67.6%) also had chemotherapy [35]. These discrepancies are mostly due to a high proportion of missing data on stage in the Cancer Analysis System database (more than 60% during 2010–2013) that was used to extract the summary stage variable.

In an international study, the proportion of stage 1–2 cancers resected varied from 34% in Norway, 43% in the USA, and 47% in the Netherlands, to 55.7% in Denmark, 61% in Slovenia, and 63% in Belgium [39]. For 2009–2011, the 12-month unadjusted survival for resected stage 1–2 exocrine cancers varied from 60% (95% CI: 50–68%) in Slovenia, 68% (65–71%) in Belgium, 69% (65–72%) in the Netherlands, 70% (68–71%) in the USA, and 77 (70–83%) in Norway [39]. Comparable data for survival by treatment and stage in England are not available, either at a national level or by specialist centre [35,40].



* **1** - London South East, **2** - London South West, **3** - London North East, **4** - London North West, **5** - London North, **6** - Cambridge, **7** - Leicester, **8** - Nottingham, **9** - Guildford, **10** - Oxford, **11** - Southampton, **12** - Plymouth, **13** - Bristol, **14** - Birmingham, **15** - Coventry, **16** - Stoke-on-Trent, **17** - Hull, **18** - Leeds, **19** - Sheffield, **20** - Newcastle, **21** - Blackburn, **22** - Liverpool, **23** - Manchester.

Fig. 3. (a) Age-standardised one- and five-year net survival (%) for exocrine pancreatic cancer by resection status in England during 2010–2013. (b) Funnel plot of age-standardised one-year net survival for resected patients with a pancreatic exocrine tumour in the 23 pancreatic cancer centre regions* in England during 2010–2013.

Recording a valid cancer stage at diagnosis is vital for treatment, as well as for actionable research, but a major limitation of the NHS data for evaluating outcomes has been the substantial proportion of missing information on stage at diagnosis. Data on stage at diagnosis are often missing in the clinical record. Since 2012, NHS Digital of Public Heath England has routinely published the percentage of all cancer patients for whom a valid stage was recorded, both at national level and by Clinical Commissioning Group (CCG), as part of the CCG Outcomes Indicator set [41]. Under this system, the validity of stage is assessed according to rules set by the UK and Ireland Association of Cancer Registries.

The completeness of stage data for all cancers diagnosed in England increased from 59.4% in 2012 to 81.4% in 2017 [41]. A similar increase was seen for pancreatic cancer, from 56% in 2013 to 80% in 2017 [35]. The improvements can be attributed to more complete pre-operative staging, better hospital recording of stage and better registration practice [42]. We have not yet been able to access those data. The lack of readily accessible data on stage at diagnosis continues to hamper accurate assessment of treatment outcomes at regional and national level.

Other factors that may have contributed to the differences in survival between pancreatic specialist centre regions include the quality of medical oncological regimens delivered in the palliative and adjuvant settings, the number of specialised surgeons or clinical nurses, and referral patterns between local or specialist hospitals, but we have not been able to access these data yet.

This study showed that one-year and five-year net survival was 21.6% and 4.2%, respectively, for patients diagnosed with an exocrine pancreatic cancer in England during the four years 2010–2013. Comparable data from the US Surveillance, Epidemiology and End Results (SEER) programme show one-year and five year relative survival of 33.5% and 9.3%, respectively, for patients diagnosed during 2009–2015 [43]. The European Cancer Registry (EUROCARE) programme showed that the European average in age-standardised one- and five-year relative survival was 26% and 6.9%, respectively, for adults diagnosed with a pancreatic cancer during 1999–2007 [10,44].

Centralisation of cancer care in high-volume providers has been a gradual but beneficial process in England, as it has led to lower post-operative mortality and morbidity for cancer [45–48] and

other non-communicable diseases [49]. A study in Finland showed that the proportion of radical surgery for pancreatic cancer was higher in healthcare districts with a high level of experience compared to regions with a medium or low level of experience, even after adjusting for demographics and stage [50].

In England, despite the introduction of pancreatic cancer specialist centres more than 10 years ago, survival remains lower than in comparably wealthy countries, and this is reflected in low resection rates, as well as in the high proportion of patients for whom data on stage and morphology are missing. Taken together, these observations reflect an inability to provide timely access to full investigation and effective treatment, reflecting systematic issues of health care funding and organisation.

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Authors' contributions

MPC, AE, BRa, JN, GP and WM designed the study. GP, WM and AE did the mapping of NHS Trust hospitals, hospices and Primary Care Units to the areas covered by the 23 Hepato-Pancreato-Biliary centres in England. AE, GP, WM and JN did the literature search. BRo and MPC created the morphologic groups. AE and WM did the data analysis. AE, JN and MPC drafted the manuscript, tables and figures. GP was involved in the analysis and provided advice. All authors contributed to the interpretation of the results, revised and critically reviewed the manuscript. JN contributed clinical insight. MPC supervised the study.

