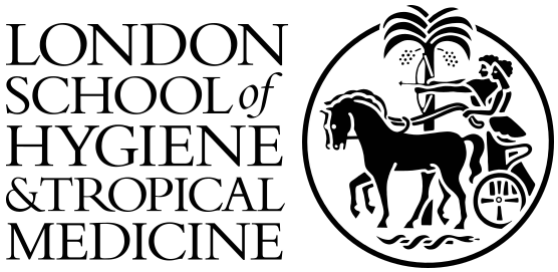

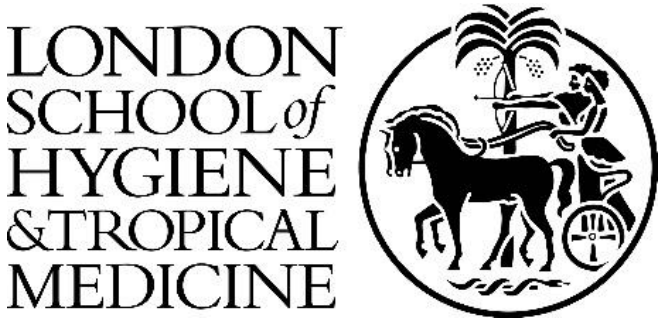

Population-based cancer survival in Kuwait

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Declaration

I, Eiman Alawadhi, confirm 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.

Signed:

Date: 19 March 2019

Dedication

I dedicate this achievement to my family, and especially to my wonderful mother; she was the one who encouraged me to follow this life-long dream of mine from the very beginning, supporting me with her selfless love and care. Her prayers, for me and my family, enlightened every step of the way. I want to say thank you to my amazingly generous father, who provided me and my family with his tremendous support, guiding and helping me endure this long and challenging journey. To my loving husband, who sacrificed a lot on my behalf, and stood by my side through all the ups and downs; my remarkable sister and brothers, who have supported me throughout this process and encouraged me when things were tough; and finally, my brave children, who went through a lot, including being away from their mother for some time, to allow me to accomplish my goal. To you all, words are not enough to express my gratitude for your unwavering love, support and guidance. Thank you sincerely, I could not have done it without you.

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I would also like to thank the Director of the Kuwait Cancer Center, and the Kuwait Cancer Registry staff. Without their help this thesis would not have been possible. I am also grateful to all the staff at the Central Record for Birth and Death Department of the Ministry of Health; without their work and dedication this thesis would not have been accomplished. I am especially thankful for their contribution to obtain the essential data I needed to pursue this thesis, for which they worked at their own time and beyond their work duties, in order to assist my research and, consequently, Kuwait as a whole.

To my fellow PhD students and friends, who have helped me in so many ways; listened to my complaints when things were tough, advised me when I was stuck, encouraged me when I was hopeless, celebrated my accomplishments, and even read through my work and worked with me on weekends to help me meet my deadlines. I am grateful to you for making this journey so much easier.

Abstract

Population-based cancer survival is a key measure of the effectiveness of health systems in managing cancer. Monitoring survival over time and between countries is also crucial to assess inequalities and drive policies for cancer control.

In this thesis, I use data from the Kuwait Cancer Registry (KCR) to produce a comprehensive profile of population-based cancer survival in Kuwait, to enable evaluation of cancer care in the country.

In order to produce robust population-based net survival estimates, it is necessary to have the full date of both the cancer diagnosis and the last known vital status for all patients. All deaths must be included, irrespective of the cause of death. A new approach to obtain follow-up data on the vital status of all registered Kuwaiti cancer patients was implemented. This enabled the estimation of population-based cancer survival in Kuwait for the first time, using robust and unbiased methods that allow comparisons to be made over time and between different populations. Further analyses of survival by stage at diagnosis were also performed, to provide a deeper understanding of cancer survival in Kuwait. Finally, an overall assessment of progress against cancer was performed, using the three main cancer control metrics: incidence, survival and mortality.

The findings demonstrate that survival has improved for many cancers in Kuwait during 2000-2013. However, further research is required to help dissect the underlying causes of the differences in survival between Kuwait and other countries with comparable income and health systems. It also highlighted the importance of more complete collection of stage data, the necessity of improving early detection, and the need for systematic production and assessment of cancer control measures in Kuwait. The findings should assist policymakers and practitioners investing in the Kuwaiti healthcare system to achieve optimal outcomes and provide guidance towards future research in the country.

Preface

This thesis is a research paper style thesis, written in accordance with the London School of Hygiene and Tropical Medicine's guidelines and regulations. It comprises two published and two as yet unpublished research papers on population-based cancer survival in Kuwait. Although the papers comprise one body of work, they also stand alone as independent studies. There are, therefore, several sections where definitions and descriptive methodology are repeated. For the two published papers, the word-processed versions are included as separate chapters and the publications are available in the appendices. Each paper is preceded by a cover letter and a preface that includes an introduction and supplementary information.

The introductory chapter looks at cancer in Kuwait and the importance of the main cancer control metrics in informing efforts to control the cancer burden, focusing on the importance of population-based cancer survival, followed by the aims and objectives. Chapters 2 and 3 include a review of the literature in support of the aim, and the description of the main statistical methods used in this thesis. Chapters 4–7 comprise a series of research papers on cancer survival in Kuwait, starting with the method to obtain data on follow-up for vital status for each patient (chapter 4), the estimation of population-based cancer survival in Kuwait (chapter 5), survival by stage at diagnosis (chapter 6), and an assessment of overall progress against cancer in Kuwait (chapter 7). Chapter 8 presents a discussion of the results of these studies, their implications, possible directions for future research, limitations, and an overall conclusion. References cited throughout the text, including those in the research papers, are listed at the end of the thesis.

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Chapter 1: Introduction

1.1 Kuwait

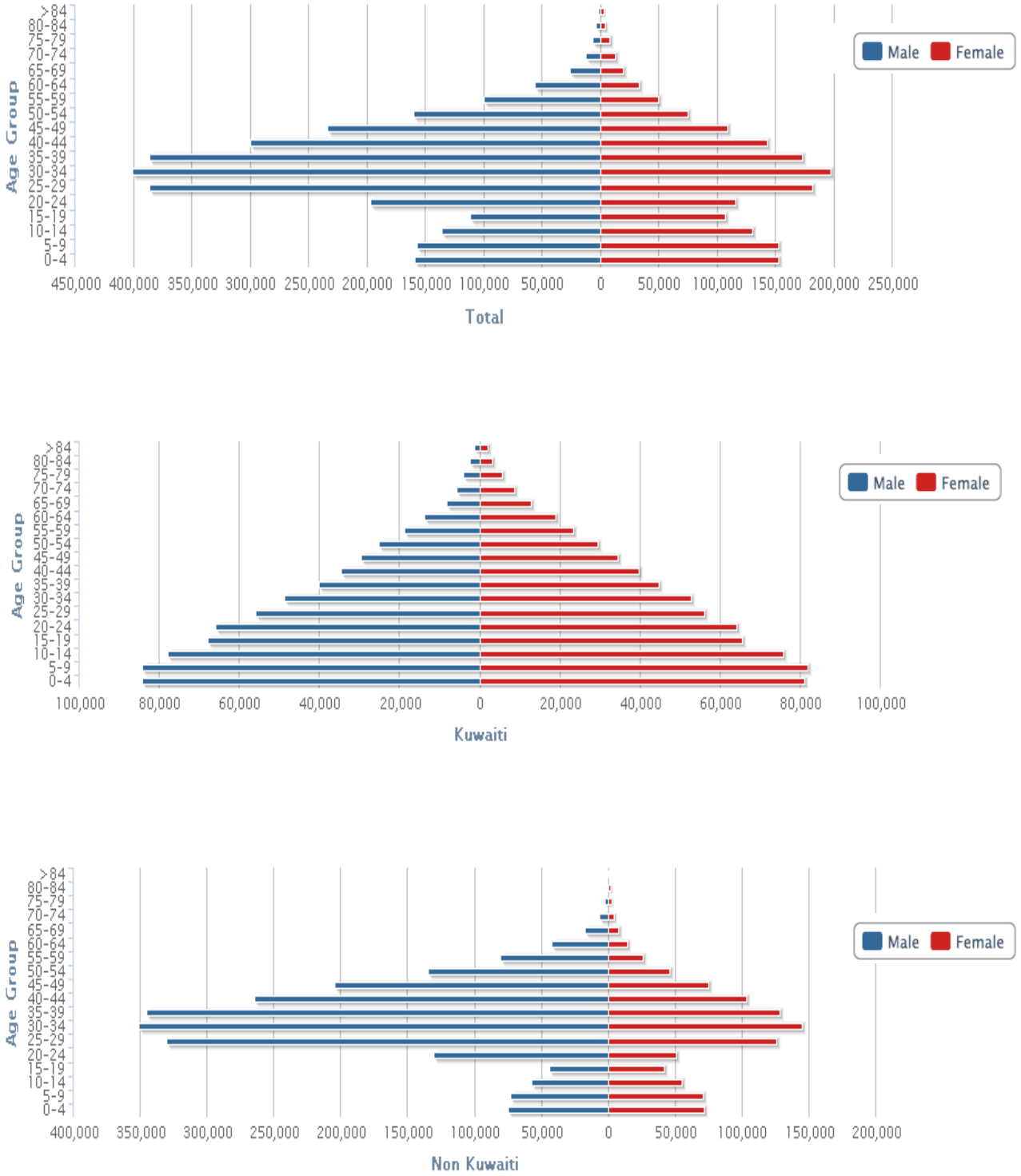
Kuwait is an Arab country in Western Asia [Figure 1.1], located at the northern tip of the Arabian or Persian Gulf. It covers an area of about 18,000 square kilometres and shares borders with Iraq and Saudi Arabia.[1] The official language is Arabic, although English is also widely spoken.[1] Kuwait is a member of the Gulf Cooperation Council (GCC) – along with the Kingdom of Bahrain, the Sultanate of Oman, Qatar, the Kingdom of Saudi Arabia and the United Arab Emirates – a union of which the members share common objectives, as well as political and cultural identities.[2] All GCC countries are considered high-income countries.[3] Kuwait enjoys a high economic status, which allows its government to provide citizens with many public services and amenities, such as free healthcare, education, retirement income, marriage grants, housing loans, guaranteed employment, and subsidies for food and other commodities.[4]

Figure 1.1 Location of Kuwait

Source: http://www.freeworldmaps.net/asia/kuwait/location.html

In 2017, the population of Kuwait reached 4,500,476, of which 63% were men and 37% women [Figure 1.2]. Kuwaiti nationals represent 30.0% of the total population, with a 1:1 male to female ratio, while non-Kuwaitis represent 70% of the total population with a 2.3:1 male to female ratio.[5] Non-Kuwaitis are mostly immigrant workers from other Asian and Arab countries.[6] The age composition of the population pyramid differs markedly between Kuwaitis and non-Kuwaitis: for Kuwaitis, the pyramid has a wide base, with proportional symmetry between the sexes at each age. This is typical of most Middle Eastern countries with low mortality and high fertility rates.[7] However, for non-Kuwaitis, the pyramid has a narrow base with a wide middle-age group, representing the working age-group; the distribution between the sexes in this group is asymmetric. Fertility rates (total births per woman) have been decreasing steadily in Kuwait, with rates dropping from 2.9 per 1,000 women in 1999 to 2.0 per 1,000 women in 2017.[3] In 2015, life expectancy at birth for Kuwaiti men and women was 73.2 and 78.0, respectively, while life expectancy for non-Kuwaiti men and women was 78.0 and 78.1, respectively (http://csg.lshtm.ac.uk/life-tables/). Life expectancy for the total population in Kuwait has also been increasing, reaching 76.8 years for men and 79.6 years for women in 2017.[1] The population of Kuwait is also projected to reach 5 million by 2020, and 7 million in 2030. This population growth is likely to be dominated by the non-Kuwaiti population particularly male expat workers.[8]

Figure 1.2 Kuwait population, by sex and age (Kuwaiti vs. non-Kuwaiti)



Source: Ministry of Health
http://stat.paci.gov.kw/englishreports/#DataTabPlace:PopulationPyramid

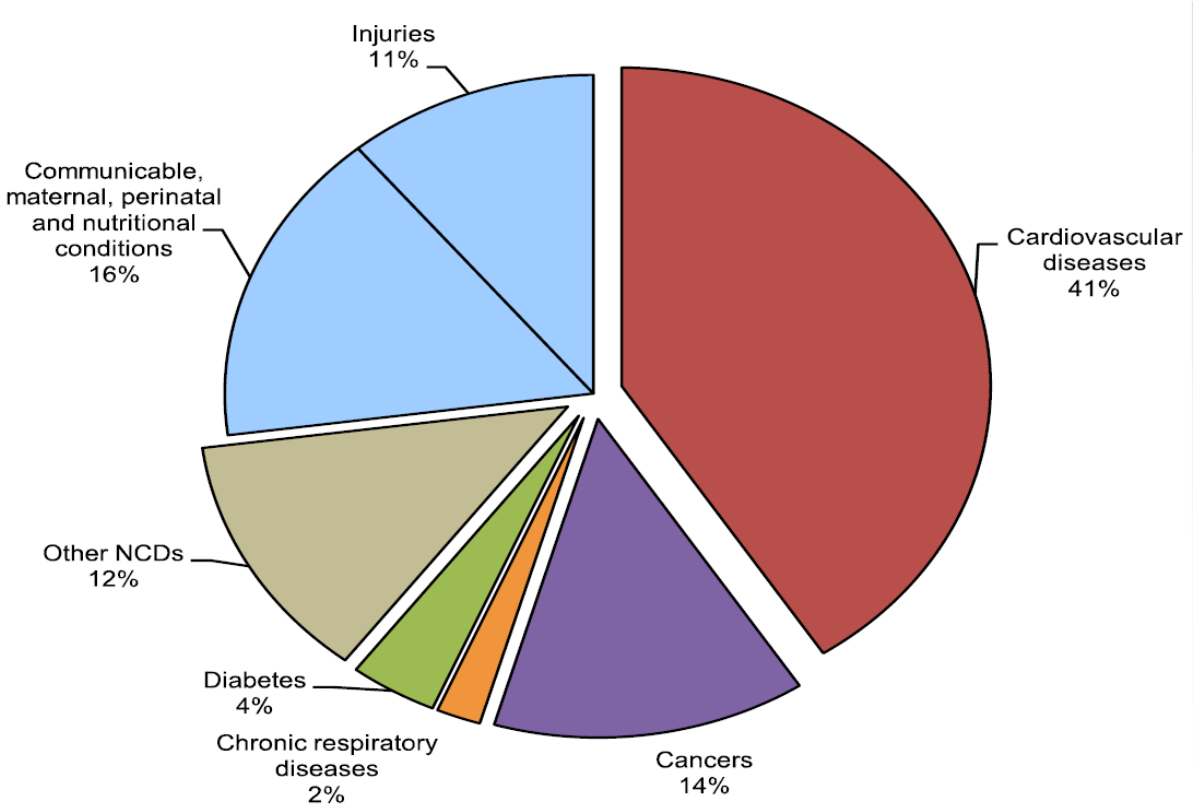
1.2 Health care in Kuwait

Kuwait's health infrastructure is considered the most modern in the region.[4] The majority of health services are provided by the public sector, via the Ministry of Health. The Ministry provides all citizens with comprehensive primary, secondary and tertiary care, distributed via primary health care centres, six general hospitals and many General Practitioner (GP) clinics and national specialised hospitals. Citizens also have the option of travelling abroad for treatment, when treatment or health services are not available in the hospitals of Kuwait. In 2015, health expenditure in Kuwait was 4.0% of the Gross Domestic Product (GDP), compared to an average of 4.2% in other GCC countries, 9.8% in the United Kingdom and 16.8% in the United States.[3] In the United Kingdom, almost all the expenditure comes from the "public" spend, while in the US it is almost half "public" and half "private".[9] In Kuwait the government's share of the total health expenditure is about 80%, while about 20% comes from out-of-pocket payments.[10] The Ministry of Health's budget for 2015-2016 had doubled over the previous five years, indicating rapid growth and increasing investment in the country's healthcare infrastructure.[10]

1.3 Cancer in Kuwait

Non-communicable diseases (NCDs) in Kuwait account for 73% of all deaths. Among the NCDs, cancer is the most common cause of death, after cardiovascular diseases [Figure 1.3]. One of the goals of the 2013 World Cancer Declaration, set by the Union for International Cancer Control (UICC), of which the Kuwait Society for Preventing Smoking and Cancer is a member, is to achieve worldwide improvement in cancer survival by 2020.[11] In 2013, the Kuwait Cancer Control Centre (KCCC) also established a cancer strategic plan for 2013-2018, with one of its goals to 'measure and improve outcomes' through 'measuring disease control rates and survival'.[12]

Figure 1.3 Causes of death in Kuwait, 2014



Source: WHO. Noncommunicable Diseases (NCD) Country Profiles. WHO, 2014. http://www.who.int/nmh/countries/kwt_en.pdf?ua=1

The most common cancers diagnosed during 1998-2012 among Kuwaiti males were prostate and colorectal cancer, and leukaemia. The leading cancers among Kuwaiti females were breast, thyroid and colorectal cancers [Table 1.1].[13] For non-Kuwaitis, the latest report, in 2013, indicated that the most commonly diagnosed cancer in men was colorectal, followed by prostate cancer and leukaemia, while the leading cancers for non-Kuwaiti women were breast followed by thyroid.

Table 1.1 The most common cancers diagnosed in Kuwait during 1998-2012

	Kuwaiti		Non-Kuwaiti*	
Rank	**Males**	**Females**	**Males**	**Females**
1	Prostate	Breast	Colorectal	Breast
2	Colorectal	Thyroid	Prostate	Thyroid
3	Leukaemia	Colorectal	Leukaemia	Corpus uteri

*2013 only

1.4 Kuwait Cancer Control Centre

The Kuwait Cancer Control Centre (KCCC) is the only centre in the country that provides the full range of cancer treatment modalities and care. It comprises facilities for specialised surgery, radiology and radiotherapy, chemotherapy, bone marrow transplantation, laboratory services, paediatric oncology and haematology services, as well as palliative care.[14] It is the only centre in the country that provides radiotherapy and chemotherapy for cancer patients.

The Kuwait Cancer Registry (KCR), the oldest population-based registry [see Section 1.6] in the Gulf region, was established in 1971, with the aim of monitoring cancer incidence in Kuwait. In 1982, it was recognised as a separate department in the KCCC.[15] The KCR is considered to be a comprehensive source of information for all cancer patients diagnosed in Kuwait. The KCR registers everyone diagnosed or treated in Kuwait. This includes patients diagnosed in the country, patients diagnosed abroad but receiving treatment in the KCCC, as well as patients diagnosed in Kuwait but receiving treatment abroad. All hospitals in Kuwait are required by law to send copies of the pathology and cytology reports of any

malignant neoplasm and specified non-malignant neoplasms, such as those of the brain, to the KCR. The registry is a member of the International Association of Cancer Registries (IACR) and the Gulf Centre for Cancer Registration (GCCR) and operates according to the guidelines of the International Association of Cancer Registries (IACR).

The KCR maintains a register of all cancer patients, including data on nationality, sex, age, year of diagnosis, basis of diagnosis, and on the date of death, which is obtained through the Ministry of Health's Biostatistics Office. The registry is responsible for producing annual population-based incidence rates. It also collects information on the death of registered patients by manually scanning all the death announcements in Kuwait during a specific calendar year; however, it is only able to capture information on deaths due to cancer.

1.5 Incidence, survival and mortality

Incidence, survival and mortality are three of the main metrics for monitoring the cancer burden. Each measure describes a different aspect of the cancer burden; however, when used in isolation, the results can be misleading. A combination of all three measures is advised when monitoring the overall progress of cancer control.

Incidence refers to the number of newly diagnosed cancer patients in a specific population or region, over a defined period of time. The incidence rate is usually expressed as the number of cancers per 100,000 person-years at risk during a specific time period, typically one year. The numerator is the number of patients newly diagnosed with cancer in a specific region during a specific time period, and the denominator is the person-years at risk. The numerator can be obtained from the cancer registry; the denominator can be approximated using the mid-year population of the defined population at risk of the disease, during the year of interest. Thus, the incidence rate in a given area or region is given by:

$$\frac{No.\ of\ cancer\ deaths\ (in\ the\ relevant\ year\ )}{persons\ comprising\ \ the\ mid\text{-}year\ population}\ x\ 100{,}000$$

$$= \quad Mortality\ rate\ per\ 100{,}000\ person\text{-}years$$

Cancer mortality refers to the number of deaths that are attributable to cancer in the general population during a given period of time, typically a year; and like incidence, it is usually expressed as a rate per 100,000 person-years. The numerator, the number of deaths attributed to cancer as the underlying cause, is obtained from national statistics agencies, and the denominator, the person-years at risk, is again approximated using the mid-year population. The mortality rate in a given area or region is given by:

$$\frac{\textit{No. of new cancers (in the relevant year)}}{\textit{No. of persons comprising the mid-year population}} \; x\,100{,}000$$

$$= \; \textit{Incidence rate per 100,000 person-years}$$

Population-based cancer survival refers to the cumulative probability for cancer patients in a defined region to survive their cancer up to a certain time since diagnosis, after controlling for competing risks of death [see Chapter 3 for more detail].

Incidence is useful in detecting high-risk populations, understanding the aetiology of disease, raising awareness, and establishing priorities for primary prevention and planning health services. Cancer mortality is useful to set priorities and assess the effects of screening programmes, because such programmes are intended to reduce mortality, although for some cancers early detection also enables removal of pre-malignant lesions or even pre-invasive (*in situ*) malignant lesions. Population-based cancer survival is considered a reliable measure of the effectiveness of the health system in dealing with cancer, either curing or prolonging the lives of cancer patients.

In general, incidence and survival are considered as independent measures. Incidence rates for a specific cancer are influenced by events that occur prior to diagnosis, for example, changes in exposure to risk factors. Incidence rates can also be influenced by changes in the international definitions of malignancy. Survival may be influenced by events that occur before and after diagnosis, such as the intensity of diagnostic activity, the thoroughness of diagnostic investigation and the availability, accessibility and timeliness of effective

treatment, as well as post-treatment surveillance and follow-up care. Events after diagnosis cannot affect incidence. On the other hand, mortality is influenced by both incidence and survival, since a patient's death due to cancer pre-supposes a diagnosis and a subsequent failure to survive the illness.

Incidence, survival and mortality trends can be combined to provide a more accurate representation of the cancer burden, illustrating variations in the impact of cancer between population sub-groups and over time. Mortality trends can be misleading when examined in isolation, because mortality rates derived from the deaths that occur in a given year depend on a combination of previous trends in incidence and survival. Comparisons of mortality rates are also based on the assumption that death registration practices are consistent and comparable between countries and over time. This assumption is not usually considered sound for international studies. Thus, in order to make robust comparisons of the effectiveness of the health service over time or between different countries, population-based survival statistics are more directly interpretable than mortality rates as an indicator of outcomes.[16]

1.6 Population-based data

To assess cancer control, population-based cancer data are required. These data can be obtained from cancer registries, whose role is to collect, store, analyse and report data systematically, for all cancer patients resident in a defined location, such as a country, province or state.[17-19]

Population-based studies differ in purpose, scope and design from clinical trials; the utility and interpretation of the results also differs. In most clinical trials, patients are randomised, and the process entails numerous controls and restrictions; such as adhering to a specific healthcare plan, excluding less healthy patients with pre-existing medical conditions, and possibly certain age groups or ethnicities. This process ensures good internal validity of the results, making them less likely to be affected by bias or confounding factors; rendering

clinical trials useful in evaluating the efficacy of drugs or other cancer treatment interventions. However, while clinical trials inform us about the efficacy of treatments in a controlled research setting, they are unable to describe the overall management of cancer patients. Typically, less than 10% of adult cancer patients are enrolled in clinical trials, in which older patients, and patients with comorbidities or advanced stage are often excluded. Trials are also, generally, carried out by doctors and healthcare facilities that are more research-oriented. They are also usually conducted at health centres where better treatments are available. Clinical trials are thus not necessarily representative of all cancer patients, or of routine healthcare practices in a region or country.[20,21]

By contrast, population-based studies of cancer survival provide information about the whole cancer population, enabling the assessment of the overall effectiveness of the healthcare system on a large-scale basis. All patients diagnosed with cancer while resident in the territory covered by the registry are included, regardless of their age, socio-economic status, comorbidities, stage at diagnosis or adherence to treatment. This enables population-based survival trends to encompass all aspects of the healthcare system: diagnostic efficiency, referral timeliness, and its ability to deliver effective treatment promptly.

1.7 Aims and objectives

The aim of this thesis is to obtain complete and reliable data on all cancer patients in Kuwait, in order to produce a comprehensive profile of population-based cancer survival, to enable the assessment of cancer care in the country. This aim is sub-divided into the following objectives:

- **Objective 1:** to obtain reliable and complete follow-up data on the last known vital status for all Kuwaiti cancer patients registered in Kuwait between 2000 and 2013, essential for robust estimation of population-based survival.
- **Objective 2:** to estimate net survival up to 5 years after diagnosis for 18 common cancers, that can be monitored and compared internationally, in order to facilitate the assessment of cancer control strategies.
- **Objective 3:** to examine the distribution of stage at diagnosis for 12 cancers in Kuwait, and to estimate stage-specific net survival at 1 and 5 years after diagnosis.
- **Objective 4:** to evaluate the overall Kuwaiti health care system in managing cancer during 2000-2013, using three cancer control metrics: incidence, survival and mortality.

Summary

- ✓ Cancer represents a substantial burden for the Kuwait health care system
- ✓ Incidence, survival and mortality need to be examined together to assess adequately progress in cancer control in Kuwait.
- ✓ Population-based data are required: these data are representative of the whole population and are useful to assess the overall health care practices in the region.

What's next?

- ✓ What population-based metrics are published for cancer in Kuwait?

Chapter 2: Literature review

2.1 Aim

The aim of this review is to identify population-based research in Kuwait on incidence, survival and mortality that examines one or more of the three main cancer control metrics; particularly to identify any studies on cancer survival in Kuwait.

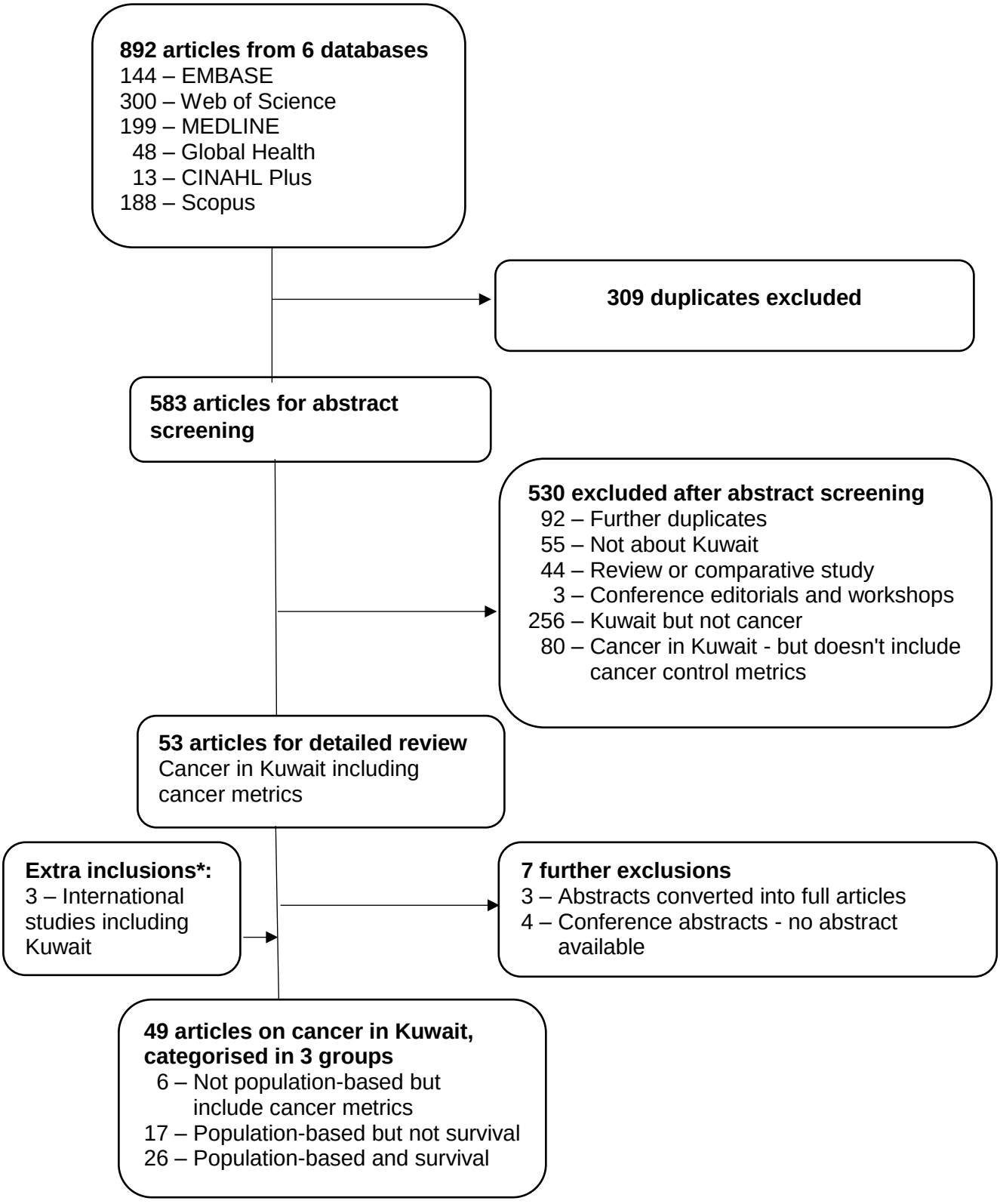
The search terms and process of the review are set out in Table 2.1 and Figure 2.1. Six databases were searched.

Table 2.1 Key topics and search terms for literature review

Key topics	***Search terms***
Region	(Kuwait*)
Disease	(cancer* OR neoplasm* OR oncol* OR tumour OR tumor* OR Leukaemia OR Leukemia OR lymph*)
Outcome	(surviv* OR death OR dead OR incidence OR mortality)

The review also included abstracts presented at medical conferences, because the availability of research in this field in Kuwait is limited.

Figure 2.1 Literature review



***Articles that did not include the key search word "Kuwait" in the title, abstract or keywords and were thus not detected in the searches**

Eight hundred and ninety-two articles, from 6 data bases, were scrutinised. Duplicates were removed and the abstracts screened to exclude articles that were not related to incidence, mortality or survival in Kuwait. Further studies were excluded if neither the full text nor the abstract was available, or if a conference abstract had subsequently been converted into a complete paper. Studies related to Kuwait but not detected by the database search were then added. These consisted of international studies that included data from Kuwait but did not mention the country in the title, abstract or keywords. Finally, 49 studies relating to cancer incidence, survival or mortality in Kuwait, for which at least an abstract was available, were reviewed.

2.2 Studies that are not population-based

Six studies (3 on incidence[22-24] and 3 on survival[25-27]) only included data from a single hospital or a sample of patients for a specific cancer.

2.3 Population-based studies on cancer incidence and mortality in Kuwait

Of the population-based studies, 17 involved cancer metrics but did not include survival. Two studies reported only the frequencies of lip, oral cavity and pharyngeal cancers[28] or leukaemia[29] in Kuwait between 1979 and 1988.

Most of the studies reported age-standardised incidence rates (ASIR) for specific cancers: nasopharynx,[30] lung,[31,32] breast,[33] pancreas,[34] Hodgkin lymphoma,[35] non-Hodgkin lymphoma,[36] and all cases of lymphoma[37] for different periods of time, with the most recent year of diagnosis in 2012, for pancreas and breast. Cancer incidence rates for all types of cancer are presented in the IARC publications: Cancer in Five Continents (CI5), the latest volume CI5 XI[38] including cancers diagnosed during 2008 to 2012.

The most comprehensive studies on cancer incidence in Kuwait were produced by the KCR, based on data from the annual reports, the most recent published for patients diagnosed in 2013.[39] These studies presented the age-standardised incidence rate (ASIR) for all cancers combined for the Kuwaiti population from 1974-2007,[40] and 1970-2009.[41] The latter study

presented ASIR for the ten most common cancers among Kuwaiti males and females. It was extended to include forecasting of the expected total number of cancer patients until the year 2029. While it is the most comprehensive in terms of types of cancer and the estimates produced, it does not include survival.

Four studies examined mortality due to cancer. One reported the frequency of deaths due to cancer in Kuwait in 1989.[42] Another study, produced by the KCR, used the death information collected by the registry.[31] This study presented frequencies of the cancers that led to most deaths, the cumulative risk of dying from cancer by the age of 74 years, and the age at death due to cancer during 2000-2009 for Kuwaiti nationals. Two studies[33,43] used mortality data from the Health and Vital Statistics Division at the Department of Statistics and Medical Records at the Kuwaiti Ministry of Health. This division produces annual reports on mortality rates by sex, age group, nationality and cause of death according to the World Health Organization's International Classification of Diseases, Tenth Revision.[44] The first study[43] compared age-standardised mortality rates (ASMR) due to "neoplasms" for Kuwaiti nationals and the total Kuwaiti population in the years 1995 and 2010. The second study[33] presented mortality rates only for breast cancer, with the aim of assessing the impact of cancer deaths on life gains in person-years of life, for females in Kuwait.

IARC's international study on incidence and mortality, GLOBOCAN, includes model-based estimates of incidence rates in 2018, for 185 countries including Kuwait.[45] Incidence rates for Kuwait were based on retrospective incidence rates, projected forward to 2018, and mortality rates were modelled using incidence:mortality ratios derived from neighbouring countries. The population used in these analyses were also projected populations for Kuwait, and not counts provided by the Department of Health Information and Medical Records at the Kuwait Ministry of Health, that were used in the other studies, including the CI5 publications. While the GLOBOCAN's estimation methods have been validated, caution is advised against comparing estimates from the recent and previous versions of

GLOBOCAN. That is mainly because changes in incidence and mortality rates could be partly due to the increasing availability and quality of the incidence data from cancer registries worldwide, which is the basis for the modelling methods used to produce the 2018 estimates.

Examining trends in incidence and mortality alongside survival trends will enable a more comprehensive understanding of the impact of cancer and the progress of cancer control in Kuwait.

2.4 Population-based cancer survival in Kuwait

Only 26 of the 49 studies published over the 41 years 1978 to 2019 included data on survival. All the studies were population-based, using data from the KCR, which collects diagnostic information for all cancer patients, but only captures follow-up data on vital status for deaths reported as due to cancer. Eight of the 27 studies on survival were only abstracts of research presented in medical conferences. This underscores the scarcity of published research on cancer survival in Kuwait.

Three studies[46-48] referred to survival, but did not include formal analyses, only the number of deaths or patients' individual time until death. A number of studies examined survival in relation to specific treatment, for cancers of the breast,[49-52] oral cavity,[53] paediatric[54,55] and adult Hodgkin lymphoma,[56] paediatric[57] and adult non-Hodgkin lymphoma,[58,59] cervical,[60] uterine,[61] rectal,[62] renal,[63] lung[64] and gastrointestinal.[58]

In the 16 studies where survival was reported, two presented median survival time,[57,64] and 14 presented overall survival (OS) up to a certain number of years after diagnosis,[50,52,54,55,62-71] i.e. survival for all causes of death combined.

Median survival summarises the length of time from either the diagnosis or the treatment of a disease, to the point at which half of the patients are still alive. In other words, 50% of the patients pass away before the median time and 50% live beyond the median time.

Overall survival is often referred to as “observed”, “crude” or “all-cause” survival. It is the cumulative probability that patients survive a certain period of time after diagnosis, usually five years, where the event of interest is death from any cause. No distinction is made between causes of death, so these estimates provide a broad view that is not specific enough to provide information on surviving a specific cancer. Changes in survival may therefore be due either to change in the number deaths from cancer or to change in the number of deaths from other causes. Robust comparisons of cancer survival between regions or over time cannot be made using overall survival.

In the 12 studies where statistical methods were indicated, overall survival was estimated using the Kaplan-Meier method.[72] This method allows the estimation of survival over time, even when patients drop out or are studied for different lengths of time.[73]

However, overall survival implies surviving any cause of death and not just cancer. In fact, all these 12 studies of “overall survival” were based only on *deaths reported as due to cancer.*[50,52,54,55,62-67,69,71] Consequently, these studies overestimate the true overall survival, because deaths from other causes were not included.

Even if the intention of these studies was to estimate cause-specific survival (i.e. based only on deaths due to cancer), the results remain problematic even if the statistical analysis may be appropriate. This is due to the fact that cause-specific survival estimates rely on the assumption that no differences or inaccuracies occur in the coding of the underlying cause of death between physicians, over time, or between regions. However, due to the variability in accurately determining the cause of death between individual physicians, different hospitals and countries, cause-specific survival estimates are unreliable within a country or region, and not comparable internationally.[74-78]

Only one study[25] followed up the patients actively to obtain their vital status; however, it was not population-based, and only included 47 patients.

Seven studies estimated survival where death was not the event of interest,[50,55,58,62,65-67,69] but recurrence or relapse, also called disease-free survival (DFS) or progression-free survival (PFS). Overall survival, disease-free survival and progression-free survival are measures used within the context of clinical trials and are useful in assessing the effects of treatment on cancer outcomes, but they are not relevant to assess the overall effectiveness of the health system in curing or prolonging the life of cancer patients following their diagnosis. Estimation of "net survival" for all the common cancers, using complete data on follow-up for vital status for all patients, and including all causes of death – not just deaths due to cancer - would therefore offer a considerable improvement in the quality and completeness of information on cancer outcomes in Kuwait [see Section 4.2].

2.5 The CONCORD programme

The CONCORD programme, hosted within the Cancer Survival Group at the LSHTM, is the most comprehensive and up-to-date study on global surveillance of population-based cancer survival. Its main goals are to compare population-based cancer survival trends between countries using standardised quality-control procedures and identical analytical methods for all datasets, and to explain the reasons for the differences in cancer survival world-wide.

The first cycle of the CONCORD programme was published in 2008, and included about 1.9 million adults diagnosed with breast, colon, rectum or prostate cancer in 31 countries. Five-year population-based survival was estimated for patients diagnosed during 1990-1994, with follow-up to the end of 1999.[79] In 2015, the second cycle of the CONCORD programme (CONCORD-2)[80] established global surveillance of cancer survival trends for the first time, analysing data for 25.7 million patients diagnosed during the period 1995-2009, with follow-up to 2009, from 67 countries. CONCORD-2 examined ten common cancers in adults: stomach, colon, rectum, liver, lung, breast (women), cervix, ovary, prostate and leukaemia. It also examined survival from acute lymphoblastic leukaemia (ALL) in children.

The latest cycle of the CONCORD programme, CONCORD-3,[81] updated survival trends to 2014. It included patients diagnosed during the period 2000-2014, with follow-up to 31 December 2014, from 71 countries and territories. Seven additional cancers were included: oesophagus, pancreas and melanoma of the skin in adults (15-99 years), and lymphoma and brain tumours in both adults and children (0-14 years).

The work presented in this thesis enabled collection of complete data on follow-up for vital status for all Kuwaiti cancer patients [see Chapter 5]. As a result, Kuwait was able to participate in the third cycle of the CONCORD programme.[81] This was the first time population-based survival estimates had been published for Kuwait.

Summary

Ample robust population-based cancer incidence and mortality metrics are reported for Kuwait, but not population-based survival.
Most survival estimates produced for Kuwait rely on vital status data obtained through the Kuwait Cancer Registry, which only captures information on “deaths due to cancer”.
Overall survival is estimated for some cancers in Kuwait. However, these are likely to be overestimates, because of the unavailability of information on deaths due to causes other than cancer. Moreover, these survival estimates are not appropriate for comparisons over time or between countries.

What’s next?

To produce robust net survival estimates for the most common cancers in Kuwait, using complete and reliable data on deaths due to any cause, to enable the assessment of the Kuwaiti health care system in managing cancer.

Chapter 3: Population-based cancer survival

When analysing survival for cancer patients we are interested to know the probability for these patients to survive their cancer for a defined period of time since diagnosis.

When working with data from population-based cancer registries to estimate population-base survival, the information on cause of death is often unavailable or unreliable. Therefore, the goal is to estimate the cumulative probability for cancer patients to survive their cancer up to a given time since diagnosis (e.g. 5 years), after accurately controlling for competing risk of death (net survival) [section 3.2]. Estimation of survival in the relative survival setting [section 3.3] allows estimation of net survival in the absence of accurate information on the cause of death.

3.1 Definition of survival

Survival analysis is generally used to analyse any data when time to an event is of interest. The outcome, therefore, is not based on whether an event occurs or not, but on the time to its occurrence. An event can be the patient's death, the occurrence of the disease, the patient's entry to the hospital etc. The event-time data, also called failure-time or survival time, are characterised by a starting point in time (e.g. the date of cancer diagnosis or beginning of treatment) and an end-point, defined by the event of interest (e.g. death from cancer or death due to any cause), or the end of follow-up. The survival time can be measured in days, weeks or years. This type of time-to-event analysis allows patients to be "censored". Censoring occurs when a patient does not experience the event of interest during the follow-up time. This could be due to patients being lost to follow-up or due to competing events happening prior to the event of interest, or patients who are alive at the end of the follow-up.

The outcome of survival analysis can be expressed as a survival probability or an event rate (hazard). The survival function gives the probability that a person survives longer than a

certain time (*t)* since diagnosis. The hazard function is the rate at which an event (usually death from any cause) occurs at a specified time since diagnosis. The two measures are mathematically related and thus if one is known, the other can be derived.

$$S(t) = e^{-H(t)}$$

This formula indicates the relationship between survival and hazard, where $S(t)$ is the cumulative survival probability and $H(t)$ is the integrated or cumulative hazard of death. $H(t)$ can be calculated as follows, where λ is the hazard rate i.e. the instantaneous hazard.

$$H(t) = \int_0^t \lambda(u)du$$

In cancer survival analyses, the simplest measure of survival is overall survival (also called observed or all-cause survival), in which the event is a patient's death from any cause. This indicator can be useful in a clinical setting, aiding predictive tools and clinical decision making.[82] However, since patients are subject to several forces of mortality, differences in overall survival cannot be attributed solely to cancer. Therefore, to evaluate survival due to the actual disease of interest, independent of competing causes, the goal is to estimate "net survival".

3.2 Net survival

If cancer is the disease of interest, net survival entails the idea that the overall hazard of death for cancer patients is given by the sum of two quantities: the hazard of death due to cancer and the hazard of death due to other causes:

λ_O		λ_P		λ_E
Overall hazard (hazard of death in cancer cohort)	**=**	**competing hazard** (hazard of death in the general	**+**	**excess hazard** (hazard of death due to cancer)

Compared to the general population who only experience the background hazard of death, for their specific age, sex and calendar year of death, cancer patients have the additional hazard of dying due to their cancer. Therefore, the excess hazard (cancer-related hazard) can be obtained by removing the competing hazard from the cancer patients' overall hazard of death.

$$\lambda_E = \lambda_O - \lambda_P$$

Net survival is a survival function, derived from the excess hazard (λ_E) alone.

The mathematical relationship between the net survival function $S_E(t)$, and the excess hazard function λ_E is shown here:

$$S_E(t) = \exp\left(-\int_0^t \lambda_E(u)du\right)$$

Net survival can be interpreted as the probability that cancer patients survive their cancer up to a specified time (say, five years) since diagnosis, after controlling for competing risks of death.

Net survival derived from data that include *all* cancer patients diagnosed in a defined region (population-based survival), can be used as a measure of the overall effectiveness of all aspects of a given health system in managing cancer care. It can be sensitive to changes in diagnostic techniques, screening, early diagnostic activities, patterns of care or the efficacy of cancer treatments. This indicator, if age-standardised, is also particularly important in enabling valid comparisons over time and between sub-populations, and for international comparisons, making it a key parameter for epidemiological research and surveillance, and valuable for guiding cancer and health policy.[20,83,84]

3.3 Data settings: cause-specific and relative survival

Net survival can be estimated in two general settings: the cause-specific setting, when the exact cause of death is accurately known, or the relative survival setting, when the exact cause of death is unknown, unreliable or inaccessible.

Cause-specific survival relies on information on the underlying cause of death, and uses cancer-specific deaths as the event of interest. Deaths due to other causes are censored in order to estimate the cancer-specific hazard (excess hazard). The survival for a defined calendar period of time can be estimated using standard methods such as the Kaplan-Meier[72] or the actuarial (life table) method.[85]

In a relative survival setting, the cause of death is not required for analysis. Therefore, we do not need to distinguish whether the patient died from cancer or from another cause. In this setting, to estimate the excess hazard of death due to cancer, we need to remove the hazard due to causes other than cancer (*competing* hazard; background mortality in the general population) from the overall hazard of death. This entails the assumption that the time to death due to cancer and the time to death due to competing causes are conditionally independent, given that the patients share the same characteristics (for example same age, sex, ethnicity and year of death). The background mortality in the general population from which the cancer patients are drawn is assumed to be representative of the hazard of death due to causes other than cancer (the competing hazard). This assumption holds because deaths specific to each single cancer form a negligible part of the total population mortality.

The relative survival setting is particularly important when making comparisons of cancer survival. The fact that information on the cause of death is not used to derive the excess hazard of death due to cancer eliminates any issues related to differences or inaccuracies in coding the underlying cause of death between the regions or countries compared [see Section 2.4].

To control for background mortality, we use a set of region-specific life tables of age-specific all-cause mortality rates in the general population, stratified by sex and calendar year of death, and by other characteristics, such as ethnicity or socioeconomic level when possible. The use of life tables in estimating net survival, adjusts for varying levels of background mortality between certain populations, regions and over time. This enables survival estimates to represent true differences in cancer survival, after correction for background mortality between the groups or geographies compared.

The most recent and unbiased, non-parametric estimator of net survival was proposed by Pohar Perme.[86] For a cohort of cancer patients, it can be interpreted as the average ratio of their overall survival (i.e. survival due to any cause) and the population survival (i.e. survival due to causes other than cancer).

To illustrate this, the instantaneous hazard equation is presented here again:

λ_O		λ_P		λ_E
Overall hazard (hazard of death in cancer cohort)	**=**	**competing hazard** (hazard of death in the general population)	**+**	**excess hazard** (hazard of death due to cancer)

The assumption is that the hazard due to causes other than cancer (λ_{Pi}) is given by the population life tables (background mortality).

When integrated over time, we have:

$$\int_0^t \lambda_{Oi}(u)du = \int_0^t \left[\lambda_{Pi}(u) + \lambda_{Ei}(u)\right]du$$

Using the mathematical relationship between survival and hazard, we then get

Or,

$$exp\left(-\int_0^t \lambda_{Oi}(u)du\right) = exp\left(-\int_0^t \lambda_{Pi}(u)du\right) exp\left(-\int_o^t \lambda_{Ei}(u)du\right)$$

$$S_{Oi}(t) = S_{Pi}(t) . S_{Ei}(t)$$

Which is equivalent to the excess (net) survival:

$$S_{Ei}(t) = \frac{S_{Oi}(t)}{S_{Pi}(t)}$$

And for a cohort of size n, the excess (net) survival becomes

$$S_E(t) = \frac{1}{n}\sum_{i=1}^{n}\frac{S_{Oi}(t)}{S_{Pi}(t)}$$

To estimate the net survival, the overall survival probability $S_{Oi}(t)$ for each individual cancer patient (i), and their corresponding expected survival $S_{Pi}(t)$ if they didn't have the disease (derived from the general population life tables), are compared along time since diagnosis. The cumulative net survival $S_E(t)$ is therefore the mean of the individual net survival estimates for that cohort of patients. In other words, net survival is a summary of the excess hazard (λ_E) through time and over individuals.

The net survival estimate produced by using the Pohar Perme estimator[86] accounts for the fact that the risk of death from competing causes is higher in older patients, in other words, that the hazard from competing causes increases with age (informative censoring). This estimator takes account of this bias using inverse probability weighting, where weights are placed on both the cumulative overall hazard and the cumulative competing (population) hazard, in order to derive the cumulative excess hazard of death due to cancer.

To calculate the weights, the general population life tables from which the cancer patients are drawn are used. The weights are equal to each individual's expected survival at a given time, i.e. the probability that the patient is still alive at that time if their survival were to be the same as the general cancer-free population, given the same demographic characteristics (age, sex and year of death). This process of inverse weighting will place a greater weight on survival for the elderly, who are progressively more under-represented in the cancer cohort with the passage of time since diagnosis, due to their higher risk of competing causes of death. This will inflate the number of people remaining at risk to mimic a cohort of patients that would have been observed without the effect of competing causes of death (deaths other than cancer). Consequently, the bias of informative censoring is dealt with.