Declaration of competing interest

John P Neoptolemos is a member of the Medical Advisory Board of Pancreatic Cancer UK. Georgia Papacleovoulou is employed by Pancreatic Cancer UK.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.01.012.

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Research Paper 5 - Supplementary Materials

Supplementary data

Pancreatic cancer incidence and survival and the role of specialist centres in resection rates in England, 2000 to 2014: a population-based study

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S1 Table. Classification of Interventions and Procedures Version 4 (OPCS-4) codes of major resections for pancreatic cancer

OPCS-4 Codes for major resections for Pancreatic Cancer	
J55.1	Total pancreatectomy and excision of surrounding tissue
J55.2	Total pancreatectomy not elsewhere classified
J55.8	Other specified total excision of pancreas
J55.9	Unspecified specified excision of pancreas
J56.1	Pancreaticoduodenectomy and excision of surrounding tissue
J56.2	Pancreaticoduodenectomy and resection of antrum of stomach
J56.3	Pancreaticoduodenectomy not elsewhere classified
J56.4	Subtotal excision of head of pancreas with preservation of duodenum and
J56.8	Other specified excision of head of pancreas
J56.9	Unspecified excision of head of pancreas
J57.1	Subtotal pancreatectomy
J57.2	Left pancreatectomy and drainage of pancreatic duct
J57.3	Left pancreatectomy not elsewhere classified
J57.4	Excision of tail of pancreas and drainage of pancreatic duct
J57.5	Excision of tail of pancreas not elsewhere classified
J57.8	Other specified partial excision of pancreas
J57.9	Unspecified other partial excision of pancreas

S2 Table. Number of patients diagnosed with Pancreatic Exocrine Carcinomas, Pancreatic Neuroendocrine Tumours (PNET) and Other malignant tumours: England, 1995-2014.

Morphology code		Number of cases (1995-2014)	%
Pancreatic Exocrine Carcinomas			
8000	Neoplasm, malignant	22,003	16.6
8001	Tumour cells, malignant	45	0.0
8002	Malignant tumour, small cell type	1	0.0
8003	Malignant tumour, giant cell type	10	0.0
8004	Malignant tumour, fusiform cell type	4	0.0
8010	Carcinoma NOS	59,607	44.9
8011	Epithelioma, malignant	2	0.0
8012	Large cell carcinoma NOS	65	0.0
8020	Carcinoma, undifferentiated NOS	104	0.1
8021	Carcinoma, anaplastic NOS	101	0.1
8022	Pleomorphic carcinoma	24	0.0
8031	Giant cell carcinoma	13	0.0
8032	Spindle cell carcinoma	18	0.0
8033	Pseudosarcomatous carcinoma	6	0.0
8040	Tumorlet, NOS	3	0.0
8046	Non-small cell carcinoma	3	0.0
8050	Papillary carcinoma NOS	29	0.0
8070	Squamous cell carcinoma NOS	150	0.1
8071	Squamous cell carcinoma, keratinizing NOS	15	0.0
8072	Squamous cell carcinoma, large cell, nonkeratinizing	3	0.0
8140	Adenocarcinoma NOS	41,916	31.6
8141	Scirrhous adenocarcinoma	30	0.0
8143	Superficial spreading adenocarcinoma	2	0.0
8144	Adenocarcinoma, intestinal type	13	0.0
8145	Carcinoma, diffuse type	9	0.0
8160	Cholangiocarcinoma	16	0.0
8200	Adenoid cystic carcinoma	5	0.0
8201	Cribriform carcinoma	1	0.0
8210	Adenocarcinoma in adenomatous polyp	2	0.0
8211	Tubular adenocarcinoma	26	0.0
8230	Solid carcinoma NOS	1	0.0
8245	Adenocarcinoid tumour	2	0.0
8251	Alveolar adenocarcinoma	1	0.0
8260	Papillary adenocarcinoma NOS	126	0.1
8261	Adenocarcinoma in villous adenoma	5	0.0
8262	Villous adenocarcinoma	1	0.0
8263	Adenocarcinoma in tubulovillous adenoma	7	0.0
8290	Oxyphilic adenocarcinoma	7	0.0
8310	Clear cell adenocarcinoma NOS	46	0.0
8323	Mixed cell adenocarcinoma	1	0.0
8401	Apocrine adenoma	1	0.0