The excess hazard for the entire cancer cohort, from which the cumulative net survival estimate is derived, is therefore a weighted average of all the individual patients' excess hazards.

The Pohar-Perme estimator is considered the gold standard within the relative survival setting, because it accounts for informative censoring as well as producing survival estimates that are not affected by differences in background mortality. These net survival estimates are therefore ideal for comparisons between different populations, geographies and over time.[87]

3.4 Design of analysis

3.4.1 Cohort approach

In survival analysis, patients need to be followed over time, in order for the event of interest to be observed. In cases where all the patients in the cohort are followed for the same duration of time, the *cohort* approach can be used to estimate survival. The cohort approach is considered the gold standard[85,88] because all patients diagnosed during a specific period of time have had the opportunity to be followed for the full follow-up duration (for instance 1, 5 or 10 years). For example, if we want to estimate 10-year survival for the cancer patients included in this thesis [Figure 3.1], the cohort approach can be used for all patients diagnosed during 2000-2004, since all patients have a potential follow-up of at least 10 years by the end of 2015. Their conditional probabilities of surviving to the end of a given year are multiplied within successive calendar years (along the row) to obtain a cumulative probability of surviving up to ten years (solid outlines). However, for patients diagnosed during more recent periods (2005-2009 and 2010-2013), the cohort approach cannot be used to estimate 10-year survival, since not all the patients have the full ten-years of follow-up information. Other approaches are then required.

3.4.2 Complete approach

The *complete* approach, a variant of the standard cohort approach, can be used when not all patients have been followed for the same time, but there is at least one year of diagnosis for which patients have had the opportunity to be followed for the entire duration we want to analyse. In the same example, the complete approach can be used to estimate 10-year survival for patients diagnosed during 2005-2009, even when only patients diagnosed during 2005 have had the opportunity to be followed for at least ten years by the end of 2015 (dashed lines). The survival experiences for all the patients diagnosed in the five-year period (2005-2009) would be used in the analysis, and patients recently diagnosed would only contribute to some of the conditional survival probabilities. Therefore, in addition to timeliness, the complete approach has the advantage of efficiently using all the available

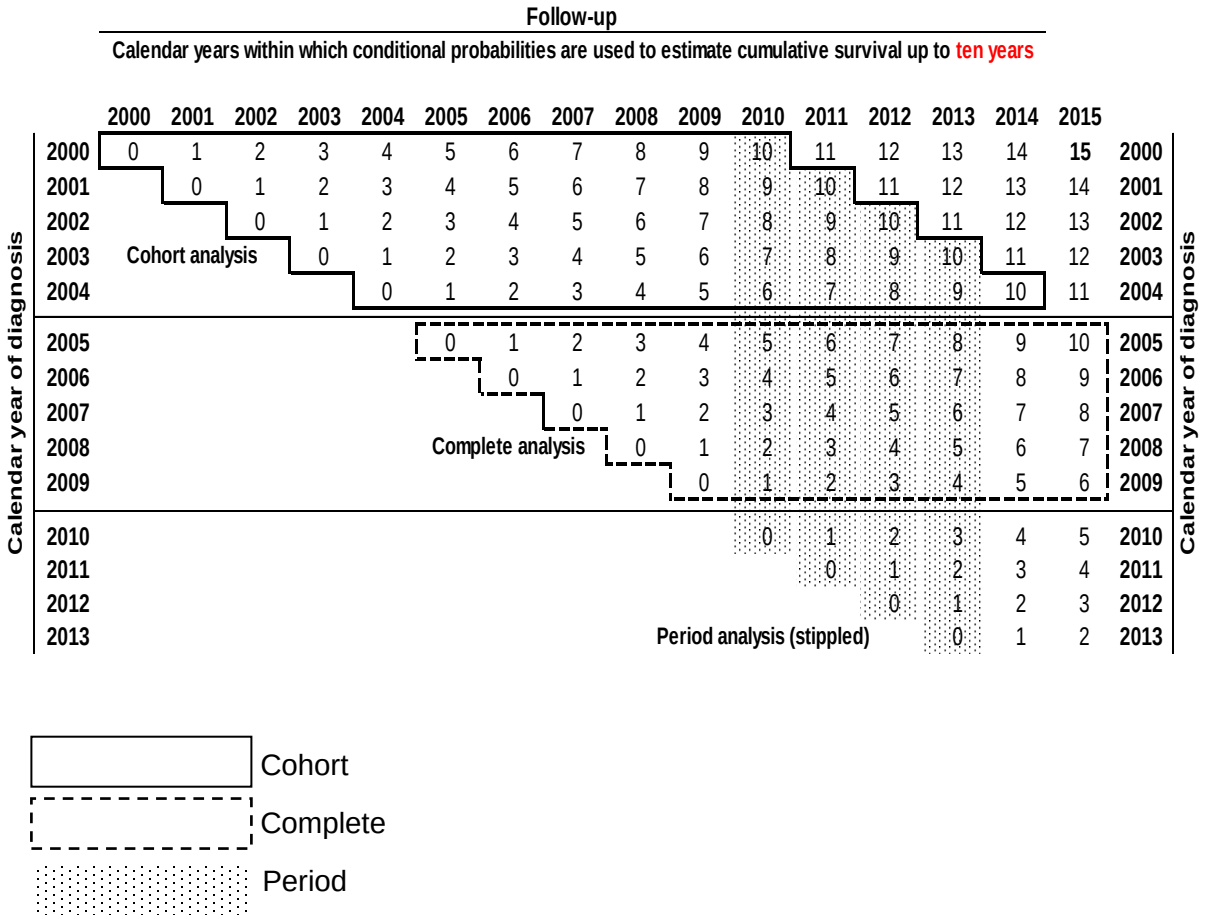
follow-up data to estimate survival, even though not all the patients have full-term follow-up data.[85,89]

3.4.3 Period approach

The *period* approach provides a short-term prediction of survival for those patients for whom follow-up is not available for the required duration, by using the conditional survival experience of patients who were diagnosed earlier. For example, the *period* approach can be used to estimate 10-year survival for patients diagnosed during 2010-2013 [Figure 3.1]. This entails using the past experience of patients diagnosed between 2000 and 2013, conditional on them still being alive at some point during the period 2010-2013 (stippled areas). Survival for the 2010-2013 cohort can then be estimated by multiplying the conditional probabilities of survival within each calendar year (column) for patients diagnosed throughout 2000-2013. For instance, survival during the first year after diagnosis is estimated using the survival experience of patients diagnosed during 2010-2013, and survival for the second year is estimated from patients diagnosed during 2009-2012, and for the third year from 2008-2011, and so forth. The assumption is that the conditional survival probabilities observed during 2010-2013 will remain equivalent to the survival probabilities observed in each later year, up to ten years since diagnosis. The measure of life expectancy at birth also depends on this assumption, where the life expectancy for a baby born today is derived from the latest available patterns of mortality for each age and sex.

Compared to the *cohort* approach, the *period* approach better predicts prognosis of recently diagnosed patients, for whom full follow-up time is not available. It is also able to detect possible changes in survival more promptly than the cohort approach.[89-91]

Figure 3.1 Cohort, complete and period approaches to survival estimation



3.5 Age standardisation

Age-standardisation is vital when comparing net survival estimates for all ages combined, because net survival can vary considerably by age, and the age structure of cancer patients differs between countries and over time. Therefore, comparisons between un-standardised cancer survival estimates for all ages combined between countries or over time are inappropriate.

In order to produce age-standardised survival estimates, age-specific survival estimates are required for each age group. The age-specific weights recommended for cancer survival analyses are is the International Cancer Survival Standard (ICSS) weights,[92] derived from a population of cancer patients rather than the general population. Three sets of weights probabilities provided depend on the type of cancer. The first set is for cancers where the incidence increases rapidly with age, such as lung. The second, for cancers like brain, that usually peak in the younger and older ages but are less common in the middle-age-groups, while the third is for cancers such as Hodgkin's lymphoma that are more common among the young.

To produce age-specific estimates for each cancer, age at diagnosis is categorised into 5 groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years. For prostate cancer, 5 different age groups are used: 15-54, 55-64, 65-74, 75-84 and 85-99 years. The age-specific survival estimates are then multiplied by the corresponding age-specific weights, to represent age-specific estimates that are proportionate to the standard population. The age-standardised survival estimate for all age groups combined is then given by the weighted average of the age-specific survival estimates.

Using the same sets of weights when comparing age-standardised estimates over time or between different regions ensures that differences are not due to different weights, and that differences in the age-structure of the cancer patient groups being compared will not contribute to observed differences in survival.

Summary

- ✓ Population-based survival (net survival) is a key indicator to evaluate the overall effectiveness of the health system in managing cancer.
- ✓ To estimate net survival, the relative survival setting is preferred, since it does not require information on the cause of death.
- ✓ Different designs of analysis are used depending on the purpose and availability of follow-up data.
- ✓ Complete and reliable data on follow-up for vital status, that includes deaths due to any cause, are required to obtain robust survival estimates.

What's next?

- ✓ How do we obtain complete data on follow-up for vital status for all Kuwaiti cancer patients?

Chapter 4: Research paper I**; Obtaining data on follow-up for vital status**

Monitoring survival, alongside incidence and mortality, is essential when assessing progress in cancer control.[16] In Kuwait, incidence and mortality are routinely produced and monitored but population-based survival estimates are not. This is mainly due to the unavailability of complete information on vital status for all cancer patients.

In order to produce robust population-based net survival estimates, it is necessary to have the full date (day, month and year) of both the cancer diagnosis and the last known vital status for all patients. When the patient has died, the date of death is required, regardless of the cause of death.[93]

Complete and high-quality information on cancer diagnosis is available from the Kuwait Cancer Registry (KCR). However, with respect to vital status information, the KCR is only able to capture cancer patients' deaths if the cause was attributed to caner. Cancer patients whose death was certified as attributable to other causes are not reported, and those patients are, in effect, "immortal" in the registry's database.

The following chapter completes the first objective of the thesis: to obtain accurate and complete follow-up data on the last known vital status for all Kuwaiti cancer patients registered in Kuwait between 2000 and 2013. This is essential for robust estimation of population-based survival.

This objective was achieved through the implementation of a new approach, performed in a series of semi-manual steps, since records are not yet electronically linked. The first step was to obtain government-issued Civil ID numbers (IDs) of patients registered during 2000-2013 from the Kuwait Cancer Registry. The second step involved both electronic and manual tracing of missing IDs using the Ministry of Health's Information System or via the patient's medical records. If patients' IDs were not available following these tracing

procedures, the vital status for the patients was recorded as “lost to follow-up”. The third step was to update the vital status for patients whose vital status was not known in the registry. This was performed by manually entering the IDs in the Public Authority of Civil Information (PACI) database, to ascertain whether the patient was dead or alive. To obtain the date of death for the deceased patients, IDs were then manually entered and searched in the electronic archive of “Death Announcements” at the Ministry of Health’s Central Records Department of Births and Deaths. Patients not found to be dead were considered alive as on 31 December 2015.

Unlike the traditional method used by the registry, this new approach enabled ascertainment of cancer patients’ deaths due to any cause, not just deaths due to cancer. It was shown to be highly effective, resolving the vital status and, if dead, the date of death, for almost all (98.3%) patients whose vital status had previously been unknown; remarkably improving the quality of the cancer patients’ vital statistics and enabling net survival analyses to be performed for the first time.

It was due to work presented in the following paper that made this possible for the Kuwaiti data to be included in the third cycle of the CONCORD programme for global surveillance of cancer survival.

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SECTION A – Student Details

Student	Eiman Alawadhi
Principal Supervisor	Dr.Claudia Allemani
Thesis Title	A novel approach to obtain follow-up data on the vital status of registered cancer patients: the Kuwait cancer registry experience

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?	The Gulf Journal of Oncology		
When was the work published?	29 January, 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	Eiman Alawadhi was the lead and corresponding author. She was reponsible for planning and carring out the literature review, data analysis, and drafting the paper. The co-authors assissted in planning the content of the paper, and provided input on the data analysis and feedback on the draft.

Student Signature: [redacted] **Date:** 15 March 2019

Supervisor Signature [redacted] **Date:** 15 March 2019

Research paper I [published]

A novel approach to obtain follow-up data on the vital status of registered cancer patients: the Kuwait Cancer Registry experience

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Introduction

Cancer is the second most common cause of death in Kuwait, following diseases of the circulatory system.[94] Reducing cancer-related deaths can be achieved primarily in two ways: by reducing cancer risk, or by improving the health-care system in terms of management and treatment of cancer patients.[83] Population-based cancer survival is a key measure of the effectiveness of a health system in managing cancer.[83,84] Monitoring survival over time, between sub-populations and between countries, is also crucial for assessing inequalities and driving policies for cancer control.[21,95]

The aim of population-based survival analysis is to estimate net survival for all cancer patients diagnosed in a given region over time. Net survival represents the cumulative probability for cancer patients to survive their cancer up to a given time (say, 5 years) since diagnosis, after controlling for competing risks of death (background mortality).[86] Net survival can be measured in two contexts: a cause-specific setting, when the exact cause of death is known and accurately reported, or a relative survival setting, when the exact cause of death is unknown, unreliable or inaccessible.

Cause-specific survival estimation requires information on the underlying cause of death, and uses as an end-point those deaths that were attributed to cancer. Patients who die from other causes are censored, in order to estimate the cancer-specific hazard of death (excess hazard). This approach relies on the assumption that the death certification and the coding of the underlying cause of death are accurate. However, due to the variability in determining the cause of death accurately between physicians, hospitals, and countries, cause-specific

survival estimates are not considered suitable for comparisons between countries or over time.[74,75,77]

The procedure for coding the underlying cause of death also differs between countries. For example, the procedures are different in Kuwait and the United Kingdom (Figure 4.1). In Kuwait, the “Death Announcement” is similar to the Medical Certificate of Cause of Death (MCCD) used in the UK,[96] which includes a section on the cause of death. Both are completed by physicians or hospital authorities, in accordance with the World Health Organisation (WHO) recommendations in the International Statistical Classification of Diseases and Related Health Problems (ICD).[97] However, the categories used to report cancer as the underlying cause of death differ in the two countries (Figure 4.1). The Kuwait Cancer Registry (KCR) reports the cause of death as “due to cancer” if either the first line (a) of the Death Announcement (the so-called “immediate cause” of death) or the third and last line (c) of the Death Announcement (the so-called “original or underlying cause” of death) is a cancer-related condition. The second line (b) of the Death Announcement is not coded, and will not be considered as the underlying cause of death even if the last line is not completed. In the UK, all three lines (Ia, Ib, Ic) of the sequence of events leading to death on the MCCD are taken into account to determine the underlying cause of death. This difference in coding the underlying cause of death may lead to under-estimation of cancer mortality rates in Kuwait, compared to the UK. Even minor misclassifications of the underlying cause of death have been shown to result in large changes in net survival estimates.[98] In addition, cause-specific estimates tend to be higher than relative survival estimates,[98,99] therefore overemphasising the effectiveness of the health system in dealing with cancer.

Estimating cancer survival within a relative survival framework eliminates any differences or inaccuracies in certifying or coding the underlying cause of death, because the cause of death is not required for analysis. Relative survival is estimated as the ratio of the cancer

patients' all-cause survival, where the endpoint is death from all causes, to the survival that the patients would have experienced if they had had the same background mortality as the general population (expected survival).[85,100] Expected survival is estimated from population life tables that adequately represent the all-cause mortality experience of the population under study.[101-103] The relative survival framework is more appropriate for the estimation and comparison of net survival.[81,98,104,105]

To produce reliable and accurate population-based survival estimates, it is necessary to have complete, reliable and long-term data for all patients diagnosed with cancer in a defined geographical area. It is thus imperative to have accurate and complete data on the date of diagnosis, the last known vital status and the date of last known vital status. When the patient has died, it is essential to know the date of death, regardless of the cause.

Many countries are able to maintain long-standing, high-quality population-based cancer registries and provide accurate incidence data. However, it is becoming increasingly difficult to obtain follow-up data and ascertain complete vital status for all patients. Many countries, including high-income countries such as Canada and Saudi Arabia, have reported difficulties in accessing this information for all cancer patients, due to technical, legal or administrative barriers.[81] A recent international meeting on strengthening the health system and breast cancer care in the Middle Eastern countries, organised by the Harvard Medical School Center for Global Health Delivery in Dubai,[106] highlighted the fact that even in high-income Middle Eastern countries, efficient civil registration and availability of unique identification codes, both crucial to obtain the data on follow-up for vital status, are still problematic. Such difficulties hinder robust survival estimation and, in many cases, prevent survival estimates from being produced at all.

An example of a national population-based registry that maintains high-quality cancer incidence data for the whole country is the Kuwait Cancer Registry (KCR), a department of the Kuwait Cancer Control Centre (KCCC).[107] However, complete data on vital status for *all*

registered cancer patients are not available, since the registry has only been able to capture information on deaths due to cancer.

This study presents a novel approach to obtain accurate and complete follow-up data on the last known vital status and the date of last known vital status, as on 31 December 2015, of all Kuwaiti cancer patients registered between 2000 and 2013, thus enabling robust estimation of population-based survival in Kuwait.

Materials and Methods

Data on 12,469 patients diagnosed during 2000-2013 were obtained from the KCR database, including the patient's hospital file number, the Civil ID number where available, and the date of diagnosis (Figure 4.2, step 1). The Civil ID number was missing for 2,026 patients, and it was necessary to obtain these numbers, either electronically from the Health Information System or manually through the medical records (Figure 4.2, step 2), so that the records for all patients could then be manually linked with the Public Authority of Civil Information (PACI) database. The PACI database is considered to be the most reliable and up-to-date source to obtain the last known vital status, and the date of last known vital status, of any person resident in Kuwait, provided that their Civil ID number is known.

Only Kuwaiti patients were included in this study, since vital status information for non-Kuwaitis is relatively incomplete. Non-Kuwaiti residents are mostly expatriate labourers employed with short contracts (e.g. two-year contracts) who generally choose to return home upon completion of their contracts or when they become terminally ill. Although the vital status (alive or dead) of non-Kuwaitis in Kuwait is also recorded in the PACI database, it cannot be used to track the vital status of persons who have left the country. Therefore, the vital status data for non-Kuwaitis are incomplete.

Tracing of Civil ID numbers

To obtain the Civil ID number for Kuwaiti patients for whom it was not available, an "electronic search" using the patient's hospital file number was queried from the Health Ministry's Health Information System (HIS) database. If the Civil ID number was not available in the HIS system, a "manual search" was performed: the patient's hospital file number was used to locate and check the physical medical file in the Medical Records Department at the KCCC, in order to identify the Civil ID number of each patient. This step was performed twice (once at the beginning of this tracing process and once after 6 months), to increase the prospect of locating patients' files that might previously have been misplaced.

If the Civil ID number could not be traced, but a date of last known vital status earlier than 31 December 2015 was available in the medical records, this date was extracted to update the database. These patients were considered lost to follow-up and will contribute to survival analysis until that date.

Vital status and date of last known vital status update

To obtain follow-up data on last known vital status and date of last known vital status, a list of Civil ID numbers, sorted by year of diagnosis, was printed. Direct linkage with the PACI database was not permitted, therefore indirect access was granted through the Central Records Department of Births and Deaths at the Ministry of Health. Employees from this Department who have access to the PACI database manually entered the Civil ID numbers to determine each patient's vital status. If the patient was alive, the employee recorded the status as "alive" on the printed sheet. If the patient was dead, the employee used the patient's Civil ID number to access the Central Records Department's computerised database in order to obtain the exact date of death from the electronic archive of "Death Announcements", which is updated on a continuous basis. Each cancer patient's updated vital status was then entered manually into our existing cancer dataset, matched to the

patient's record with the corresponding Civil ID and file numbers. The vital status was recorded as *alive* at 31 December 2015 for patients who were alive, or *dead*, with the date of death, for deceased patients.

Quality control

To ensure the correct transfer of vital status data from hard copy to the electronic database, data entry was verified by checking every 10th record on the hard copy with the vital status data that had been entered. This process was performed on all the records that had been linked with the PACI database, and errors were corrected. All dates of death entered manually were also double-checked, to ensure correct transfer from the hard copy to the electronic database.

Results

During 2000-2013, Civil ID numbers were available in the registry for 10,443 (83.7%) of 12,469 Kuwaiti cancer patients registered (Table 4.1; Figure 4.2, step 1). Among these patients, 2,781 were known to be "dead", with the cause of death attributed to cancer, while the vital status was unknown for the remaining 7,662 patients (61.4%).

The Civil ID number was not available for 2,026 patients (16.3%). Of these, 694 were known to be dead due to cancer, while the vital status of the remaining 1,332 (10.7%) patients was not known and needed to be traced and updated.

Most of the patients with unknown vital status and without Civil IDs had been diagnosed during 2000-2004; the proportion dropped from 35.4% to 0.5% for those diagnosed during 2010-2013 (Table 4.2; Figure 4.2, step 2). This combination of manual and electronic search enabled tracing of 1,175 out of 1,332 Civil ID numbers; 157 Civil ID numbers remained unavailable. However, for these patients, a date of last known vital status earlier than 31 December 2015 was available from the medical records. Therefore, these patients were considered lost to follow-up at that date. The overall proportion of patients without a Civil ID

who would be considered lost to follow-up decreased from 10.7% to 1.3%. The impact of this tracing was most marked for patients diagnosed during 2000-2004, among whom the percentage whose Civil IDs were not available fell from 35.4% to 3.7%.

Tracing the Civil ID numbers enabled the vital status to be reliably ascertained through the PACI database, and updated for 8,837 (98.3%) of 8,994 of patients for whom it was initially unknown (Table 4.3; Figure 4.2, step 3). As a result, the number known to be dead rose by 2,131. The proportion of total deaths increased from 27.9% (3,475 patients, of which 2,781 had Civil ID numbers and 694 did not) to 45.0% (5,606 patients, including 3,475 known to be dead due to cancer and 2,131 known to be dead due to other causes). About 54% (6,706) out of the 12,469 patients were shown to be alive, leaving only 157 classified as lost to follow-up.

Discussion

We present a novel approach to obtain complete follow-up data on the vital status of all Kuwaiti cancer patients. This approach enabled us to update the vital status for most (98.3%) Kuwaiti cancer patients registered during the period 2000 to 2013.

Of the deaths occurring by 31 December 2015 among cancer patients registered during 2000-2013, only 62.0% (3,475 of 5,606) had initially been recorded in the KCR database through the traditional follow-up method, relying solely on deaths that had been certified as due to cancer.

The process of tracing Civil ID numbers enabled ascertainment of the vital status for almost all registered cancer patients, including all deaths, regardless of the cause. This had a substantial impact on the proportion of cancer patients who were known to be dead, which rose from 27.9% to 45.0%, while the proportion considered to be alive at the end of follow-up dropped from 72.1% to 53.7%.

The most evident changes resulting from tracing the Civil ID numbers occurred during 2000-2004, where the proportion of patients without Civil IDs and with unknown vital status was much greater (52.5%) than in 2005-2009 (3.1%) and in 2010-2014 (1.1%). This difference was probably due to several improvements in KCR registration practices, implemented over the years: the routine practice of obtaining the patients' Civil ID during registration was progressively enforced, resulting in lower numbers of patients without ID numbers. The availability of Civil IDs is crucial to the implementation of our approach: a higher proportion of IDs made linkage between the cancer registry data and the patients' vital status records more effective. Complete and accurate data on follow-up for vital status are essential to enable robust estimation of population-based cancer survival.

Observed survival (also called all-cause survival) can be useful in predictive tools and cost-effectiveness analyses,[82] but it cannot be used to provide information on the probability of surviving a specific cancer, or to examine cancer survival trends within a given country, because its estimation also includes deaths from causes other than cancer (competing risks of death), which are likely to be decreasing over time due to continuous medical advancement. Similarly, observed survival estimates cannot be used for international comparisons of cancer survival, since background mortality also varies very widely between countries.[103,108,109] Estimates of observed survival can also substantially over-estimate the true observed survival if based only on deaths that were certified or coded as due to cancer, because deaths from causes other than cancer are not included in the computation.