8430	Mucoepidermoid carcinoma	2	0.0
8440	Cystadenocarcinoma NOS	140	0.1
8441	Serous cystadenocarcinoma NOS	1	0.0
8450	Papillary cystadenocarcinoma NOS	5	0.0
8452	Solid pseudopapillary carcinoma	31	0.0
8470	Mucinous cystadenocarcinoma NOS	62	0.0
8471	Papillary mucinous cystadenocarcinoma	47	0.0
8480	Mucinous adenocarcinoma	984	0.7
8481	Mucin-producing adenocarcinoma	919	0.7
8490	Signet ring cell carcinoma	146	0.1
8500	Infiltrating duct carcinoma	2,226	1.7
8503	Intraductal papillary adenocarcinoma with invasion	11	0.0
8510	Medullary carcinoma NOS	1	0.0
8521	Infiltrating ductular carcinoma	1	0.0
8550	Acinar cell carcinoma	161	0.1
8560	Adenosquamous carcinoma	304	0.2
8570	Adenocarcinoma with squamous metaplasia	6	0.0
Total Exocrine		***129,471***	**97.6**
Pancreatic Neuroendocrine Tumours (PNET)			
8041	Small cell carcinoma NOS	127	0.1
8150	Islet cell carcinoma	154	0.1
8151	Insulinoma, malignant	90	0.1
8152	Glucagonoma, malignant	15	0.0
8153	Gastrinoma, malignant	41	0.0
8154	Mixed islet cell and exocrine adenocarcinoma	19	0.0
8155	Vipoma	7	0.0
8240	Carcinoid tumour NOS	764	0.6
8241	Enterochromaffin cell carcinoid	2	0.0
8243	Goblet cell carcinoid	1	0.0
8244	Composite carcinoid	5	0.0
8246	Neuroendocrine carcinoma	1,888	1.4
8248	Apudoma	1	0.0
8360	Multiple endocrine adenomas	1	0.0
Total PNET		***3,115***	**2.3**
Other			
8720	Malignant melanoma NOS	1	0.0
8800	Sarcoma NOS	26	0.0
8801	Spindle cell sarcoma	4	0.0
8802	Giant cell sarcoma	3	0.0
8803	Small cell sarcoma	2	0.0
8810	Fibrosarcoma NOS	1	0.0
8830	Fibrous histiocytoma, malignant	1	0.0
8850	Liposarcoma NOS	2	0.0
8858	Dedifferentiated liposarcoma	1	0.0
8890	Leiomyosarcoma NOS	24	0.0

8891	Epithelioid leiomyosarcoma	1	0.0
8900	Rhabdomyosarcoma NOS	1	0.0
8920	Alveolar rhabdomyosarcoma	1	0.0
8933	Adenosarcoma	7	0.0
8940	Mixed tumour, malignant NOS	3	0.0
8971	Pancreatoblastoma	6	0.0
8980	Carcinosarcoma NOS	8	0.0
8990	Mesenchymoma, malignant	4	0.0
9070	Embryonal carcinoma NOS	1	0.0
9080	Teratoma, malignant NOS	1	0.0
9120	Haemangiosarcoma	1	0.0
9130	Haemangioendothelioma, malignant	1	0.0
9363	Melanotic neuroectodermal tumor	2	0.0
9364	Peripheral neuroectodermal tumour	5	0.0
Total Other		***107***	**0.1**
All pancreatic tumours		132,693	**100.0**

***NOS= not otherwise specified**

S3 Table. Age-standardised net survival (%) at one and five years after diagnosis from pancreatic exocrine tumours in the 23 pancreas regions in England, 2010-2013 inclusive.