The accuracy of death certification and of the coding of the underlying cause of death can vary between countries and over time within a country. These can arise from inaccuracies in the certification of death when compared with autopsy findings and clinical data, differences among physicians in completing the death certificates, and variations in coding the underlying the cause of death.[74,75,77] Inaccuracies in certifying the cause of death have been found in Kuwait when original death certificates were compared with the patients'

medical records, indicating poor agreement in the certification of death between the original and revised certificates.[110]

Other differences in death registration practices can arise from changes to the death certificate forms used in a country, when coding rules are updated or revisions of the ICD are introduced, from changes in diagnostic terminology and measurement, or when there is a lack of training in certifying the cause of death.[111-113]

For all these reasons, international comparisons of population-based cancer survival require statistical methods that do not rely on the cause of death (net survival). By eliminating the effect of background mortality, differences and trends in net survival reflect differences in cancer outcome, rather than differences in competing causes of death. Net survival estimates are thus better suited for international comparisons and to evaluate the impact of changes in health policy over time.

Our approach to obtain follow-up data through individual record linkage between the KCR database and the PACI database provides the most complete and up-to-date information on the vital status for almost all Kuwaiti cancer patients. However, to conduct this update manually is labour-intensive and time-consuming, and requires extensive quality checks on the manual entry and extraction of data. If performed efficiently, electronic linkage between the cancer registry database and the vital status data stored in the PACI database would be more accurate and timely, but it is more complex and requires ministerial agreement and collaboration.

The use of this novel approach will provide the Kuwait Cancer Registry with more accurate and complete information on Kuwaiti cancer patients' vital status, on a routine basis. It will allow clear distinction between patients who are alive and patients who are dead from any cause (i.e. not just those who have died from cancer). These data, together with the use of

appropriate life tables of background mortality, would enable Kuwait to monitor routinely net survival trends and to compare cancer survival in Kuwait with survival in other countries.

Conclusion

Robust estimates of population-based cancer survival are crucial to assess the effectiveness of the health system in managing cancer. Complete and reliable data on follow-up for vital status of *all* cancer patients, regardless of the cause of death, are essential to produce robust cancer survival estimates that can be monitored over time and compared internationally.

Prior to this study, there was no system to update the vital status for all Kuwaiti cancer patients. With support from the Kuwait Ministry of Health and the Ministry of Interior/PACI this approach could be performed routinely by the KCR to ensure (a) that virtually all deaths of Kuwaiti cancer patients, regardless of the cause, are systematically recorded; and (b) that the follow-up on the vital status of all cancer patients is accurately updated through record linkage between the KCR database and the PACI database. The ultimate goal would be to establish routine electronic linkages with the PACI system, making the process more efficient and timely.

Several countries in the Gulf Cooperation Council (e.g. Qatar, Bahrain and United Arab Emirates) have an administrative system similar to the one in Kuwait. This study may assist cancer registries in these countries to integrate the conceptual framework in their administrative system, to improve their follow-up procedures and to enhance the quality of cancer patients' vital statistics.

Figures

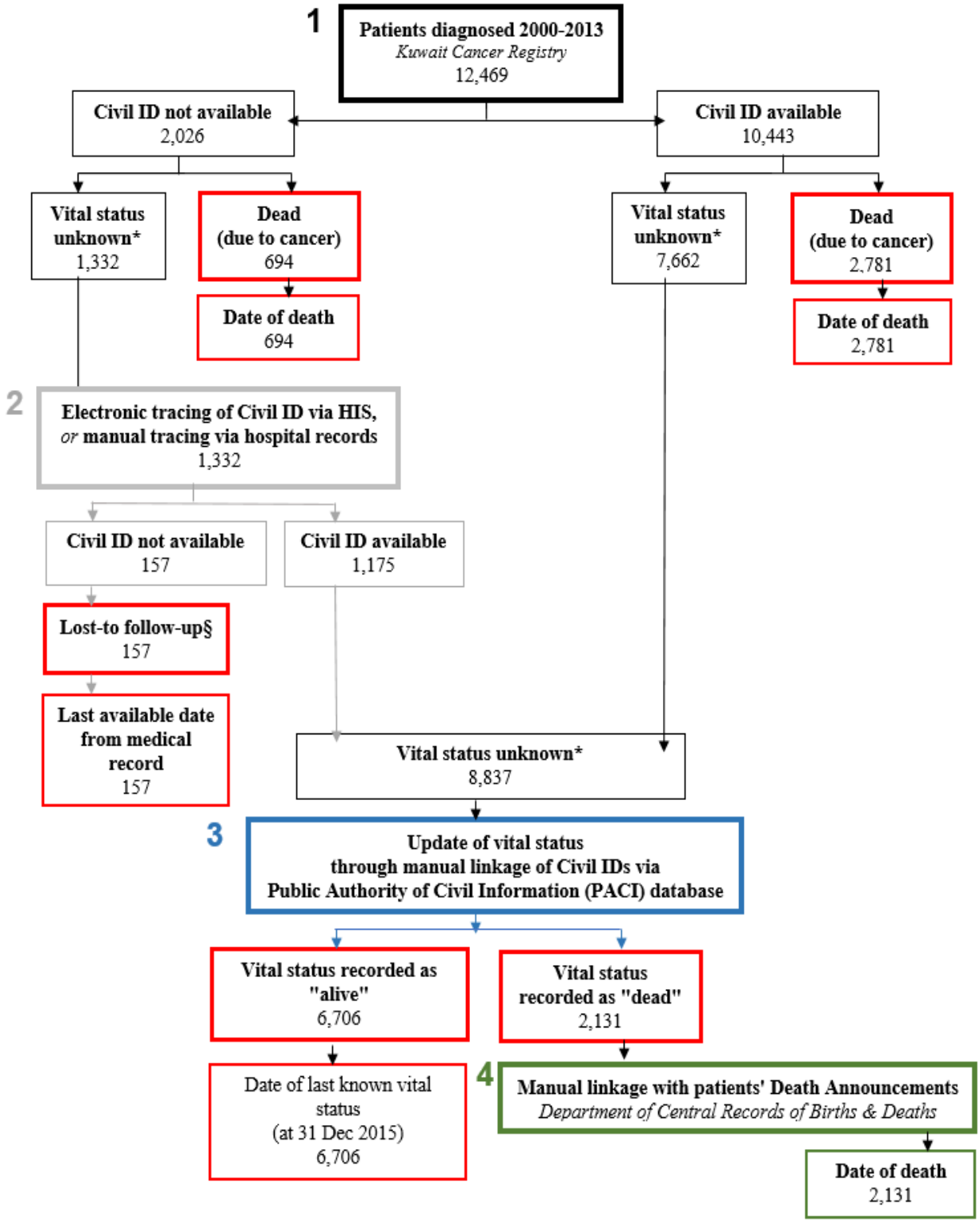
Figure 4.1 An example of the "cause of death" sections of the UK's Medical Certificate of Cause of Death (MCCD) and of the Kuwait Death Announcement, used to determine the underlying cause of death

Medical Certificate of Cause of Death in the UK		
Cause of death *the disease or condition thought to be the underlying cause should appear in the lowest completed line of part I*		
I	(a) *disease or condition leading directly to death*	*Intraperitoneal haemorrhage*
	(b) *other disease or condition, if any, leading to* I(a)	*Ruptured metastatic deposit in liver*
	(c) *other disease or condition, if any, leading to* I(b)	*Primary adenocarcinoma of colon*
II	*Other significant conditions* **contributing to death** *but not related to the disease or condition causing it*	*Non-insulin dependent diabetes mellitus*

Death Announcement in Kuwait	
Deaths in less than a week old children	**Deaths in more than a week olds**
Basic disease or condition in child [ ][ ][ ][ ]	(a) Immediate cause: *Intraperitoneal Haemorrhage* [K][6][6][1]
Other disease or condition in child	(b) Secondary cause: *Ruptured metastatic deposit in liver*
Disease or condition in mother that led to child's death [ ][ ][ ][ ][ ]	(c) Original/ Underlying cause: *Primary adenocarcinoma of colon* [C][1][8][9]

*Death Announcements in Kuwait are completed in Arabic with exception to the codes.

Figure 4.2 Process of updating patients' vital status



*Unknown vital status: patients not reported as dead due to cancer; HIS: Health Information System
§ Patients reported alive in medical records, at a specific date prior to 31 December 2018

Tables

Table 4.1 Number of Kuwaiti cancer patients, with and without Civil ID numbers, by period of diagnosis

	Calendar period of diagnosis							
	No.	%	No.	%	No.	%	No.	%
	2000-04		2005-09		2010-13		All periods	
All patients	**3,489**		**4,545**		**4,435**		**12,469**	
Civil ID number available	**1,656**	**47.5**	**4,402**	**96.9**	**4,385**	**98.9**	**10,443**	**83.7**
Dead (due to cancer)	496	14.2	1,400	30.8	885	20.0	2,781	22.3
Unknown vital status	**1,160**	**33.3**	**3,002**	**66.1**	**3,500**	**78.9**	**7,662**	**61.4**
Civil ID number not available	**1,833**	**52.5**	**143**	**3.1**	**50**	**1.1**	**2,026**	**16.3**
Dead (due to cancer)	597	17.1	69	1.5	28	0.6	694	5.6
Unknown vital status	**1,236**	**35.4**	**74**	**1.6**	**22**	**0.5**	**1,332**	**10.7**

Table 4.2 Kuwaiti patients with unknown vital status and Civil ID numbers not available, before and after the tracing

	Calendar period of diagnosis							
	No.	%	No.	%	No.	%	No.	%
Unknown vital status	2000-04		2005-09		2010-13		All periods	
Before Tracing								
Civil ID number not available	1,236	**35.4**	74	**1.6**	22	**0.5**	1,332	**10.7**
After tracing								
Civil ID number traced	1,107	31.7	49	1.1	19	0.4	1,175	9.4
Civil ID number not available	129	**3.7**	25	**0.5**	3	**0.1**	157	**1.3**

Unknown vital status: patients not reported as dead due to cancer

Table 4.3 Vital status, pre- and post-update: Kuwaiti cancer patients diagnosed during 2000-2013

	Pre-update		Post update	
Vital Status	**No.**	**%**	**No.**	**%**
Dead (due to cancer)	3,475	27.9	-	-
Dead (due to any cause)	-	-	5,606	45.0
Alive	-	-	6,706	53.7
Lost to follow-up	-	-	157	1.3
Unknown*	8,994	72.1	-	-
Total	**12,469**	100.0	**12,469**	100.0

* These patients were presumed alive (not known to be dead) in the KCR before applying our approach to update the follow-up data

Chapter 5: Research paper II; Population-based cancer survival in Kuwait

To produce robust population-based net survival estimates, complete and accurate data are required on the date of cancer diagnosis, the last known vital status and, for those patients who have died, the date of death, irrespective of the cause. To estimate the survival of all patients diagnosed with cancer in a given population is crucial to assess the overall effectiveness of the health-care system in managing cancer. One of the goals of the 2013 World Cancer Declaration is to achieve worldwide improvement in cancer survival by 2020. In order to achieve this goal, routine measurement and monitoring of survival is imperative.

Through the work presented in Chapter 5, complete and reliable data on follow-up for vital status were obtained for all Kuwaiti patients registered in the Kuwait Cancer Registry during 2000-2013. This was the first time such data had become available, providing Kuwait with the first population-based 5-year net survival estimates for Kuwaiti patients diagnosed with one of 18 common cancers during 2000-2013. It also enabled Kuwait to participate in the third cycle of the CONCORD programme on the global surveillance of cancer survival.[81]

In the following chapter, I proceed to use the CONCORD programme protocol and data quality control procedures, as well as the same design of analysis and statistical methods, to extend the analyses, to produce population-based survival estimates at 1, 3 and 5 years, and to monitor survival trends over 14 years, for three calendar periods (2000-2004, 2005-2009 and 2010-2013) and sex.

The inclusion of this dataset in the CONCORD programme has allowed appropriate comparisons between Kuwait and 70 other countries also included in CONCORD-3. The emphasis, however, was placed mainly on comparisons between Kuwait and other high-income countries, where discrepancies in survival were noted and discussed.

This chapter fulfils the second objective of my thesis: to produce net survival estimates for Kuwait that could be monitored and compared internationally, in order to facilitate the assessment of cancer control strategies.

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SECTION A – Student Details

Student	Eiman Alawadhi
Principal Supervisor	Dr.Claudia Allemani
Thesis Title	Cancer survival trends in Kuwait, 2000-2013: a population-based study

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?	The Gulf Journal of Oncology		
When was the work published?	29 January, 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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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)	Eiman Alawadhi was the lead and corresponding author on the paper. She was responsible for planning and carring out the literature review, data analysis, and drafting the paper. The co-authors assissted in planning the content of the paper, and provided input on the data analysis and feedback on the draft.

Student Signature: [redacted] **Date:** 15 March 2019

Supervisor Signature: [redacted] **Date:** 15 March 2019

Research paper II [published]

Cancer survival trends in Kuwait, 2000-2013: A population-based study

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Introduction

Cancer is the second most common cause of death in Kuwait, after cardiovascular diseases.[94] To evaluate the effectiveness of health systems in controlling the cancer burden and preventing cancer-related deaths, three population-based metrics need to be assessed: incidence, survival and mortality.[16] Population-based metrics are obtained using data on *all* cancer patients residing in a defined geographic area. These data are collected by population-based cancer registries. While trends in cancer incidence and mortality are routinely monitored in Kuwait, population-based cancer survival trends are not.

Because survival time is dependent on two events, diagnosis and death, complete data on the eventual death of all cancer patients, regardless of the cause of death, are required to produce reliable and accurate survival estimates.[80] Producing population-based cancer survival estimates from complete and good-quality data for Kuwait is important for several reasons. Firstly, population-based survival represents a reliable measure for assessing the effectiveness of all aspects of the health system, from awareness and diagnosis to the system's ability to treat and cure cancer. Age-standardised survival estimates are essential for making valid comparisons over time, between sub-populations and countries, to guide cancer control policies.[83] To understand progress against cancer fully, therefore, it is essential to assess survival estimates alongside incidence and mortality.

This study aims to produce a comprehensive profile of population-based cancer survival in Kuwait: robust estimates of net survival up to 5 years for 18 common cancers that can be monitored and compared internationally to facilitate assessment of cancer control in Kuwait.

Material and methods

The data used in this study were obtained from the Kuwait Cancer Registry (KCR). Cancer notification in Kuwait is mandatory by ministerial regulation. The KCR is considered to be a comprehensive source of information for all cancer patients diagnosed or treated in Kuwait. Kuwait incidence data on patients diagnosed since 1979 have been published in "Cancer Incidence in Five Continents",[114] which is generally considered an imprimatur of high-quality data.

The KCR maintains an index of all cancer patients through collecting information on malignant neoplasms according to the International Association of Cancer Registries (IACR) guidelines (www.iarc.fr). Since January 2000, the registry has adopted the third edition of the International Classification of Diseases for Oncology (ICD-O-3)[115] for all clinical coding, including topography, morphology and behaviour.

Data were obtained for Kuwaiti adults (age 15-99 years) and children (age 0-14 years) diagnosed between 1 January 2000 and 31 December 2013 with one of 18 cancers or groups of cancers: oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast (women), cervix, ovary, prostate and melanoma of the skin in adults, together with brain tumours, leukaemias and lymphomas in both adults and children.

Data were collected according to the CONCORD protocol.[81] Topography and morphology were coded to the International Classification of Diseases for Oncology (third edition, ICD-O-3),[115] including its first revision.[116] Solid tumours were defined by anatomical site (topography), while leukaemias, lymphomas and melanoma of the skin were defined by morphology (Table 5.1).

The KCR provided data for all haematopoietic malignancies (ICD-O-3 morphology codes in the range 9590-9992) in adults and children. For adults, we analysed “lymphoid (HAEMACARE groups 1-19)” or “myeloid (HAEMACARE groups 20-25)” malignancies, in

consultation with specialists in the HAEMACARE[117] and InterLymph[118] working groups (Table 5.2). For children, we analysed survival for acute lymphoblastic leukaemia (ALL) and lymphomas, based on the International Classification of Childhood Cancer 3rd edition (ICCC-3)[119] (Table 5.3).

Only primary, invasive malignancies (ICD-O behaviour code 3) were included in survival analyses. The only exception was brain tumours, where tumours of benign or uncertain behaviour (code 0 or 1) were also included (Table 5.4). Other ineligibilities included records that were incomplete or outside the age range specified in the CONCORD protocol, as well as tumours that were metastatic from another primary site, or were unknown whether primary or metastatic.

Follow-up data on each patient's vital status (alive, dead, lost to follow-up), at 31 December 2014, were obtained through a mixture of passive and active methods, to include all deaths regardless of the cause of death. Passive follow-up is the term used when cancer registries routinely receive notification of deaths from a vital statistics office, or when they link cancer registrations to vital statistics records at routine intervals, using unique identifiers such as name or identity numbers. Active follow-up refers to the process whereby a registry actively seeks data on the vital status for each patient via direct contact with hospitals, the patient's family or local authorities.[80,120] The follow-up procedures in this study involved a series of steps that included identifying the unique national identification numbers (Civil ID numbers) of all the Kuwaiti patients, and manually linking them to the country's centralised registration database, the Public Authority of Civil Information (PACI). This provided accurate information on all deaths, irrespective of whether the cause of death was cancer-related. The dates of death for deceased patients were obtained by manual search of the Civil ID numbers from the electronically archived "Death Announcements" at the Central Records Department of Births and Deaths. In cases where the patient's vital status could not be ascertained, the date when the patient was last known to be alive was extracted from the

patient's medical hospital files: the tumour registry record was updated, the vital status was recorded as "lost to follow-up", and the patient was censored from analysis at the date he or she was last known to be alive.

Quality control

Quality and completeness were assessed using the standardised quality-control procedures from the CONCORD programme for global surveillance of cancer survival.[81]

The data quality checks were performed in three consecutive phases. Phase one, *protocol adherence*, examines each individual variable within a given record for compliance with the CONCORD protocol. Phase two, *exclusions*, assesses logical coherence between the variables in each tumour record, and excludes records, such as tumours known to the registry only from a death certificate, or detected solely through autopsy. These records must be excluded from survival analyses since follow-up time is not available. Other exclusions are related to records with vital status unknown, or an invalid date sequence, or inconsistencies between sex and site, site and morphology, age and site, or age and site and morphology.

Duplicate registrations were also excluded. When two or more primary, invasive malignancies with the same site existed in the same person and the records had the same date of diagnosis, the record with the most complete information was retained. If these records presented different dates of diagnosis, the record with the earliest date of diagnosis was retained.

Phase three, *editorial*, evaluates, for each cancer, the distribution of key data quality indicators. Table 5.4 provides a summary of the records that were excluded from survival analysis, and the number of patients included in analyses, together with the distribution of the quality indicators.

Statistical analysis

We estimated net survival for patients diagnosed with one of 18 malignancies during 2000-2004, 2005-2009 and 2010-2013. Survival was estimated at 1, 3 and 5 years after diagnosis, for males, females and both sexes combined.

For patients diagnosed in 2000-2004 and in 2005-2009, for whom follow-up was available for the full duration of the survival analysis (either one, three or five years), estimates were produced using the cohort approach. The cohort approach is considered the gold standard,[88] because it provides a survival estimate for a cohort of patients who were all diagnosed during the same year or calendar period and followed up for at least the duration for which survival estimates are required, in this case 1, 3 or 5 years. For 2010-2013, we applied the "period" approach,[90] which offers reliable prediction of the eventual survival of recently diagnosed patients who have not all been followed up for the whole time of analysis.

Net survival is the term used to describe the probability that cancer patients survive their cancer up to a given time (e.g. five years) following diagnosis, after controlling for competing causes of death (background mortality).[121] To control for background mortality, we used life tables of all-cause mortality in the general population.[103] Life tables were constructed by single year of age ("complete" life tables), sex, calendar year of death and ethnicity (Kuwaiti, non-Kuwaiti).

To estimate net survival, we used the Pohar-Perme estimator,[86] implemented with the program stns[122] in Stata version 14 (StataCorp LP, College Station, TX). This estimator accounts for the fact that competing risks of death are higher in older cancer patients.

For each cancer, calendar period and sex, we present age-standardised net survival estimates for up to 5 years after diagnosis. For adults, we used the International Cancer Survival Standard (ICSS) weights,[92] in which age at diagnosis is categorised into 5 groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years and, for prostate cancer, 15-54, 55-64, 65-74,

75-84 and 85-99 years. Of the three sets of ICSS weights, we used group 2 (cancers for which incidence does not increase steeply with age) for melanoma of the skin, cervix uteri and brain (adults), and group 1 (cancers for which incidence does increase steeply with age) for oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast, ovary and prostate, and both groups of haematopoietic malignancies. For children, we estimated survival for the age groups 0-4, 5-9 and 10-14 years; age-standardised estimates were obtained by assigning equal weights to the three age-specific estimates.[123,124] Cumulative survival probabilities in the range 0-1 are presented for convenience as percentages in the range 0-100%.

Survival was not estimated if fewer than ten patients were available for analysis. When the total number of available patients was fewer than 50, unstandardised estimates were produced for all ages combined. When the number of patients was 50 or more, age-specific estimates were produced where possible and an age-standardised summary estimate was derived. Where an age-specific estimate could not be obtained, the data from adjacent age groups were merged, and a combined estimate was assigned to both age groups. If two or more age-specific estimates could not be produced, only the unstandardised estimates for all ages combined were presented. 95% confidence intervals (CI) for both unstandardised and standardised survival estimates were derived assuming a normal distribution, truncated to the range 0-100. Standard errors to construct the CIs were calculated using the Greenwood method.[125] If no death or censoring occurred within 5 years, or if all patients died within 5 years (survival probability 1 or 0), we obtained a binomial approximation for the lower or upper bound respectively, of the CI.

Results

Of 8,931 tumour records for adults (8,477) and children (454) diagnosed during 2000-2013, 8,484 (95.0%) were included in the survival analyses (Table 5.4). Of the 8,273 eligible adults and 437 children, 2.6% adults and 1.8% children were excluded, mainly because the tumour

was registered from a death certificate only or detected solely at autopsy (DCO) (2.3% and 1.1%, respectively). The proportion of tumours that were microscopically verified by histology or cytology, or had a specific morphology code, was 99.8% in adults and 100% in children. Only 1.0% of adults and 4.7% of children were lost to follow-up.

Cancers with the highest net survival over the 14 years (2000-2013) were those of prostate, breast (women), and rectum in adults, and lymphoma in children. Survival was lowest for liver, pancreas, and lung cancer in adults, and for brain tumours in children (Table 5.5).

During 2010-2013, one-year age-standardised net survival in adults was lowest for liver cancer at 37.6% (95% CI 27.8-47.3%) and highest for prostate cancer at 98.0% (94.0-100.0%) (Figure 5.1). Survival was over 80% for five adult cancers (prostate, breast, rectum, cervix and colon). In children, one-year net survival for lymphoma and acute lymphoblastic leukaemia (ALL) was greater than 80% over the whole period (2000-2013), reaching 98.3% (95.2-100.0%) and 95.7% (91.2-100.0%) respectively, by 2010-2013. During 2010-2013, however, one-year survival for children with brain tumours was 45.2% (23.9-66.0%).

Five-year survival in adult patients diagnosed during 2010-2013 was lowest for lung cancer at 13.4% (95% CI 8.8-18.0%) and highest for prostate cancer at 84.0% (74.1-94.0%) (Figure 5.1). Prostate was the only cancer for which 5-year survival exceeded 80%. During this period, 5-year survival improved for lethal cancers, with four cancers showing survival below 25% (stomach, liver, pancreas and lung) compared to five in 2000-2004 (oesophagus, stomach, liver, pancreas and lung) and seven in 2005-2009 (oesophagus, stomach, liver, pancreas, lung, brain and myeloid neoplasms).

In children, the highest 5-year survival observed during 2010-2013 was for lymphoma (96.3%, 95% CI 91.4-100.0%), followed by ALL (88.4%; 80.6-96.2%). The largest improvement in survival in children over the 14-year period (2000-2013) was, however, for ALL: a 12.3% increase versus 6.3% for lymphoma.

For women, 1- and 5-year net survival for all cancers was between 1% and 25% higher than in men, with the exception of oesophagus, colon, and brain tumours, where survival was 5-18% higher in men. The most notable differences in age-standardised five-year net survival between men and women were observed for myeloid neoplasms and lung cancer, which had a 25.1% and 13.1% difference between men (15.3%, 10.4%) and women (40.8%, 23.5%), respectively. Survival among boys and girls was generally similar (differences less than 5%).

For almost all cancers, larger differences were observed between survival at 1 and 3 years since diagnosis than between 3 and 5 years; reductions between 1- and 3-year survival ranged from 4-26% (for lymphoid neoplasms- lung) versus 1-10% (liver - colon) between 3- and 5-year survival. Greater reductions were seen between 1- and 3-year survival estimates among women than men (Figure 5.2).

Over the 14-year period (2000-2013), 5-year survival increased for most adult cancers (Figure 5.3). The largest increase in age-standardised survival was for lymphoid neoplasms (16.1%), followed by cancers of the stomach (7.4%) and breast (6.9%). Five-year survival from cancers of the lung, rectum, ovary and cervix remained stable (less than 2% change), while survival declined for myeloid neoplasms and colon cancer in adults (13.0% and 6.3% respectively).

Discussion

This study presents a comprehensive profile of trends in population-based cancer survival up to five years for Kuwaiti patients diagnosed with one of 18 common cancers, by sex. It is the first study reporting cancer survival for males and females separately, allowing gender differences to be addressed. It is also the first to include shorter-term survival (1 and 3 years), which is particularly useful for the more lethal cancers. The survival estimates presented here are crucial for healthcare managers and policymakers to assess the

effectiveness of healthcare delivery for cancer, and to plan future strategies for cancer control.[126,127]

Our study estimated population-based survival, which is a key measure of the effectiveness of the health system in dealing with cancer.[21] Survival estimates derived from hospital-based registries or clinical trials are likely to be restrictive in their selection of patients, accessibility to healthcare services, and availability of treatments. By contrast, population-based survival estimates include *all* patients diagnosed in a particular region. Patients are included irrespective of their age, stage at diagnosis, comorbidities, socio-economic status or any other factor. These estimates, therefore, constitute the gold standard for evaluating the overall effectiveness of any given health care system.[20]

Obtaining high-quality, complete and reliable incidence and follow-up data on vital status for all cancer patients was necessary to produce robust population-based survival estimates.[128] In this study, the proportion of DCO cases among Kuwaiti patients was only 2.3% in adults and 1.1% in children, reducing the chance of survival overestimation.[129] The total proportion of loss to follow-up was also low (1.2%), illustrating the efficacy of the new follow-up procedure performed [see paired article also published in this issue]. This new approach enabled follow-up data on vital status to be updated for all Kuwaiti cancer patients, using a mixture of both active and passive follow-up procedures, thus ensuring that all deaths were included in the survival analyses, regardless of the cause of death. While passive follow-up is a very powerful tool, in Kuwait this procedure did not allow reliable capture of information on the deaths of all Kuwaiti registered cancer patients. Before this study, only deaths due to cancer were known to the KCR, and survival estimates for Kuwait were therefore likely to have been overestimated.

Our analyses show that survival for many cancers increased during 2000-2013. However, survival for some cancers remained static, or declined slightly, with an apparent drop in

survival between 2000-2004 and 2005-2009. This pattern is probably due to improvements in data quality over the 14-year period; the proportions of DCO and loss to follow-up were highest during 2000-2004 and eventually both fell to 0% for all cancers diagnosed between 2010-2013 (except for pancreatic cancer and lymphoid neoplasms in adults, which remained at 1% DCO). The increases in survival observed between 2005-2009 and 2010-2013, despite improvements in data quality, may therefore be indicative of true advances in survival.

In this study, differences in net survival by sex in Kuwait were consistent with findings from the United States,[130] Canada,[131] Europe[132] and Korea,[133] with women generally having an advantage over men. For colon cancer, however, higher survival was seen in Kuwait for men than women. This may be due to women having more aggressive forms of neoplasia, and presenting at a more advanced stage than men.[134] Our study also suggested a more favourable prognosis for men than women with oesophageal and brain tumours, however, a larger cohort is required to understand better these disparities between men and women.

For some cancers, mostly those diagnosed during 2000-2004, sparse data restricted interpretation of survival estimates for Kuwait. For melanoma, survival could not be estimated for patients diagnosed during 2000-2009, due to the small number of cases. This was also observed in neighbouring Gulf Arab countries (www.globocan.iarc.fr). The low incidence of melanoma could be attributable to the population's skin colour, conservative traditional wear and limited exposure to sunlight due to high temperatures in the country. Pooling data over longer periods could enable more robust estimates to be produced, but this would hinder the examination of trends.

The availability of updated data on follow-up for vital status allowed, for the first time, the inclusion of Kuwaiti data in the third cycle of the CONCORD programme, the largest and most up-to-date global surveillance study of cancer survival.[81] The CONCORD programme

uses the same data quality control procedures and the same statistical methods for all participating countries. This means that the same time periods, cancer definitions, data preparation, exclusions, and analytical methods were used for all datasets. Consequently, this enables appropriate and robust survival comparisons to be made between results from this study in Kuwait and results for 70 other countries included in CONCORD-3.

In particular, during 2010-2013, age-standardised 5-year net survival for adult patients diagnosed with cancer in Kuwait was generally lower than survival for patients diagnosed during 2010-2014 in 40 high-income non-Arab countries included in CONCORD-3.[81] Differences ranged from as little as 3-5% (compared to the average survival of the high-income countries) for rectum, colon, lung and ovarian cancer, and from 6-19% for prostate, stomach, cervix and breast cancer and myeloid malignancies. By contrast, survival for children diagnosed with lymphoma or acute lymphoblastic leukaemia (ALL) in Kuwait was similar to that of other high-income countries.

The fact that survival for adults in Kuwait is generally lower than in other high-income countries, particularly for stomach, prostate, breast and cervical cancer, may be partially explained by differences in diagnostic activity. With screening programmes available in most high-income countries,[135-137] diagnosing asymptomatic or less aggressive and non-lethal tumours that do not necessarily progress to symptomatic diagnoses or death is more likely, thus raising survival.[138] Screening can also lead to prolonged survival time and improvements of outcome due to early-stage diagnosis.[139] Kuwait only has one breast cancer screening programme established in 2014,[140] and is currently in the process of implementing a cervical cancer screening programme in 2018. It is thus necessary to evaluate whether the implementation of screening programmes could reduce some of the survival deficit between Kuwait and other high-income countries. Assessing the comorbidity of cancer patients in Kuwait, which tends to compromise the effectiveness and compliance of treatment,[141] could also further help explain these differences.

For myeloid neoplasms, survival in Kuwait during 2010-2013 (25.6%) was considerably lower than in other high-income countries (e.g. 45-57% in the US, UK, Korea, Canada, Australia and Sweden). This may be due to differences in the subtypes of myeloid malignancies, which in our definition included myelodysplastic syndromes and refractory anaemias. These morphologies usually entail better prognosis than the more lethal subtype: acute myeloid leukaemia (AML).[142] The lower survival in Kuwait, therefore, could be due to a higher proportion of patients with AML (almost 50% during this period compared to 36% reported in other European countries),[142] reducing the pooled estimate for all myeloid malignancies combined. Additional comparisons of subtypes, and possibly treatment modalities, are thus also required to understand these differences.

For pancreatic cancer, survival in Kuwait during 2010-2013 (23.6% CI 12.0-35.2%) was much higher than in other high-income countries for which reliable estimates were available (e.g. 6-12 % in the US, UK, Korea, Canada, Australia and Sweden). Due to the lethal nature of the disease, many countries had unreliable estimates, attributable to high proportions of DCOs. However, for Kuwait, the proportion of DCOs during this period was very low, as was the percentage of patients lost to follow-up (2.1% and 0% respectively; data not shown). It is thus unlikely that poor data quality is the cause of the high survival observed in Kuwait, although the relatively small number of patients (92 patients) may limit the interpretability of the estimates. The higher survival from pancreatic cancer may also be attributable to earlier stage at diagnosis or a higher proportion of neuroendocrine tumours, which are generally considered indolent and have a more favourable prognosis than ductal adenocarcinomas of the pancreas.[143] Supplementary assessments on patients' stage at diagnosis and the distribution of morphologies are needed in order to identify the underlying cause for this difference.

Survival estimates for other Arab countries in CONCORD-3 with similar income and health care systems were only available for Qatar. However, most of the estimates for Qatar were

considered less reliable, due to the high proportion of patients censored within 5 years, preventing robust conclusions. Further comparisons with neighbouring countries, using complete and high-quality data, are therefore necessary to determine whether differences between regions that share similar culture, tradition, climate, income and healthcare systems do in fact reflect true inequalities in cancer care.

Conclusion

During the 14-year period up to 2013, cancer survival improved for most Kuwaiti adults and children. Survival for some cancers remained static or even declined, and this requires continuous surveillance and monitoring. Women generally have a more favourable prognosis than men.

These results should prompt ministerial health planners and politicians in Kuwait to allow robust estimates to be produced through continuous surveillance of population-based cancer survival, and the systematic provision of cancer data and follow-up information on vital status for *all* cancer patients. The data presented here should assist policymakers and practitioners investing in the Kuwaiti healthcare system to achieve optimal outcomes by promoting early diagnosis and screening programmes and detecting and treating cancer more efficiently.

Further research is required to help dissect the underlying causes for the differences in survival between Kuwait and other countries with comparable income and health systems, in order to investigate whether the differences are attributable to late diagnosis, treatment, or pathological characteristics of the tumour

Tables

Table 5.1 Definition of malignancies

Malignancy	Topography or morphology codes*	Description
Oesophagus	C15.0-C15.5; C15.8-C15.9	Oesophagus
Stomach	C16.0-C166; C168-C16.9	Stomach
Colon	C18.0-C18.9; C19.9	Colon and rectosigmoid junction
Rectum †	C20.9; C21.0-C21.2, C21.8	Rectum, anal canal and anorectal
Liver	C22.0-C22.1	Liver and intrahepatic bile ducts
Pancreas	C25.0-C25.4; C25.7-C25.9	Pancreas
Lung‡	C34.0-C34.3; C34.8-C34.9	Lung and bronchus
Breast (women) †	C50.0-C50.6; C50.8-C50.9	Breast
Cervix	C53.0-C53.1; C53.8-C53.9	Cervix uteri
Ovary	C48.0-C48.2; C56.9; C57.0-C57.4; C57.7-C57.9	Ovary, fallopian tube and uterine ligaments, other and unspecified female genital organs, peritoneum and retroperitoneum
Prostate	C61.9	Prostate gland
Brain (adults and children)	C71.0-C71.9	Brain
Melanoma of the skin	M8720-8790	Melanoma of the skin, with skin of labia majora, vulva, penis and scrotum
Haematological malignancies (adults and children) ¥	M9590-9992	Myeloid and lymphoid neoplasms (adults); Acute lymphoblastic leukaemia and lymphoma (children)

* International Classification of Diseases for Oncology 3rd edn (ICD-O-3. † Excludes skin of anus, perianal skin, and skin of breast(C44.5). ‡ Excludes trachea (C39.9). ¥ Grouping of leukaemias and lymphomas is based on HAEMACARE groups and the InterLymph recommendations for adults, and on the ICCC-3 (3rd edn) group I & II for children (appendix)

Table 5.2 Definition of adult haematological malignancies

HAEMACARE groups		ICD-O-3 morphology codes	
No.	**Description**	**Lymphoid neoplasms**	**Myeloid neoplasms**
1	Lymphoma NOS	9590	
2	NH Lymphoma NOS	9591, 9597	
3	Composite HL and NHL	9596	
4	HL nodular lymphocyte predominance	9659	
5	Classical HL	9650, 9661, 9662, 9651, 9663, 9664, 9665, 9667, 9652, 9653, 9654, 9655	
6	CLL/SLL	9670, 9823	
7	Immunoproliferative diseases	9760, 9671, 9761, 9762	
8	Mantle cell/centrocytic	9673	
9	Follicular B lymphoma	9690, 9691, 9695, 9698	
10	Diffuse B lymphoma	9675, 9678, 9679, 9680, 9684, 9688, 9712, 9735, 9737, 9738	
11	Burkitt's leukaemia/lymphoma	9687, 9826	
12	Marginal zone lymphoma	9689, 9699, 9764	
13	T lymphoma cutaneous	9700, 9701, 9709, 9718, 9708, 9726	
14	Other T cell lymphoma	9702, 9705, 9714, 9716, 9717, 9725, 9948, 9719, 9827, 9831, 9834	
15	Lymphoblastic lymphoma/acute (precursor cell) lymphoblastic leukaemia	9727, 9728, 9729, 9811, 9812, 9813, 9814, 9815, 9816, 9817, 9818, 9835, 9836, 9837	
16	Plasma cell neoplasms	9731,9732, 9733, 9734	
17	Mature B cell leukaemia	9833	
18	Mature B-cell leukaemia, hairy	9940	
19	Lymphatic leukaemia NOS	9820, 9832	
20	Leukaemia NOS		9800, 9801, 9805, 9806, 9807, 9808, 9809
21	Myeloid leukaemia NOS		9860, 9898
22	Acute myeloid leukaemia		9840, 9861, 9865, 9866, 9867, 9869, 9870, 9871, 9872, 9873, 9874, 9891, 9895, 9896, 9897, 9910, 9911, 9920, 9930, 9931, 9984, 9987
23	Myeloproliferative neoplasms*		9740, 9741, 9742, 9863, 9875, 9950, 9960, 9961, 9962, 9963, 9964
24	Myelodysplastic syndrome		9980, 9982, 9983, 9985, 9986, 9989, 9991, 9992
25	Myelodysplastic/myeloproliferative neoplasms**		9945, 9876, 9946, 9975

NOS: Not otherwise specified, * this group includes chronic myeloid leukaemias (several morphology codes), ** Note: this group includes chronic myelomonocytic leukaemia (M-9945) and Juvenile Myelomonocytic leukaemia (M-9946)

Table 5.3 Definition of childhood haematological malignancies

ICCC-3 groups		ICD-O-3 morphology codes	
No.	**Description**	**Acute lymphoblastic leukaemia**	**Lymphomas & RE neoplasms**
Ia	Lymphoid leukaemias	9835, 9836, 9837	
IIa	Hodgkin lymphomas		9650–9655, 9659, 9661–9665, 9667
IIb	Non Hodgkin lymphomas (except Burkitt lymphoma)		9591, 9597, 9670, 9671, 9673, 9675, 9678–9680, 9684, 9688, 9689–9691, 9695, 9698–9702, 9705, 9708, 9709, 9712, 9714, 9716–9719, 9725, 9726, 9727–9729, 9731–9734, 9735, 9737, 9738, 9760–9762, 9764–9769, 9970, 9971 **and** 9811, 9812, 9813, 9814, 9815, 9816, 9817, 9818 **only if topography is NOT in C42.0, C42.1, C42.3, C42.4, C80.9**
IIc	Burkitt lymphoma		9687
IId	Miscellaneous lymphoreticular neoplasms		9740–9742, 9750, 9751, 9752, 9753, 9754–9758, 9759
IIe	Unspecified lymphomas		9590, 9596

Table 5.4 Data quality indicators for patients diagnosed during 2000-2013, for adults and children by cancer site

	Patients submitted	Ineligible¶		Eligible patients	Exclusions||		No of cases 2000-2004		2005-2009		2010-2013		Total	††MV (%)	Non-specific morphology (%)	Lost to follow-up (%)
		In situ (%)	Other (%)		DCO (%)	Other (%)	M	F	M	F	M	F				
Adult cancers																
Oesophagus	**97**	0.0	0.0	97	7.2	0.0	12	15	12	12	26	13	**90**	100.0	0.0	2.2
Stomach	**233**	0.0	6.4	218	5.0	0.0	35	24	48	31	36	33	**207**	100.0	0.0	1.0
Colon	**938**	0.1	0.3	934	2.8	0.0	106	131	165	160	172	174	**908**	100.0	0.0	2.2
Rectum	**335**	0.0	0.3	334	1.2	0.0	37	48	64	66	60	55	**330**	100.0	0.0	0.9
Liver	**303**	0.0	0.3	302	13.2	0.3	48	20	75	31	62	25	**261**	100.0	0.4	1.1
Pancreas	**265**	0.0	0.4	264	8.3	0.8	31	26	54	37	46	46	**240**	100.0	0.4	0.8
Lung	**586**	0.2	0.2	584	4.3	0.0	131	49	142	49	135	53	**559**	100.0	0.2	1.3
Melanoma	**21**	0.0	14.3	18	0.0	0.0	2	3	2	5	4	2	**18**	100.0	0.0	0.0
Breast	**2,698**	3.6	0.2	2,595	0.5	0.6	0	628	0	953	0	987	**2,568**	100.0	0.1	0.4
Cervix	**183**	9.8	0.0	165	1.2	0.0	0	62	0	59	0	42	**163**	100.0	0.0	0.6
Ovary	**279**	0.0	17.6	230	2.6	1.3	0	62	0	92	0	67	**221**	99.5	0.9	0.5
Prostate	**521**	0.6	0.0	518	1.7	0.0	116	0	169	0	224	0	**509**	100.0	0.0	0.8
Brain	**259**	0.0	0.0	259	8.9	2.3	42	25	50	34	42	37	**230**	96.5	3.9	0.9
Myeloid neoplasms	**350**	0.0	0.6	348	0.6	0.0	44	40	77	59	68	58	**346**	98.8	2.6	0.9
Lymphoid neoplasms	**1,409**	0.0	0.1	1,407	0.1	0.0	208	167	330	207	271	222	**1,405**	99.6	0.8	1.6
Total	**8,477**	**1.4**	**1.0**	**8,273**	**2.3**	**0.3**	812	1,300	1,188	1,795	1,146	1,814	**8,055**	**99.8**	**0.4**	**1.0**
Childhood cancers																
Brain	**57**	0.0	0.0	57	8.8	5.3	13	5	16	6	5	4	**49**	100.0	0.0	2.0
ALL	251	0.0	0.0	251	0.0	0.0	54	29	55	43	40	30	**251**	100.0	0.0	5.2
Lymphoma	146	0.0	11.6	129	0.0	0.0	35	13	29	16	23	13	**129**	100.0	1.6	4.7
Total	**454**	**0.0**	**3.7**	**437**	**1.1**	**0.7**	102	47	100	65	68	47	**429**	**100.0**	**0.5**	**4.7**

¶ In situ malignant disease (ICD-O-3 behaviour code 2). Other: records with incomplete data; or tumours that are benign (behaviour code 0), of uncertain behaviour (1), metastatic from another organ (6), or unknown if primary or metastatic (9); or patients falling outside the age range 0–14 years (children) or 15–99 years (adults); or other conditions. ||DCO=tumours registered from a death certifi cate only or detected solely at autopsy. Other: vital status or sex unknown; or invalid sequence of dates; or inconsistency of sex-site, site-morphology, age-site, age-morphology, or age-site-morphology. †† MV=microscopically verified. Non-specific morphology (solid tumours only): ICD-O-3 morphology code in the range 8000–8005.

Table 5.5 Age-standardised net survival (NS, %) at one, three and five years, Kuwaiti adults (15-99 years) and children (0-14 years) diagnosed during 2000-2013, followed to 31 December 2014

		Males						Females						Both sexes					
		2000-2004		2005-2009		2010-2013		2000-2004		2005-2009		2010-2013		2000-2004		2005-2009		2010-2013	
		NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI
Adults																			
Oesophagus	1 year	*56.0*	*27.9 - 84.1*	*30.6*	*5.0 - 56.1*	*53.1*	*31.9 - 74.4*	*34.4*	*11.6 - 57.3*	*26.2*	*3.0 - 49.4*	*45.3*	*20.6 - 70.0*	*44.2* §	*25.3 - 63.1*	*28.4*	*10.3 - 46.5*	*50.3*	*33.6 - 66.9*
	3 years	*21.8*	*0.0 - 44.7*	*0.1*	*0.0 - 0.3*	*32.0*	*11.7 - 52.3*	*14.4*	*0.0 - 31.0*	*17.7*	*0.0 - 37.3*	*15.2*	*0.0 - 32.2*	*17.6* §	*2.9 - 32.4*	*9.5*	*0.0 - 20.6*	*25.0*	*10.3 - 39.8*
	5 years	*21.8*	*0.0 - 44.7*	..		*32.3*	*11.8 - 52.8*	*14.4*	*0.0 - 31.0*	*17.7*	*0.0 - 37.3*	*15.7*	*0.0 - 33.3*	*17.6* §	*2.9 - 32.4*	*9.5*	*0.0 - 20.6*	*25.4*	*10.5 - 40.4*
Stomach	1 year	*53.6*	*36.5 - 70.8*	*57.2*	*43.1 - 71.2*	**49.0**	35.0 - 63.1	*46.6*	*27.0 - 66.2*	*45.5*	*28.2 - 62.7*	**51.4**	41.4 - 61.3	**45.8**	32.5 - 59.2	**47.4**	37.7 - 57.2	**50.5**	39.2 - 61.8
	3 years	*29.6*	*13.7 - 45.4*	*21.3*	*9.8 - 32.9*	**23.7**	11.1 - 36.4	*17.1*	*2.7 - 31.6*	*19.8*	*6.3 - 33.4*	**15.4**	7.2 - 23.5	**20.3**	11.0 - 29.5	**16.1**	10.1 - 22.1	**27.9**	16.0 - 39.8
	5 years	*19.9*	*5.2 - 34.6*	*13.1*	*3.7 - 22.5*	*14.5*	*2.9 - 26.2*	*17.1*	*2.7 - 31.6*	*19.8*	*6.3 - 33.4*	**15.5**	7.3 - 23.7	**15.0**	7.1 - 22.9	**13.4**	7.1 - 19.7	**22.4**	12.6 - 32.3
Colon	1 year	**86.1**	78.0 - 94.2	**73.2**	64.0 - 82.5	**86.4**	79.5 - 93.3	**85.4**	80.6 - 90.2	**79.0**	70.4 - 87.6	**77.0**	68.0 - 86.1	**85.8**	79.0 - 92.5	**76.1**	69.6 - 82.6	**82.6**	76.7 - 88.4
	3 years	**73.1**	61.1 - 85.0	**59.3**	48.7 - 69.8	**76.6**	66.0 - 87.1	**70.1**	62.9 - 77.2	**60.2**	50.5 - 69.9	**60.3**	50.2 - 70.4	**72.7**	63.0 - 82.3	**59.5**	52.1 - 66.9	**68.9**	61.0 - 76.7
	5 years	**62.6**	48.6 - 76.5	**48.0**	37.9 - 58.0	**58.8**	45.0 - 72.6	**59.6**	51.0 - 68.3	**51.8**	41.7 - 62.0	**54.1**	42.8 - 65.3	**64.8**	53.1 - 76.5	**50.2**	42.7 - 57.7	**58.5**	49.4 - 67.7
Rectum	1 year	*90.4*	*80.0 - 100.0*	**93.4**	88.3 - 98.4	**86.0**	77.1 - 95.0	**86.4**	79.1 - 93.7	*90.6*	*83.2 - 98.0*	**93.5**	84.9 - 100.0	**87.0**	81.6 - 92.4	**92.3**	86.5 - 98.2	**87.9**	80.5 - 95.3
	3 years	*69.1*	*52.7 - 85.6*	**64.2**	55.6 - 72.8	**66.0**	54.5 - 77.4	**74.2**	63.6 - 84.8	*78.6*	*67.7 - 89.5*	**69.1**	55.2 - 82.9	**70.6**	62.5 - 78.7	**67.1**	55.9 - 78.3	**67.0**	57.6 - 76.4
	5 years	*59.3*	*41.6 - 77.0*	**54.0**	44.9 - 63.1	**55.1**	42.4 - 67.8	**60.2**	47.8 - 72.7	*66.1*	*53.5 - 78.8*	**56.7**	41.4 - 72.0	**59.3**	48.1 - 70.4	**53.3**	42.4 - 64.2	**58.2**	48.5 - 67.9
Liver	1 year	*37.2*	*23.4 - 51.1*	*38.3*	*27.1 - 49.5*	*31.1*	*19.6 - 42.6*	*27.2*	*8.1 - 46.2*	*32.8*	*16.6 - 48.9*	*52.4*	*34.7 - 70.1*	*34.3* §	*22.8 - 45.8*	*36.8*	*27.4 - 46.1*	**37.6**	27.8 - 47.3
	3 years	*13.6*	*3.8 - 23.5*	*15.9*	*7.4 - 24.4*	*9.8*	*2.8 - 16.9*	*16.3*	*0.9 - 31.8*	*17.5*	*4.4 - 30.6*	*27.8*	*12.3 - 43.3*	*14.6* §	*5.9 - 23.2*	*16.5*	*9.2 - 23.8*	**19.4**	11.5 - 27.4
	5 years	*8.6*	*0.5 - 16.7*	*10.9*	*3.6 - 18.3*	*7.9*	*1.6 - 14.2*	*16.3*	*0.9 - 31.8*	*15.2*	*2.6 - 27.7*	*26.7*	*10.2 - 43.2*	*11.4* §	*3.5 - 19.2*	*12.4*	*5.8 - 19.1*	**18.6**	9.8 - 27.3
Pancreas	1 year	*24.0*	*9.2 - 38.9*	*20.7*	*10.0 - 31.3*	*33.7*	*19.9 - 47.4*	*32.3*	*14.5 - 50.0*	*38.3*	*22.8 - 53.7*	*48.9*	*34.2 - 63.6*	*27.8* §	*16.0 - 39.5*	**24.3**	17.2 - 31.4	**40.9**	30.1 - 51.8
	3 years	*10.1*	*0.5 - 19.8*	*3.8*	*0.0 - 8.4*	*13.9*	*3.3 - 24.4*	*16.2*	*2.6 - 29.9*	*22.5*	*9.3 - 35.8*	*19.0*	*7.0 - 30.9*	*12.9* §	*4.3 - 21.6*	**10.6**	5.2 - 16.0	**22.3**	12.5 - 32.2
	5 years	*10.1*	*0.5 - 19.8*	*1.9*	*0.0 - 5.0*	*10.9*	*1.1 - 20.7*	*12.3*	*0.3 - 24.3*	*17.3*	*5.1 - 29.6*	*16.4*	*4.8 - 28.0*	*11.2* §	*3.1 - 19.3*	**7.0**	3.0 - 11.0	**23.6**	12.0 - 35.2
Lung	1 year	**37.7**	29.6 - 45.9	**43.9**	35.5 - 52.4	**41.0**	32.8 - 49.2	*33.2*	*20.1 - 46.3*	*49.5*	*35.4 - 63.6*	**58.7**	49.5 - 68.0	**35.9**	28.4 - 43.4	**46.4**	39.2 - 53.7	**46.3**	39.4 - 53.1
	3 years	**14.2**	9.6 - 18.8	**26.0**	18.0 - 34.0	**16.6**	10.4 - 22.7	*20.7*	*9.1 - 32.2*	*22.1*	*10.1 - 34.0*	**23.2**	13.7 - 32.8	**15.1**	10.3 - 19.9	**25.1**	18.5 - 31.8	**19.9**	14.4 - 25.5
	5 years	**14.5**	7.8 - 21.2	**15.7**	9.9 - 21.6	**10.4**	5.8 - 15.0	*11.6*	*2.5 - 20.6*	*17.5*	*6.5 - 28.5*	**23.5**	13.8 - 33.2	**13.3**	8.9 - 17.7	**16.3**	11.1 - 21.5	**13.4**	8.8 - 18.0
Melanoma of the skin	1 year	..		..		..		..		..		..		..		..		*67.5*	*32.8 - 100.0*
	3 years	..		..		..		..		..		..		..		..		*71.0*	*34.4 - 100.0*
	5 years	..		..		..		..		..		..		..		..		*49.0*	*0.0 - 98.4*
Breast (women)	1 year	..		..		..		**95.1**	91.5 - 98.7	**92.2**	88.4 - 95.9	**93.3**	89.9 - 96.7	..		..		..	
	3 years	..		..		..		**82.5**	74.4 - 90.6	**76.7**	70.7 - 82.7	**83.2**	77.0 - 89.4	..		..		..	
	5 years	..		..		..		**68.3**	58.0 - 78.7	**71.0**	63.8 - 78.2	**75.2**	66.4 - 83.9	..		..		..	