HPB territory	One-year						Five-year					
	No Resection			Resection			No Resection			Resection		
	Net survival	95% CI		Net survival	95% CI		Net survival	95% CI		Net survival	95% CI	
London South East	**13.4**	13.1	13.6	**72.1**	67.0	77.3	**2.8**	2.8	2.8	**21.9**	20.5	23.3
London South West	**31.0**	29.7	32.3	**82.7**	74.8	90.6	**5.4¬**	5.2	5.5	**22.6¬**	20.2	25.0
London North East	**12.5**	12.2	12.8	**68.6**	60.4	76.8	**1.8**	1.8	1.9	**29.9¬**	26.2	33.7
London North West	**19.5**	18.7	20.3	**76.1¬**	68.5	83.8	**4.5¬**	4.4	4.6	**20.2¬**	18.2	22.3
London North	**16.1**	15.7	16.4	**71.2**	65.5	77.0	**2.6**	2.5	2.6	**19.4**	18.0	20.9
Cambridge	**14.6**	14.3	14.9	**76.1**	70.8	81.3	**0.2¬**	0.2	0.2	**19.0**	17.8	20.2
Leicester	**11.2**	10.9	11.5	**74.1**	65.2	83.0	**1.2¬**	1.2	1.2	**16.2¬**	14.7	17.7
Nottingham	**14.6**	14.2	14.9	**72.2**	63.5	80.8	**1.7**	1.7	1.7	**16.1¬**	14.5	17.7
Guildford	**15.7**	15.2	16.1	**83.3**	76.4	90.2	**1.2¬**	1.1	1.2	**20.1**	18.2	22.0
Oxford	**13.5**	13.1	14.0	**68.6**	63.2	74.0	**1.9¬**	1.8	1.9	**24.1**	22.2	26.1
Southampton	**14.5**	14.2	14.8	**78.2**	72.7	83.7	**1.3¬**	1.2	1.3	**19.8**	18.4	21.2
Plymouth	**14.9**	14.5	15.3	**62.3**	56.9	67.8	**3.4¬**	3.4	3.5	**16.7¬**	15.5	17.9
Bristol	**16.3**	15.7	16.8	**76.8**	68.7	84.9	**2.1¬**	2.1	2.1	**12.6¬**	11.5	13.6
Birmingham	**14.7**	14.4	15.0	**70.5**	65.1	75.9	**1.4**	1.4	1.4	**15.7**	14.8	16.6
Coventry	**13.1**	12.6	13.6	**66.8¬**	57.9	75.7	**1.4***	0.0	2.8	**21.5¬**	19.1	23.9
Stoke-On-Trent	**13.0**	12.6	13.5	**78.8**	69.5	88.1	**0.7¬**	0.7	0.7	**6.6¬**	6.2	7.1
Hull	**15.4**	14.9	15.9	**64.8¬**	56.5	73.2	**1.0¬**	1.0	1.0	**21.4¬**	19.1	23.7
Leeds	**16.0**	15.7	16.3	**69.0**	63.0	75.1	**1.3¬**	1.3	1.3	**23.8**	22.0	25.6
Sheffield	**13.6**	13.2	14.0	**67.4**	60.6	74.2	**1.3¬**	1.3	1.3	**14.2¬**	13.2	15.2
Newcastle	**12.5**	12.3	12.8	**79.7**	73.6	85.8	**0.8¬**	0.8	0.8	**22.1¬**	20.3	23.9
Blackburn	**11.6**	11.4	11.9	**79.7**	72.1	87.4	**1.9¬**	1.9	1.9	**25.4¬**	22.5	28.2
Liverpool	**15.0**	14.6	15.4	**66.1**	60.9	71.4	**4.2¬**	4.1	4.2	**19.6**	18.2	21.0
Manchester	**18.8**	18.2	19.3	**71.7**	66.9	76.6	**2.6**	2.6	2.7	**22.7**	21.2	24.3

* unstandardised estimate; ¬ estimates based on sparse data

Supplementary Figure

Pancreatic cancer incidence and survival and the role of specialist centres in resection rates in England, 2000 to 2014: a population-based study

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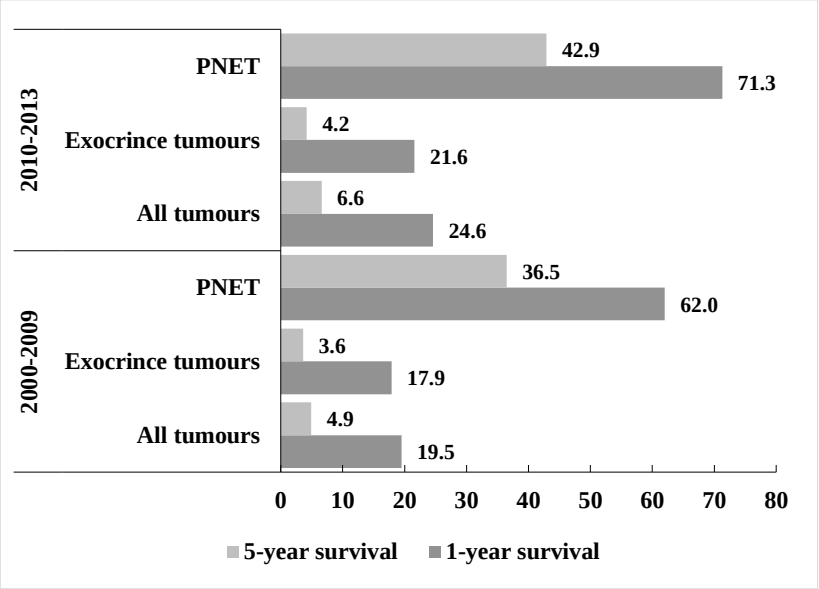
S1 Figure. Age-standardised one- and five-year net survival* (%) for pancreatic cancer by morphology group and calendar period of diagnosis in England, 2000-2013 inclusive.



* Survival in 2000-2009 was estimated with complete approach analysis and in 2010-2013 with period approach analysis.