§ Survival estimate considered less reliable (i.e. proportion of patients lost to follow-up or registered only from a death certificate or at autopsy is greater than 15%); Italics denote survival estimates that are not age-standardised; ALL, Acute lymphoblastic leukaemia

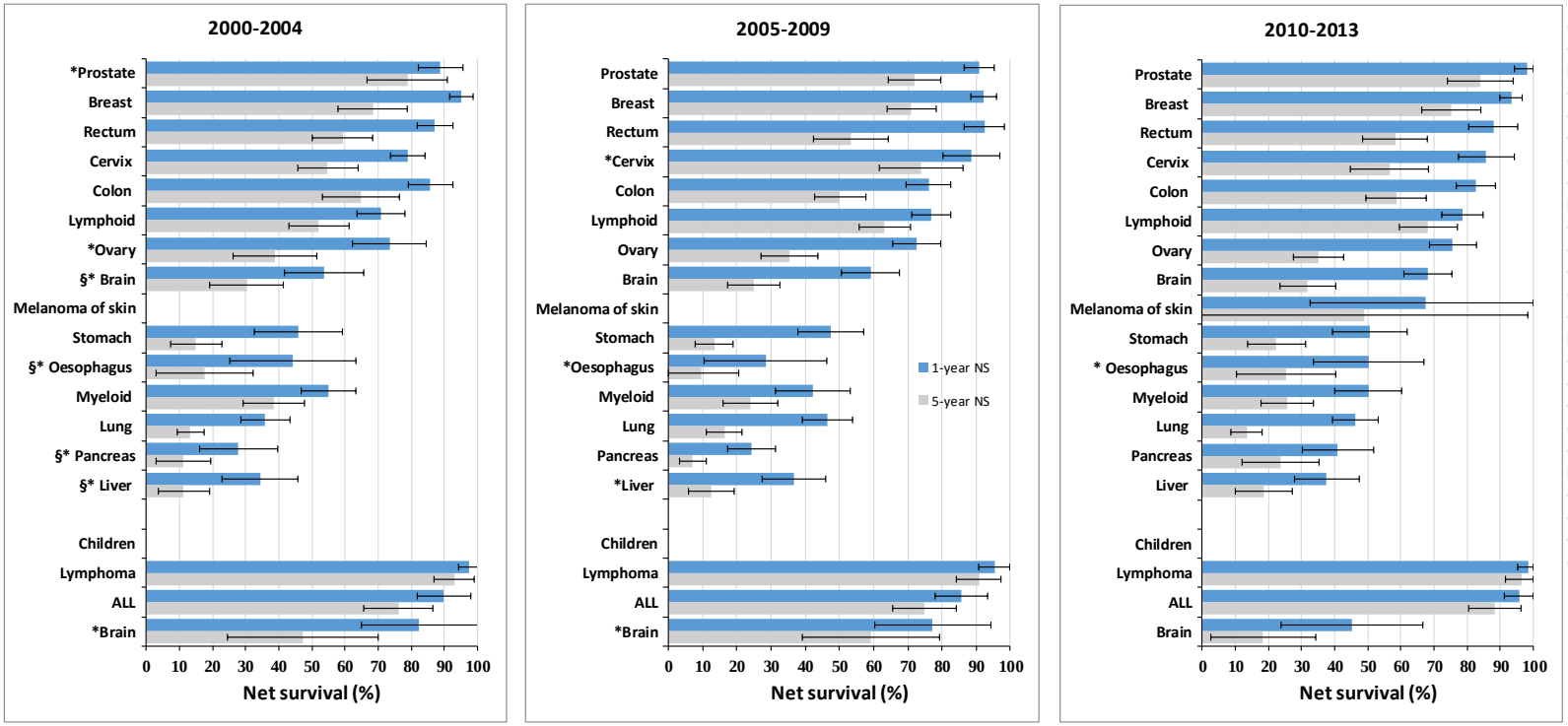
Table 5.5 (continued) Age-standardised net survival (NS, %) at one, three and five years, Kuwaiti adults (15-99 years) and children (0-14 years) diagnosed during 2000-2013, followed to 31 December 2014

		Males						Females						Both sexes					
		2000-2004		2005-2009		2010-2013		2000-2004		2005-2009		2010-2013		2000-2004		2005-2009		2010-2013	
		NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI
Adults																			
Cervix	1 year	..		..		..		**79.0**	73.7 - 84.3	*88.7*	*80.4 - 97.0*	**85.7**	77.3 - 94.2	..		..		..	
	3 years	..		..		..		**57.9**	49.1 - 66.6	*79.9*	*69.1 - 90.7*	**60.5**	48.3 - 72.7	..		..		..	
	5 years	..		..		..		**54.8**	45.2 - 64.3	*73.8*	*61.7 - 86.0*	**56.6**	44.2 - 69.0	..		..		..	
Ovary	1 year	..		..		..		*73.4*	*62.2 - 84.5*	**72.6**	65.5 - 79.7	**75.6**	68.5 - 82.6	..		..		..	
	3 years	..		..		..		*60.5*	*47.8 - 73.2*	**43.4**	34.4 - 52.4	**43.0**	34.6 - 51.3	..		..		..	
	5 years	..		..		..		*38.9*	*26.3 - 51.5*	**35.4**	25.2 - 45.6	**35.1**	25.6 - 44.7	..		..		..	
Prostate	1 year	*88.8*	*82.0 - 95.5*	**91.0**	86.6 - 95.4	**98.0**	94.3 - 100.0	..		..		..		..		..		..	
	3 years	*79.9*	*70.3 - 89.6*	**79.1**	72.6 - 85.7	**93.4**	87.3 - 99.5	..		..		..		..		..		..	
	5 years	*78.8*	*66.7 - 90.9*	**71.9**	63.7 - 80.0	**84.0**	74.1 - 94.0	..		..		..		..		..		..	
Brain	1 year	*50.2*	*35.2 - 65.3*	*60.7*	*47.1 - 74.3*	*81.3*	*69.3 - 93.2*	*59.7*	*40.7 - 78.8*	*67.9*	*52.3 - 83.5*	*70.3*	*55.5 - 85.1*	*53.7* §	*41.7 - 65.6*	**59.1**	50.6 - 67.6	**68.0**	60.9 - 75.2
	3 years	*30.4*	*16.5 - 44.3*	*26.7*	*14.5 - 38.8*	*50.4*	*35.0 - 65.8*	*34.2*	*15.8 - 52.7*	*44.6*	*28.1 - 61.2*	*38.6*	*22.6 - 54.5*	*31.7* §	*20.4 - 43.0*	**29.4**	21.4 - 37.5	**37.3**	28.5 - 46.1
	5 years	*28.0*	*14.4 - 41.6*	*20.2*	*9.1 - 31.3*	*42.3*	*25.8 - 58.8*	*34.2*	*15.8 - 52.7*	*41.9*	*25.4 - 58.3*	*34.6*	*18.5 - 50.8*	*30.3* §	*19.1 - 41.5*	**24.9**	17.3 - 32.6	**31.8**	23.2 - 40.4
Myeloid neoplasms	1 year	*61.9*	*47.5 - 76.4*	**33.1**	23.4 - 42.8	**49.5**	35.6 - 63.4	*80.1*	*67.8 - 92.5*	*71.5*	*60.0 - 83.0*	**58.5**	49.6 - 67.4	**55.0**	46.8 - 63.3	**42.2**	31.2 - 53.3	**50.2**	40.1 - 60.3
	3 years	*53.1*	*38.0 - 68.2*	**23.0**	14.5 - 31.5	**17.9**	9.4 - 26.5	*67.6*	*53.0 - 82.3*	*59.9*	*47.3 - 72.4*	**39.2**	30.2 - 48.3	**44.3**	35.3 - 53.3	**27.9**	19.1 - 36.8	**28.6**	20.2 - 37.0
	5 years	*48.5*	*33.1 - 64.0*	**17.0**	11.0 - 23.0	**15.3**	7.9 - 22.8	*63.1*	*47.8 - 78.4*	*58.7*	*45.9 - 71.5*	**40.5**	31.1 - 49.9	**38.6**	27.1 - 50.0	**24.0**	15.9 - 32.0	**25.6**	17.7 - 33.6
Lymphoid neoplasms	1 year	**69.7**	60.0 - 79.5	**77.7**	70.9 - 84.5	**77.3**	68.5 - 86.1	**71.1**	60.7 - 81.6	**72.1**	62.0 - 82.2	**78.9**	70.1 - 87.8	**70.8**	63.4 - 78.1	**76.7**	71.1 - 82.4	**78.5**	72.2 - 84.8
	3 years	**52.4**	41.5 - 63.4	**67.0**	58.5 - 75.5	**74.6**	64.5 - 84.7	**61.4**	49.4 - 73.5	**67.6**	55.7 - 79.6	**72.0**	61.5 - 82.5	**56.7**	48.4 - 65.0	**68.4**	61.5 - 75.4	**74.1**	66.7 - 81.5
	5 years	**45.3**	34.5 - 56.2	**59.9**	50.8 - 69.0	**65.5**	54.4 - 76.6	**54.1**	41.9 - 66.3	**65.8**	53.7 - 77.8	**73.8**	62.0 - 85.5	**52.1**	42.9 - 61.2	**63.2**	55.8 - 70.7	**68.2**	59.5 - 76.9
Children																			
Brain	1 year	*75.0*	*51.7 - 98.4*	*81.3*	*62.8 - 99.7*	*48.0*	*12.5 - 83.5*	..		..		*50.0*	*9.2 - 90.8*	*82.4*	*64.8 - 99.9*	*77.3*	*60.2 - 94.4*	**45.2**	23.9 - 66.6
	3 years	*41.7*	*15.7 - 67.7*	*62.6*	*39.8 - 85.3*	*24.0*	*0.0 - 50.5*	..		..		*25.0*	*0.0 - 56.9*	*53.0*	*30.2 - 75.8*	*63.7*	*44.1 - 83.2*	**20.7**	3.3 - 38.0
	5 years	*33.4*	*8.8 - 58.0*	*56.4*	*33.0 - 79.7*	*20.6*	*0.0 - 44.0*	..		..		*25.0*	*0.0 - 56.9*	*47.1*	*24.4 - 69.8*	*59.2*	*39.2 - 79.1*	**18.4**	2.6 - 34.3
ALL children	1 year	**88.42**	81.7 - 95.2	**80.0**	68.5 - 91.5	**95.1**	88.5 - 100.0	*100.0*	*87.7 - 100.0*	**90.5**	85.0 - 95.9	**96.9**	92.9 - 100.0	**89.8** §	81.7 - 97.9	**85.7**	77.9 - 93.4	**95.7**	91.2 - 100.0
	3 years	**82.6**	74.5 - 90.7	**73.4**	60.9 - 85.9	**90.1**	80.6 - 99.7	*95.7*	*87.6 - 100.0*	**84.3**	77.8 - 90.8	**94.4**	89.5 - 99.3	**84.5** §	75.1 - 93.8	**78.4**	69.5 - 87.2	**91.0**	84.1 - 98.0
	5 years	**71.26**	61.6 - 80.9	**70.1**	57.2 - 82.9	**88.9**	79.1 - 98.7	*90.7*	*78.6 - 100.0*	**81.2**	73.8 - 88.5	**91.7**	84.7 - 98.7	**76.1** §	65.7 - 86.5	**74.9**	65.6 - 84.1	**88.4**	80.6 - 96.2
Lymphoma	1 year	**98.3**	95.0 - 100.0	**96.3**	91.6 - 100.0	**100.0**	87.2 - 100.0	*92.3*	*78.4 - 100.0*	*93.8*	*82.3 - 100.0*	**96.7**	90.8 - 100.0	**97.5**	94.3 - 100.0	**95.6**	90.8 - 100.0	**98.3**	95.2 - 100.0
	3 years	**94.1**	88.1 - 100.0	**96.3**	91.6 - 100.0	**100.0**	80.5 - 100.0	*92.3*	*78.4 - 100.0*	*87.5*	*71.8 - 100.0*	**96.7**	90.8 - 100.0	**94.4**	88.9 - 99.9	**93.1**	87.4 - 98.8	**98.4**	95.3 - 100.0
	5 years	**92.1**	85.0 - 99.2	**92.7**	86.1 - 99.3	**96.7**	90.8 - 100.0	*92.3*	*78.4 - 100.0*	*87.5*	*71.8 - 100.0*	**96.7**	90.8 - 100.0	**93.0**	86.2 - 99.8	**90.7**	83.2 - 98.2	**96.3**	91.4 - 100.0

§ Survival estimate considered less reliable (i.e. proportion of patients lost to follow-up or registered only from a death certificate or at autopsy is greater than 15%); Italics denote survival estimates that are not age-standardised; ALL, Acute lymphoblastic leukaemia

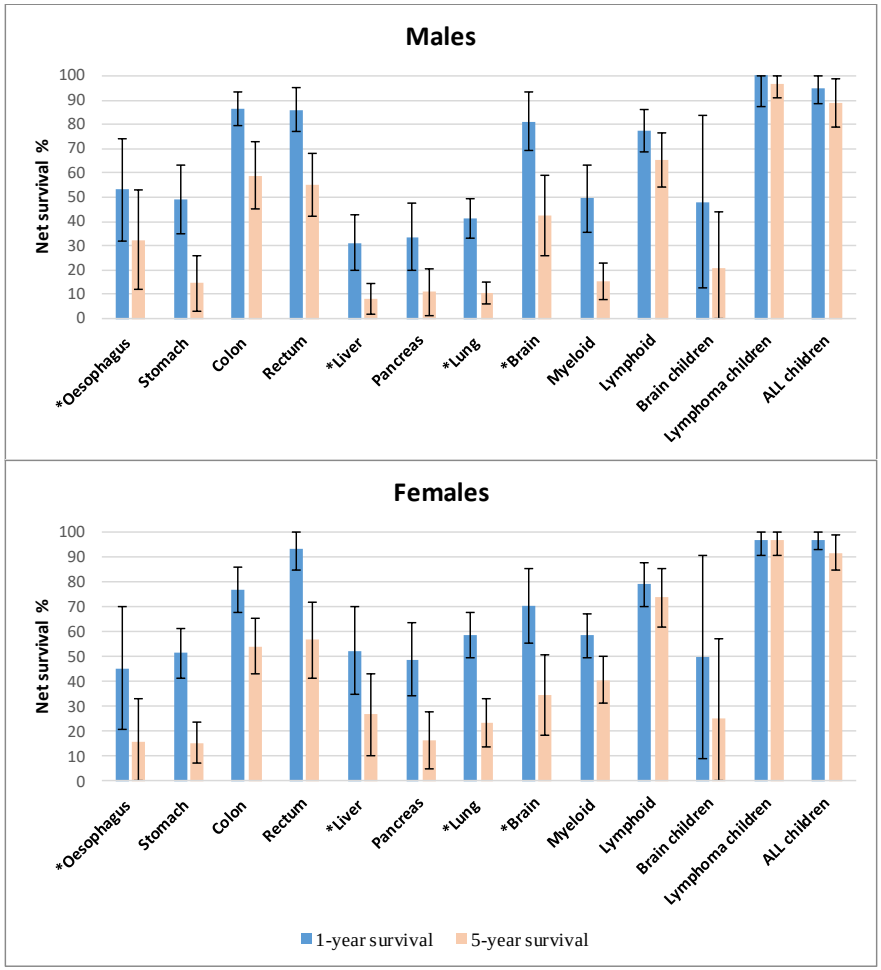
Figures

Figure 5.1 Age-standardised 1- and 5-year net survival (%) in adults (15-99 years) and children (0-14 years); Kuwait, patients diagnosed during 2000-2013



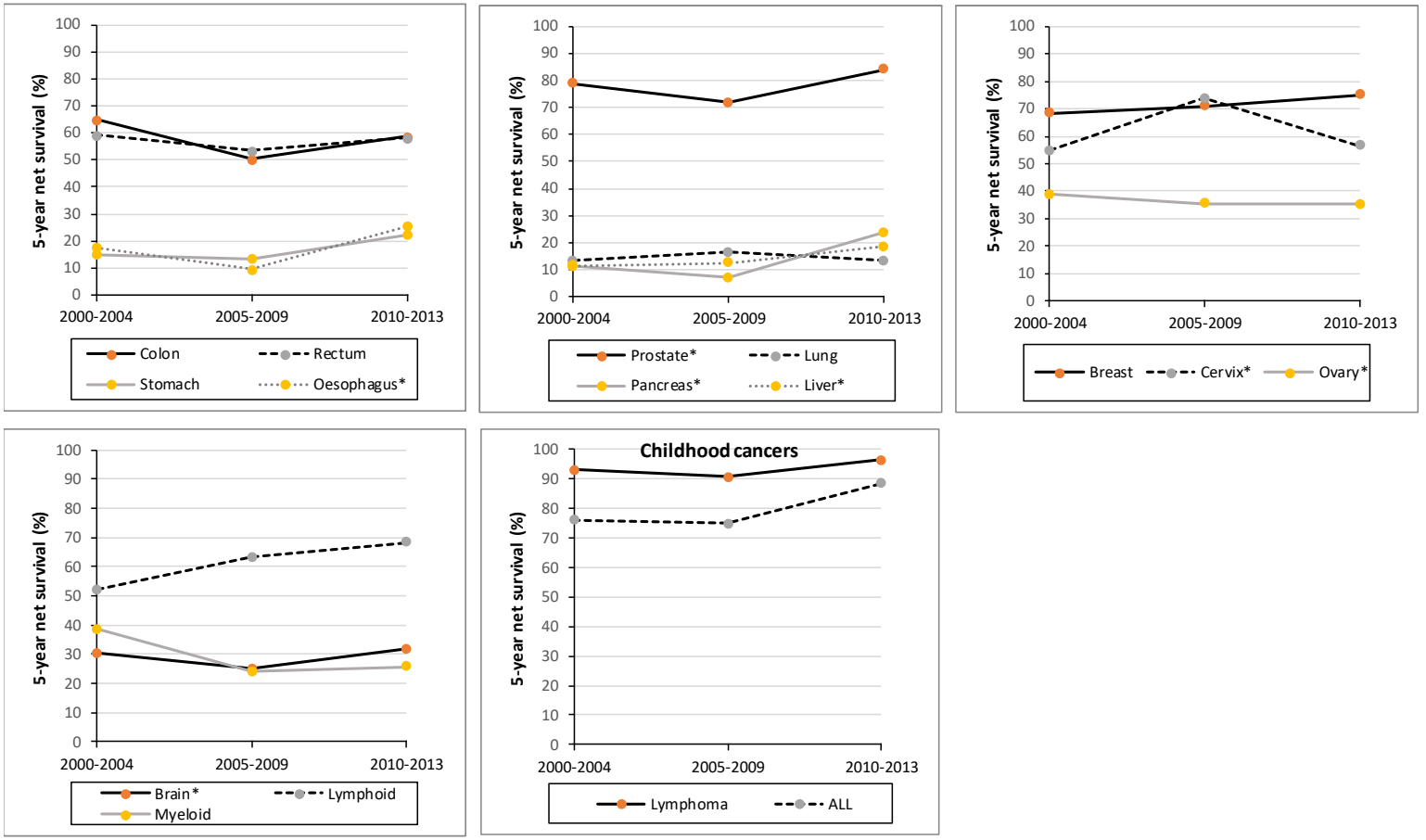
ALL: Acute lymphoblastic leukaemia; § Survival estimate considered less reliable (i.e. proportion of lost to follow-up within five years ≥ 15%); * Survival estimates not age-standardised

Figure 5.2 Age-standardised 1- and 5-year net survival (%) in adults (15-99 years) and children (0-14 years); Male and female patients diagnosed during 2010-2013



*One or both survival estimates are not age-standardised

Figure 5.3 Trends in age-standardised five-year net survival (%) in Kuwaiti adults (15-99 years) and children (0-14 years) during 2000-2013, Kuwait



* denotes not all estimates are age-standardised, ALL: Acute lymphoblastic leukaemia

Chapter 6: Research paper III; **Survival by stage at diagnosis**

In the previous chapter, net survival up to 5 years was estimated for Kuwaiti patients diagnosed with one of 18 common cancers over a 14-year period (2000-2013). Survival has improved for most cancers, but differences were observed between cancer survival in Kuwait and in other high-income countries included in CONCORD-3.

Stage at diagnosis is a key predictor of patients' outcome. The distribution of stage at diagnosis can provide a useful evaluation of diagnostic activity, the level of knowledge of cancer symptoms in the general population, and the thoroughness of the staging procedures in a given country or region. Examination of population-based survival trends by stage at diagnosis also provides a more thorough understanding of the cancer care system and its ability to provide timely and optimal stage-specific treatment. Stage-specific survival may also help explain differences in survival between populations and regions.

The aim of this chapter is to extend the evaluation of survival in Kuwait through examining the distribution of Surveillance Epidemiology and End Results (SEER) Summary Stage at diagnosis for 12 cancers in Kuwait during 2000-2013, and assessing stage-specific net survival at 1 and 5 years. Comparisons of stage-specific survival between Kuwait and the United States are performed for colon, lung and breast cancer, using the same staging system, calendar period, cancer definitions, data quality control procedures and analytical methods.

The results of this chapter revealed that early diagnosis was not very frequent in Kuwait throughout the period 2000-2013, highlighting the need for urgent investment in early detection, as well as increasing public awareness of cancer symptoms and its risk factors. The completeness of data on the stage of diagnosis for cancer patients in Kuwait also appeared to decline over the 14-year period in Kuwait. This emphasises the need for further

investment in the Kuwait Cancer Registry, and improved access to patients' medical data to aid the ascertainment of data on stage at diagnosis.

Stage-specific survival estimates highlighted cancers for which earlier diagnosis could achieve the greatest benefit. Differences in stage-specific survival between Kuwait and the US also revealed that late diagnosis in Kuwait could be a major contributing factor to the lower survival for all patients combined. This could also partially explain the difference in survival between Kuwait and the US, and possibly other high-income countries as well.

In this chapter, I have achieved the third objective of my thesis: to assess the distribution of stage at diagnosis for 12 cancers in Kuwait, and to estimate stage-specific net survival at 1 and 5 years, to improve understanding of any disparities in cancer survival between Kuwait and other countries.

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SECTION A – Student Details

Student	Eiman Alawadhi
Principal Supervisor	Dr.Claudia Allemani
Thesis Title	Cancer survival by stage at diagnosis in Kuwait: a population-based study

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?			
When was the work published?			
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Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	No

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of Oncology
Please list the paper's authors in the intended authorship order:	Alawadhi E, Al-Awadi A, Elbasmi A, Coleman MP, Allemani C.
Stage of publication	**Submitted**

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)	Eiman Alawadhi was the lead and corresponding author on the paper. She was responsible for planning and carring out the literature review, data analysis, and drafting the paper. The co-authors assissted in planning the content of the paper, and provided input on the data analysis and feedback on the draft.

Student Signature: [redacted] **Date:** 15 March 2019

Supervisor Signature: [redacted] **Date:** 15 March 2019

Research paper III [unpublished]

Cancer survival by stage at diagnosis in Kuwait: a population-based study

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Introduction

Stage at diagnosis, the anatomic extent of a disease, is a major determinant of patients' outcomes.[144] It is crucial in predicting patients' prognosis and to inform treatment decisions, as well as to assess the effect of public health interventions such as screening programmes and educational or awareness campaigns, which aim to improve early-stage diagnosis. Stage information is also valuable to help plan the provision of cancer-related resources and services, to monitor compliance to treatment guidelines, and to offer more detailed analyses of cancer outcomes.[145]

Evaluation of the distribution of stage at diagnosis helps to assess the intensity of diagnostic activity in a given country or region. Examination of population-based survival trends by stage at diagnosis helps to determine the effectiveness of the health system in offering stage-specific optimal treatment to all patients. In Kuwait, net survival was lower than in other high-income countries.[146] Differences in the distribution of stage at diagnosis are likely to be a key determinant of these discrepancies. The distribution of stage at diagnosis for each cancer can also reflect the level of symptom awareness, as well as the thoroughness of the staging procedures within a region or country.[147]

Population-based cancer survival by stage has never been assessed in Kuwait. In order to provide a better understanding of cancer survival in the country, our study aims to assess the distribution of stage at diagnosis in Kuwait for 12 cancers for which data are available, and to estimate stage-specific net survival at 1 and 5 years since diagnosis. Differences in stage-specific survival between Kuwait and the United States will also be assessed.

Material and methods

We obtained data from the Kuwait Cancer Registry for all adult Kuwaiti patients (aged 15-99 years) diagnosed during 2000-2013 with one of 18 malignancies.[81,146] Data on stage were available for 12 cancers: oesophagus, stomach, colon, rectum, liver, pancreas, lung, melanoma, breast (women), cervix, ovary and prostate. All tumours were defined by anatomical site (topography), and coded to the International Classification of Diseases for Oncology (third edition, ICD-O-3)[115] and its first revision.[116]

Data were assessed for quality and completeness according to the protocol and standardised quality-control procedures from the CONCORD programme for global surveillance of cancer survival.[148] Records considered ineligible for survival analyses were excluded. Full details of exclusions and data quality indicators have been published.[146]

Follow-up data were available until 31 December 2015. Information on follow-up was obtained using a new method[149] combining active and passive follow-up procedures, which has been shown to be highly effective in ascertaining each patient's vital status. Complete dates of death of deceased cancer patients were obtained from the Central Records Department of Births and Deaths, at Kuwait's Ministry of Health. When the vital status could not be ascertained, the patients were considered lost to follow-up, and were censored from survival analyses at the date most recently known to be alive from medical records.

We present the distribution of stage at diagnosis for the 12 malignancies based on the Surveillance Epidemiology and End Results (SEER) Summary Stage 2000,[150] which categorises the extent of the disease as localised, regional (with lymph node involvement, or direct extension, or both) or distant metastasis.

Patients were grouped into 3 consecutive calendar periods (2000-2004, 2005-2009 and 2010-2013). We estimated stage-specific net survival only for cancers with at least 10 patients in each stage category and calendar period. Due to low numbers for most cancers,

we present unstandardised 1- and 5-year stage-specific survival estimates for all ages combined.

Standardisation is crucial when comparing populations or regions that differ with respect to age. Due to Kuwait's relatively small population and the rarer nature of some cancers, however, age-standardisation was only possible for three cancers: colon, lung and breast. To make comparisons between Kuwait and the US, stage-specific survival estimates were obtained from the CONCORD-2 supplementary studies on US data for colon,[151] lung[152] and breast cancer.[153] To be able to compare results in Kuwait with the US, survival was estimated for the calendar period 2004-2009. For these analyses, we present age-standardised stage-specific 5-year net survival, where possible.

Net survival is the probability for cancer patients to survive their cancer up to a given time following diagnosis (e.g., 1 or 5 years), after correcting for competing causes of death (background mortality). To control for background mortality, we used life tables of all-cause mortality in the general population. We used life tables by single year of age ("complete" life tables), sex, calendar year of death, and nationality (Kuwaiti, non-Kuwaiti).[148]

We used the Pohar-Perme estimator[86] to estimate net survival, implemented with the programme stns[122] in Stata version 14.[154] This estimator accounts for the fact that the hazard of death due to causes other than cancer (competing causes) is higher among older patients.

For patients diagnosed during 2000-2003 and 2004-2009, the *cohort* approach was used to estimate survival. The cohort approach is considered the gold standard,[85] and can be used only when all patients in the cohort have had the opportunity to be followed up for the full duration of the follow-up required, in this case, five years. For patients diagnosed during 2010-2013, the *complete* approach was used because five years of follow-up data were not available for all patients by December 2015. This approach enables survival estimates to be produced for recently diagnosed patients.[89]

Net survival estimates were age-standardised where possible, using the International Cancer Survival Standard (ICSS) weights,[92] in which age at diagnosis is categorised into 5 groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years. The 95% confidence intervals (CI) for all unstandardised and age-standardised estimates were derived assuming a normal distribution, truncated to the range 0-100. Confidence intervals were constructed using standard errors calculated using the Greenwood method.[125] When no deaths or censorings occurred within 5 years, or if all patients died (survival probability 1 or 0), a binomial approximation was obtained for the upper and lower bound of the CI.

Results

Colon (46.6%), rectal (39.7%), breast (49.4%) and cervical cancer (36.2%) were most commonly diagnosed at regional stage, while liver (29.9%), pancreas (48.3%) and lung (41.2%) were mostly diagnosed at distant stage (Table 6.1). For oesophagus (~23%), stomach (~32%), melanoma (~22%) and ovary (~32%), the proportion of stage at diagnosis was similar for both regional and distant stage. The proportion of men diagnosed with prostate cancer at localised stage (25.7%) was similar to the proportion of men diagnosed at distant stage (24.0%).

Overall, stage data were available for 74.1% of patients diagnosed during 2000-2013. This proportion decreased from 88.9% in 2000-2004 to 59.4% in 2010-2013. Over this 14-year period, the highest proportion of unknown stage was for liver (52.1%) and oesophageal cancer (42.2%); the lowest was for colon (19.1%) and breast cancer (21.1%).

Between 2000-2004 and 2005-2009, when the availability of data on stage was reasonably high, a common trend was observed in the stage distribution for most cancers: the proportion of patients diagnosed at localised and regional stage decreased, while that of distant and unknown stage increased. The exceptions were colon and liver cancer, where the proportion of patients diagnosed at localised stage remained similar, and cancers of the breast and

prostate, where the proportion diagnosed at a localised stage increased slightly (18.7% to 22.4%, and 23.3 to 25.4%, respectively).

Stage-specific survival

In general, survival for all cancers was lower for patients diagnosed at more advanced stage (Table 6.2). For patients diagnosed during 2010-2013, for whom unknown stage at diagnosis was the highest, survival for patients with unknown stage was either similar or higher than the survival of all stages combined, for almost all cancers. This trend was also observed for patients diagnosed with unknown stage during 2000-2004 and 2005-2009.

During 2005-2009, one-year survival for colon, rectal, breast and ovarian cancer was generally similar for patients diagnosed at localised or regional stage (Figure 6.1). One- and five-year survival for colon, rectal, breast, cervical and prostate cancer, was high (almost 90% or higher) and relatively similar, for patients diagnosed at localised stage. Five-year survival for all cancers was relatively low, ranging from 43.5% for prostate to 0% for stomach, for patients diagnosed at distant stage.

During the same period, the greatest difference in five-year survival between regional and distant stage at diagnosis, was observed for colon, rectum and breast (>50%), followed by prostate, stomach and ovary (about 30%). For some of the more lethal cancers, the difference in one-year survival between regional and distant stage was substantially smaller (around 25%), e.g., for stomach (70.4% *vs*. 44.7%) and pancreatic cancer (47.1% *vs.* 18.6%).

Comparisons between Kuwait and the United States

During 2004-2009, the proportion of patients diagnosed at localised stage was substantially lower in Kuwait than in the US for colon (10.7% vs. 37.8%) and breast (21.9% vs. 59.1%), while the proportions of regional, distant and unknown stages were higher, with differences ranging from 5% to 21% (Figure 6.2). For lung cancer, the proportion of localised stage was

much lower in Kuwait than in the US (3.5% vs.17.7%), however the proportion was similar in the two countries for regional (22.5% vs. 23.4%) and distant stage (47.6% vs. 50.0%).

Age-standardised five-year net survival in Kuwait for all stages combined for colon (50.6%), lung (15.3%) and breast (70.8%) was lower than in the US (64.6%, 19.0% and 88.6%, respectively) (Table 6.3).

For colon cancer, stage-specific five-year net survival was similar in Kuwait and the US for both regional disease (73.0% *vs*. 70.2%, and distant stage (13.7% *vs.* 13.8%).

For lung cancer, the only age-standardised stage-specific survival estimate available for Kuwait was for distant stage. Survival for patients diagnosed at distant stage in Kuwait was somewhat higher than in the US (8.0% *vs.* 4.8%). For breast cancer, stage-specific survival was generally similar in Kuwait and the US: slightly lower for localised stage (94.4% *vs.* 98.3%) and slightly higher for distant stage (28.4% *vs.* 24.5%). For regional stage, stage-specific survival in Kuwait was lower than in the US (75.7% *vs.* 82.3%).

Discussion

This is the first population-based study to date in Kuwait to assess the distribution of stage at diagnosis and stage-specific survival, over a 14-year period, for up to 12 malignancies. To examine the distribution of stage at diagnosis is essential to interpret the variations in survival over time and helps identify cancers for which earlier diagnosis can achieve the greatest benefit. Differences in population-based survival between different populations or regions may also be partly explained by differences in stage of disease at diagnosis.[155,156] This study produced stage-specific net survival estimates up to 5 years for colon, lung and breast cancer, taking into account the differences in the age profile of cancer patients and the risk of death from other causes, thus enabling robust comparisons of stage-specific survival over time.

Age-standardisation is essential to compare survival over time, or between different regions, since net survival can vary considerably by age, and the age structure of cancer patients differs between countries and over time. However, due to the small number of patients available for analysis in Kuwait, age-standardisation by stage was not possible for many cancers. Comparisons of stage-specific survival over time in Kuwait were therefore performed using unstandardised estimates.

During 2000-2013, stage was known for 74% of the patients. The proportion of patients with known stage decreased over the 14-year period, reaching its lowest (59%) during 2010-2013. The mean age, as well as the age distribution, were also generally similar for the patients with known and unknown stage at diagnosis during 2010-2013, with exception to pancreatic cancer, where the proportion of older patients (> 85 years) was greater among patients with unknown stage. The survival for patients with known stage, for most cancers, was also generally similar to that for patients with unknown stage. The unavailability of information on stage in this case is therefore less likely due to physicians' staging practices, or to patients not being medically fit for staging and treatment. A plausible explanation could be that more patients are receiving their first treatment abroad, and therefore are not staged in Kuwait. Receiving treatment abroad is a service provided by the government, covering full treatment costs. With the Ministry of Health's increased budget for overseas treatment in 2009, more patients have been utilising this option.[157] The increased proportion of unknown stage for patients diagnosed during 2010-2013, could thus be due to more patients receiving treatments abroad.

During 2005-2009, 1- and 5-year stage-specific survival for patients diagnosed at localised stage was about 90% or higher for colon, rectal, breast, cervical and prostate cancer. In Kuwait, these cancers are most commonly diagnosed at regional stage, and the proportion of patients diagnosed at localised stage is low, ranging from 25.4% for prostate to 10.5% for colon cancer. Furthermore, the largest difference in survival was observed between patients

diagnosed at regional and distant stage. This difference in five-year net survival was most evident (greater than 50%) for cancers of the colon, rectum and breast, followed by those of prostate, stomach and ovary, where this difference was about 30%. This further highlights the cancers for which early diagnosis is important, and where greater efforts are essential to ensure that more patients are diagnosed at an earlier stage, particularly for cancers for which early detection tests and procedures are available.[137]

For colon, lung and breast, we compared survival in Kuwait to that in the US, where survival is among the highest worldwide.[81] We used the calendar period, cancer definitions, data quality control procedures and analytical methods used for the CONCORD-2 supplementary analyses of stage-specific survival for the US,[95] allowing, therefore, appropriate and robust comparisons.

Stage-specific survival for colon cancer in Kuwait was similar to survival in the US for patients diagnosed at regional and distant stage. Due to low number of patients, it was not possible to estimate stage-specific survival for localised stage in Kuwait, however, the proportion of patients diagnosed at localised stage, which generally entails good prognosis, was substantially higher in the US (37.8%) than in Kuwait (10.7%). This difference in the proportion of patients diagnosed at early stage could partially explain the lower survival for all stages combined observed in Kuwait.

For lung cancer, survival for all stages combined was lower in Kuwait (15.3%) than in the US (19.0%). Comparisons of stage-specific estimates were only possible for distant stage. The proportion of distant stage, however, constitutes the majority of lung cancer patients, which was similar in Kuwait and the US (47.6% and 50.9%, respectively). Stage-specific survival for distant stage was somewhat higher in Kuwait (8.0%) than in the US (4.8%). Therefore, the lower survival for all stages combined in Kuwait is probably attributable to differences in the proportion of patients diagnosed at localised stage, which was substantially lower in Kuwait (3.5%) than in the US (17.7%). Further investigation is

necessary to explain the higher survival for patients diagnosed at distant stage in Kuwait. While the introduction of targeted therapies has improved the treatment of advanced lung cancer,[158] the very high cost of these treatments can limit their adoption and application.[159] In Kuwait, treatment is fully covered by the government, so financial limitations will probably have little effect on the usage of such therapies. In the US, medical insurance coverage can limit patients' access to some of the less cost-effective treatments, particularly for patients with a poor prognosis. Therefore, to understand these differences in stage-specific survival, it would be necessary to assess the differences in the modality and access to treatment between the countries.

For breast cancer, the difference in early stage at diagnosis may explain the lower survival observed for all stages combined between Kuwait (70.8%) and the US (88.6%). The lower proportion of women diagnosed at a localised stage could be due to lack of screening. Unlike the US, screening programmes for breast cancer were not available for women diagnosed during 2004-2009, since screening officially commenced in Kuwait in 2014.[140] Differences in early stage diagnoses between the two countries could also be due to other factors such as the population's awareness of early symptoms, knowledge of risk factors and access to timely diagnostic tests.

Survival in Kuwait was also lower than in several other high-income countries.[146] This could also be attributable to differences in diagnostic activity and the tendency towards later diagnosis in Kuwait. Differences in survival can arise due to several other reasons that require further investigation: prevalence of comorbidities; attitudes and behaviours towards treatment; differences in primary care systems; delays in access to treatment; and the efficacy of treatment.

The small population of Kuwait limited our analyses, where the estimation of stage-specific survival by sex was not possible due to small number of patients available for analysis. The interpretation of stage-specific trends over the 14-year period 2000-2013 was also affected

by a high proportion of unknown stage, which was higher for patients diagnosed during 2010-2013 than for patients diagnosed in earlier years.

Conclusion

Complete information on stage at diagnosis is required in order to assess the effectiveness of cancer control strategies. In Kuwait, the quality of and completeness of stage data can be improved in several ways, the most urgent of which is investing in the Kuwait Cancer Registry. This would include increasing the labour force, enabling the staff to cope with the increasing number of diagnoses, and continuously updating the staff's knowledge and skills in order to adapt to changes in staging and coding guidelines. Another way would be to implement more systematic procedures for retrieving patients' medical notes from different hospitals, particularly in the case of those receiving treatment abroad. Finally, investing in an electronic medical record system where all patients' medical data would be stored electronically could improve the timelines substantially, and maximise efficiency to access patients' data.

This study supplements our previous knowledge on the effect of stage at diagnosis as a major determinant of outcome. Our study also shows that a low proportion of early-stage diagnoses could be a major contributing factor to lower survival in Kuwait than in other high-income countries. Investment in early detection, and increasing public awareness of cancer risk factors and symptoms will be vital to reduce the proportion of late-stage diagnoses and, ultimately, improve outcomes.

Tables

Table 6.1 Number of patients and distribution of SEER Summary Stage at diagnosis, by cancer and calendar period, Kuwaiti adults (15-99 years)

Cancer site	No. of cases							
	2000-2004		2005-2009		2010-2013		All periods	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Oesophagus								
Localised	**6**	22.2	**2**	8.3	**3**	7.7	**11**	12.2
Regional	**10**	37.0	**6**	25.0	**4**	10.3	**20**	22.2
Distant	**4**	14.8	**8**	33.3	**9**	23.1	**21**	23.3
Unknown	**7**	25.9	**8**	33.3	**23**	59.0	**38**	42.2
Stomach								
Localised	**2**	3.4	**2**	2.5	**2**	2.9	**6**	2.9
Regional	**32**	54.2	**23**	29.1	**19**	27.5	**74**	35.8
Distant	**13**	22.0	**34**	43.0	**13**	18.8	**60**	29.0
Unknown	**12**	20.3	**20**	25.3	**35**	50.7	**67**	32.4
Colon								
Localised	**25**	10.6	**34**	10.5	**25**	7.2	**84**	9.3
Regional	**162**	68.4	**151**	46.5	**110**	31.8	**423**	46.6
Distant	**39**	16.5	**99**	30.5	**90**	26.0	**228**	25.1
Unknown	**11**	4.6	**41**	12.6	**121**	35.0	**173**	19.1
Rectum								
Localised	**19**	22.4	**18**	13.9	**13**	11.3	**50**	15.2
Regional	**48**	56.5	**53**	40.8	**30**	26.1	**131**	39.7
Distant	**9**	10.6	**31**	23.9	**17**	14.8	**57**	17.3
Unknown	**9**	10.6	**28**	21.5	**55**	47.8	**92**	27.9
Liver								
Localised	**3**	4.4	**5**	4.7	**4**	4.6	**12**	4.6
Regional	**17**	25.0	**8**	7.6	**10**	11.5	**35**	13.4
Distant	**15**	22.1	**39**	36.8	**24**	27.6	**78**	29.9
Unknown	**33**	48.5	**54**	50.9	**49**	56.3	**136**	52.1
Pancreas								
Localised	**2**	3.5	**4**	4.4	**1**	1.1	**7**	2.9
Regional	**23**	40.4	**15**	16.5	**15**	16.3	**53**	22.1
Distant	**22**	38.6	**49**	53.9	**45**	48.9	**116**	48.3
Unknown	**10**	17.5	**23**	25.3	**31**	33.7	**64**	26.7
Lung								
Localised	**9**	5.0	**7**	3.7	**2**	1.1	**18**	3.2
Regional	**78**	43.6	**43**	22.5	**30**	16.0	**151**	27.1
Distant	**66**	36.9	**84**	44.0	**80**	42.6	**230**	41.2
Unknown	**26**	14.5	**57**	29.8	**76**	40.4	**159**	28.5
Melanoma								
Localised	**1**	20.0	**1**	14.3	**1**	16.7	**3**	16.7
Regional	**2**	40.0	**1**	14.3	**1**	16.7	**4**	22.2
Distant	**1**	20.0	**3**	42.9	**0**	0.0	**4**	22.2
Unknown	**1**	20.0	**2**	28.6	**4**	66.7	**7**	38.9
Breast								
Localised	**117**	18.7	**213**	22.4	**149**	15.1	**479**	18.7
Regional	**431**	68.9	**461**	48.6	**374**	37.9	**1266**	49.4
Distant	**47**	7.5	**126**	13.3	**102**	10.3	**275**	10.7
Unknown	**31**	5.0	**149**	15.7	**361**	36.6	**541**	21.1
Cervix								
Localised	**19**	30.7	**15**	25.4	**6**	14.3	**40**	24.5
Regional	**28**	45.2	**20**	33.9	**11**	26.2	**59**	36.2
Distant	**5**	8.1	**3**	5.1	**2**	4.8	**10**	6.1
Unknown	**10**	16.1	**21**	35.6	**23**	54.8	**54**	33.1
Ovary								
Localised	**10**	16.1	**10**	10.9	**3**	4.5	**23**	10.4
Regional	**30**	48.4	**23**	25.0	**18**	26.9	**71**	32.1
Distant	**16**	25.8	**36**	39.1	**19**	28.4	**71**	32.1
Unknown	**6**	9.7	**23**	25.0	**27**	40.3	**56**	25.3
Prostate								
Localised	**27**	23.3	**43**	25.4	**61**	27.2	**131**	25.7
Regional	**36**	31.0	**21**	12.4	**15**	6.7	**72**	14.2
Distant	**33**	28.5	**53**	31.4	**36**	16.1	**122**	24.0
Unknown	**20**	17.2	**52**	30.8	**112**	50.0	**184**	36.2
All cancers								
Localised	**240**	15.2	**354**	15.9	**270**	11.9	**864**	14.2
Regional	**897**	56.7	**825**	37.1	**637**	28.2	**2359**	38.9
Distant	**270**	17.1	**565**	25.4	**437**	19.3	**1272**	21.0
Unknown	**176**	11.1	**478**	21.5	**917**	40.6	**1571**	25.9

Table 6.2 Unstandardised net survival (NS, %) at one and 5 years since diagnosis, by SEER Summary Stage and calendar period; Kuwaiti adults (15-99 years) diagnosed during 2000-2013, followed to 31 December 2015

Cancer site	Calendar period	1-year net survival										5-year net survival									
		Localised		Regional		Distant		Unkown stage		All stages		Localised		Regional		Distant		Unkown stage		All stages	
		NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI
Stomach	**2000-2004**	..		**53.2**	35.7 - 70.6	**40.6**	14.6 - 66.7	**46.6**	18.7 - 74.6	**50.8**	37.7 - 63.9	..		**20.7**	6.3 - 35.1	**11.1**	0.0 - 29.3	**20.3**	0.0 - 42.2	**18.9**	8.0 - 29.9
	2005-2009	..		**70.4**	51.8 - 88.9	**44.7**	28.2 - 61.2	**40.3**	19.6 - 61.1	**52.6**	41.5 - 63.6	..		**32.1**	13.0 - 51.1	**0.0**	0.0 - 0.0	**15.2**	0.6 - 29.8	**15.9**	7.8 - 24.0
	2010-2013	..		**59.0**	37.1 - 80.8	**30.9**	7.5 - 54.4	**55.2**	38.7 - 71.7	**51.6**	39.7 - 63.5	..		**31.9**	9.3 - 54.4	**8.0**	0.0 - 19.9	**28.9**	12.2 - 45.6	**20.6**	8.4 - 32.9
Colon	**2000-2004**	**100.0**	86.3 - 100.0	**89.4**	84.3 - 94.5	**79.7**	66.8 - 92.5	**90.9**	74.7 - 100.0	**89.5**	85.2 - 93.7	**84.6**	66.9 - 100.0	**69.5**	61.0 - 77.9	**23.1**	9.2 - 37.0	**82.4**	52.1 - 100.0	**64.8**	57.6 - 72.0
	2005-2009	**100.0**	89.7 - 100.0	**97.9**	95.1 - 100.0	**66.2**	56.7 - 75.8	**70.5**	56.1 - 85.0	**85.3**	81.3 - 89.4	**90.0**	76.3 - 100.0	**77.2**	69.4 - 84.9	**16.2**	8.8 - 23.7	**58.8**	41.7 - 76.0	**57.8**	51.9 - 63.7
	2010-2013	**100.0**	86.3 - 100.0	**97.6**	94.1 - 100.0	**64.2**	54.2 - 74.3	**87.1**	80.8 - 93.4	**85.6**	81.8 - 89.5	**97.6**	80.7 - 100.0	**83.3**	72.8 - 93.8	**29.7**	18.5 - 40.8	**64.6**	51.8 - 77.4	**63.3**	56.3 - 70.2
Rectum	**2000-2004**	**89.4**	74.0 - 100.0	**95.0**	88.1 - 100.0	..		..		**90.4**	83.5 - 97.2	**77.4**	54.7 - 100.0	**53.6**	38.7 - 68.6	..		..		**60.7**	49.2 - 72.3
	2005-2009	**100.0**	81.5 - 100.0	**97.6**	92.4 - 100.0	**75.6**	60.3 - 90.9	**93.2**	83.8 - 100.0	**92.4**	87.3 - 97.4	**99.0**	88.5 - 100.0	**70.2**	55.9 - 84.5	**19.9**	5.2 - 34.7	**61.5**	41.8 - 81.2	**60.8**	51.3 - 70.3
	2010-2013	**100.0**	75.3 - 100.0	**100.0**	88.4 - 100.0	**59.8**	36.9 - 82.7	**94.4**	87.5 - 100.0	**91.8**	86.3 - 97.2	**86.6**	65.8 - 100.0	**76.3**	55.0 - 97.7	**23.5**	3.0 - 44.0	**72.7**	45.1 - 100.0	**67.0**	51.7 - 82.3
Liver	**2000-2004**	..		**32.2**	10.4 - 54.0	**27.5**	6.2 - 48.8	**35.1**	18.8 - 51.4	**34.3**	22.8 - 45.8	..		**7.2**	0.0 - 18.0	**6.9**	0.0 - 17.4	**9.7**	0.0 - 20.0	**11.4**	3.5 - 19.2
	2005-2009	..		..		**26.5**	12.7 - 40.3	**41.5**	28.3 - 54.7	**36.8**	27.4 - 46.1	..		..		**4.4**	0.0 - 10.5	**19.3**	8.2 - 30.4	**12.4**	5.8 - 19.1
	2010-2013	..		**50.5**	21.5 - 79.5	**29.7**	12.0 - 47.4	**33.5**	20.2 - 46.8	**36.5**	26.3 - 46.8	..		**0.3**	0.0 - 1.0	**0.0**	0.0 - 0.0	**11.1**	1.7 - 20.6	**8.3**	1.8 - 14.9
Pancreas	**2000-2004**	..		**18.5**	3.3 - 33.7	**24.7**	7.0 - 42.3	**40.3**	11.8 - 68.8	**27.8**	16.0 - 39.5	..		**9.2**	0.0 - 20.0	**5.0**	0.0 - 12.6	**10.1**	0.0 - 24.9	**11.2**	3.1 - 19.3
	2005-2009	..		**47.1**	22.8 - 71.3	**18.6**	8.0 - 29.3	**26.6**	9.2 - 44.0	**27.8**	18.6 - 37.0	..		**6.9**	0.0 - 17.4	**4.5**	0.0 - 9.9	**4.4**	0.0 - 11.1	**8.2**	2.5 - 13.8
	2010-2013	..		**87.1**	70.4 - 100.0	**24.8**	12.4 - 37.2	**46.0**	28.6 - 63.4	**43.1**	32.9 - 53.2	..		**12.1**	0.0 - 28.3	**7.0**	0.1 - 14.0	**25.0**	6.0 - 44.1	**15.3**	6.8 - 23.8
Lung	**2000-2004**	..		**44.9**	33.6 - 56.2	**29.7**	18.6 - 40.7	**29.3**	11.7 - 46.8	**38.0**	30.6 - 45.3	..		**17.1**	8.1 - 26.2	**6.8**	0.7 - 12.8	**8.9**	0.0 - 19.9	**13.7**	8.2 - 19.3
	2005-2009	..		**59.8**	44.8 - 74.8	**34.2**	23.9 - 44.4	**46.4**	33.2 - 59.5	**45.0**	37.8 - 52.2	..		**23.6**	10.0 - 37.2	**7.6**	1.8 - 13.5	**17.8**	7.1 - 28.5	**15.7**	10.1 - 21.3
	2010-2013	..		**61.5**	43.9 - 79.2	**39.6**	28.8 - 50.4	**49.8**	38.5 - 61.2	**47.9**	40.6 - 55.1	..		**17.7**	2.3 - 33.0	**6.7**	0.4 - 12.9	**19.0**	7.5 - 30.5	**13.9**	7.6 - 20.3
Breast	**2000-2004**	**99.0**	96.7 - 100.0	**96.8**	95.0 - 98.7	**85.5**	75.2 - 95.9	**87.6**	75.9 - 99.2	**96.0**	94.3 - 97.7	**88.6**	81.4 - 95.7	**76.7**	72.3 - 81.2	**44.5**	29.6 - 59.3	**66.7**	48.8 - 84.6	**76.1**	72.4 - 79.9
	2005-2009	**99.3**	97.7 - 100.0	**98.0**	96.5 - 99.5	**80.1**	73.0 - 87.1	**94.3**	90.3 - 98.4	**95.4**	93.9 - 96.8	**98.2**	94.4 - 100.0	**80.8**	76.8 - 84.9	**30.7**	22.5 - 39.0	**78.3**	70.3 - 86.4	**77.7**	74.7 - 80.7
	2010-2013	**99.7**	98.4 - 100.0	**97.8**	96.1 - 99.6	**79.3**	71.3 - 87.3	**97.3**	95.4 - 99.2	**96.2**	94.8 - 97.5	**95.0**	89.2 - 100.0	**85.4**	80.2 - 90.7	**38.2**	27.9 - 48.6	**89.0**	83.7 - 94.2	**82.6**	79.3 - 85.9
Cervix	**2000-2004**	**84.6**	68.6 - 100.0	**89.8**	78.5 - 100.0	..		**80.2**	56.4 - 100.0	**84.4**	75.2 - 93.6	**54.4**	31.9 - 76.9	**59.3**	40.6 - 78.0	..		**80.4**	56.6 - 100.0	**57.8**	45.0 - 70.6
	2005-2009	**93.6**	81.3 - 100.0	**80.7**	63.5 - 97.8	..		**90.7**	78.1 - 100.0	**88.7**	80.4 - 97.0	**88.4**	71.5 - 100.0	**68.3**	47.1 - 89.4	..		**72.9**	52.5 - 93.3	**73.8**	61.7 - 86.0
	2010-2013	..		**91.1**	74.9 - 100.0	..		**78.6**	61.7 - 95.4	**86.3**	75.6 - 96.9	..		**94.7**	77.9 - 100.0	..		**62.2**	42.1 - 82.2	**71.8**	57.2 - 86.5
Ovary	**2000-2004**	**100.0**	69.2 - 100.0	**77.3**	62.2 - 92.4	**56.7**	33.7 - 79.7	..		**73.4**	62.2 - 84.5	**100.0**	69.2 - 100.0	**36.0**	18.5 - 53.4	**6.4**	0.0 - 16.3	..		**38.9**	26.3 - 51.5
	2005-2009	**100.0**	69.2 - 100.0	**95.8**	87.6 - 100.0	**64.4**	48.8 - 80.0	**74.9**	57.2 - 92.6	**79.0**	70.5 - 87.4	**81.1**	57.3 - 100.0	**54.2**	32.6 - 75.8	**23.1**	9.5 - 36.7	**43.4**	22.5 - 64.3	**42.6**	32.0 - 53.3
	2010-2013	..		**84.1**	66.9 - 100.0	**64.3**	43.0 - 85.6	**81.9**	67.4 - 96.3	**78.3**	68.3 - 88.3	..		**61.6**	37.6 - 85.6	**0.1**	0.0 - 0.2	**60.6**	41.9 - 79.3	**40.3**	22.1 - 58.5
Prostate	**2000-2004**	**100.0**	87.2 - 100.0	**91.7**	80.8 - 100.0	**72.4**	56.3 - 88.6	**88.5**	72.7 - 100.0	**88.8**	82.0 - 95.5	**93.3**	69.3 - 100.0	**88.2**	69.1 - 100.0	**40.9**	20.6 - 61.1	**96.9**	72.8 - 100.0	**78.8**	66.7 - 90.9
	2005-2009	**100.0**	91.8 - 100.0	**88.0**	72.8 - 100.0	**83.6**	72.1 - 95.0	**87.1**	76.9 - 97.3	**90.6**	85.3 - 96.0	**96.6**	80.6 - 100.0	**76.3**	55.0 - 97.6	**43.5**	27.1 - 59.9	**72.5**	55.5 - 89.4	**71.3**	61.6 - 80.9
	2010-2013	**100.0**	97.3 - 100.0	**100.0**	78.2 - 100.0	**99.5**	91.7 - 100.0	**94.4**	88.9 - 99.8	**97.9**	94.7 - 100.0	**100.0**	100.0 - 100.0	**56.2**	11.3 - 100.0	**81.4**	57.2 - 100.0	**98.3**	84.1 - 100.0	**98.1**	88.6 - 100.0

SEER: Surveillance, Epidemiology and End Results; CI: Confidence interval

Table 6.3 Number of patients, SEER Summary Stage distribution (%) and age-standardised net survival (NS,%), for adults in Kuwait (Kuwaiti) and the United States (all races), 2004-2009

Cancer	SEER SS	Kuwait			United States		
		No.of patients (%)	NS (%)	95% CI	No.of patients (%)	NS (%)	95% CI
Colon	**All stages**	365	**50.6**	43.4 - 57.8	534,721	**64.6**	64.4 - 64.9
	Localised	(10.7)	**..**	.. ..	(37.8)	**89.7**	89.4 - 90.0
	Regional	(46.9)	**73.0**	66.8 - 79.3	(34.9)	**70.2**	69.8 - 70.6
	Distant	(29.9)	**13.7**	7.7 - 19.7	(19.3)	**13.8**	13.4 - 14.1
	Unknown	(12.6)	**..**	.. ..	(7.9)	**49.4**	48.6 - 50.2
Lung	**All stages**	227	**15.3**	10.7 - 20.0	955,184	**19.0**	18.8 - 19.1
	Localised	(3.5)	**..**	.. ..	(17.7)	**55.1**	54.7 - 55.5
	Regional	(22.5)	**..**	.. ..	(23.4)	**26.4**	26.0 - 26.7
	Distant	(47.6)	**8.0**	3.8 - 12.2	(50.9)	**4.8**	4.7 - 4.9
	Unknown	(26.4)	**..**	.. ..	(8.0)	**13.8**	13.4 - 14.3
Breast	**All stages**	1,092	**70.8**	64.0 - 77.6	926,271	**88.6**	88.4 - 88.8
	Localised	(21.9)	**94.4**	88.4 - 100.0	(59.1)	**98.3**	98.1 - 98.6
	Regional	(51.0)	**75.7**	67.2 - 84.3	(30.2)	**82.3**	81.9 - 82.7
	Distant	(12.5)	**28.4**	22.3 - 34.5	(5.2)	**24.5**	23.7 - 25.2
	Unknown	(14.7)	**65.7**	53.6 - 77.9	(5.4)	**72.6**	71.9 - 73.4

SEER SS: Surveillance, Epidemiology, and End Results Summary Stage; KW: Kuwait; US: United States; CI: Confidence interval

Figures

Figure 6.1 Trends in unstandardised net survival (NS, %) at 1 and 5 years, by SEER Summary Stage at diagnosis, Kuwait 2005-2009

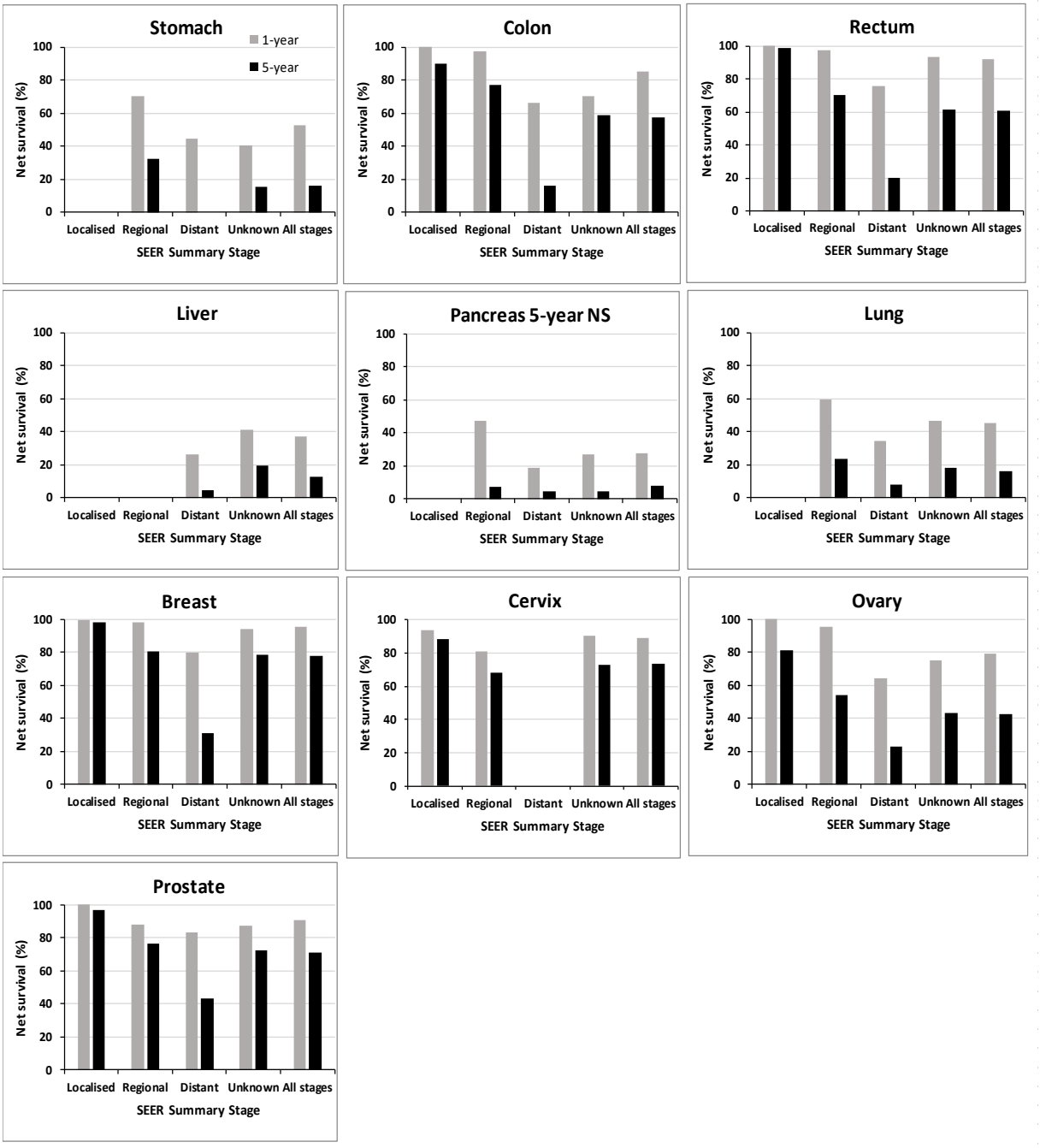
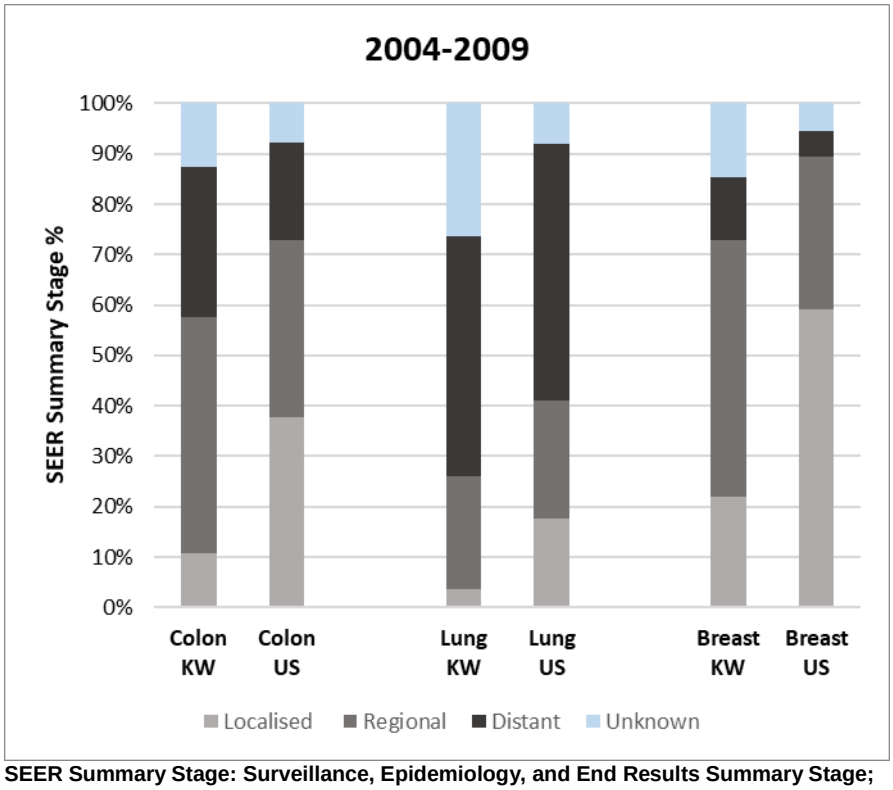


Figure 6.2 Distribution (%) of SEER Summary Stage for adults in Kuwait (Kuwaiti) and the United States (all races), 2004-2009



SEER Summary Stage: Surveillance, Epidemiology, and End Results Summary Stage; KW: Kuwait; US: United States

Chapter 7: Research paper IV; Progress against cancer in Kuwait: Trends in incidence, survival and mortality

Continuous monitoring of the cancer burden is essential to evaluate progress against cancer. However, for this evaluation to be comprehensive, trends in incidence, survival and mortality should be considered simultaneously.[16,104,160]

Cancer incidence and mortality rates in Kuwait have been reported previously and, through this thesis, net survival for 18 of the most common cancers has also been estimated. However, survival in the context of incidence and mortality has not yet been assessed.

This chapter addresses the final objective of this thesis: to evaluate the overall effectiveness of the Kuwaiti health care system in managing cancer during 2000-2013, using the three major cancer control metrics (incidence, survival and mortality).

To achieve this, incidence, survival and mortality were estimated for all Kuwaiti adults (15-99 years) and children (0-14 years), diagnosed with one of the 18 most common cancers during 2000-2004, 2005-2009 and 2010-2013. Data on all malignant neoplasms and cancer deaths were obtained from the Kuwait Cancer Registry (KCR). Follow-up data on vital status of all registered cancer patients were obtained using our new approach to ensure that all deaths, irrespective of cause, were included [see Chapter 4]. To calculate incidence and mortality rates, population counts for Kuwaiti residents by year, age group and sex, were obtained from Kuwait's Statistics Department at the Public Authority of Civil Information (PACI). Average annual incidence and mortality rates were produced, by calendar period, for each index cancer, age-standardised to the world standard population. Five-year net survival, corrected for background mortality using life tables of all-cause mortality by single year of age, sex and calendar period, was estimated by calendar period using the Pohar-Perme estimator, [see Chapter 5].

Evaluating incidence, survival and mortality revealed several patterns from which progress against cancer can be inferred. Patterns of increased survival combined with decreased incidence and mortality, explicitly imply progress in cancer control. However, other patterns showing improved prevention strategies, more effective removal of cancer precursors, enhanced early diagnostic activity, or better treatment and access to care, can also be regarded as progress.

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SECTION A – Student Details

Student	Eiman Alawadhi
Principal Supervisor	Dr.Claudia Allemani
Thesis Title	Progress against cancer in Kuwait: trends in incidence, survival and mortality

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?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	No

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Asia Pacific Journal of Cancer Prevention
Please list the paper's authors in the intended authorship order:	Alawadhi E, Al-Awadi A, Elbasmi A, Coleman MP, Allemani C.
Stage of publication	**Submitted**

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)	Eiman Alawadhi was the lead and corresponding author on the paper. She was responsible for planning and carring out the literature review, data analysis, and drafting the paper. The co-authors assissted in planning the content of the paper, and provided input on the data analysis and feedback on the draft.

Student Signature: [redacted] **Date:** 15 March 2019

Supervisor Signature: [redacted] **Date:** 15 March 2019

Research paper IV [unpublished]

Progress against cancer in Kuwait: trends in incidence, survival and mortality

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Introduction

The question of whether progress is being made in alleviating the cancer burden is of great interest to health professionals, policymakers and the general public alike. To assess progress is critical to determine whether primary prevention, diagnostic procedures and treatment modalities are efficient and effective. It is also crucial to evaluate whether the current cancer control policies are adequate, or if further changes in the cancer care system are required.

The goal of primary prevention is to reduce the incidence of cancer and overall population morbidity. For those people who are eventually diagnosed with cancer, the goal of diagnosing the disease and treating it effectively is to reduce cancer deaths in the population, but evaluating progress based solely on mortality rates can be misleading for several reasons. Mortality rates are based on the selection and coding of the underlying cause of death, which can be affected by several factors: technological capabilities in detecting cancer that can affect the coding of cancer as the primary cause, changes in the selection and coding of the cause of death, and differences in accurately determining the underlying cause of death between individual physicians, different hospitals and regions.[161] Also, in many countries, not all deaths are registered.[162] Moreover, mortality rates are not well suited to evaluate changes in the diagnostic capabilities or treatment of cancer, in a specific period of time. That is primarily because mortality rates are derived from deaths of patients who may have been diagnosed over many years in the past, and may not have received the same cancer management and treatment. The interpretation of mortality is also complex, since it is influenced both by the development of new cases (incidence) and the effectiveness of the health system in managing and treating the cancer (survival).[16]

Population-based cancer survival is the appropriate indicator to assess the effectiveness of the cancer care system, since it encompasses all aspects of the healthcare system; from accurate and early diagnosis, to effective and prompt delivery of treatment.[20] While increased survival is desirable, this might not always be indicative of true progress. For instance, an increase in survival can sometimes be observed as a result of early detection through improved diagnostic procedures or screening. However, if early detection is not coupled with effective treatment, the survival duration will increase but the mortality might not necessarily decease. This represents a situation where survival is increasing but no deaths are prevented or delayed.

On the other hand, a lack of improvement in survival does not necessarily imply worse outcomes. For example, advanced detection procedures that enable the removal of malignant but pre-invasive or *in situ* tumours can shift the biological spectrum of invasive malignancies that are diagnosed towards more aggressive cancers: this can prompt survival trends to plateau or even decline, despite an overall reduction in incidence and mortality. Therefore, in order to achieve a comprehensive evaluation of the progress against cancer, trends in incidence, survival and mortality should be evaluated simulatanouely.[16,104,160]

In Kuwait, incidence, survival and mortality have been previously assessed; however, there is no existing research evaluating these metrics simultaneously. In this study, we aim to evaluate progress against cancer in Kuwait via assessing survival in the context of incidence and mortality, for Kuwaiti children (0-14 years) and adults (15-99 years) diagnosed with one of 18 common cancers during 2000-2013.

Materials and Methods:

Data on all malignant neoplasms were obtained from the Kuwait Cancer Registry (KCR). The KCR is a national population-based cancer registry that collects and maintains high-quality and complete incidence data.[107] The International Classification of Diseases for Oncology (ICD-O-3)[115] is used for all clinical coding.

Data were obtained for all Kuwaiti adults (aged 15-99) and children (aged 0-14) diagnosed during 2000-2013 with an index cancer: oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast (women), cervix, ovary, prostate and melanoma of the skin in adults, in addition to brain tumours, leukaemias and lymphomas in both adults and children. To define the cancers, we used the anatomical site (topography) for all the solid tumours, and morphology for leukaemias, lymphomas, and melanoma of the skin.

Data on cancer deaths occurring during 2000-2013 were also obtained from the KCR. The registry captures all cancer deaths in a specific year, through manual scanning of all "Death Announcements" at the National Centre for Health Information. An individual for whom the immediate cause or the underlying cause of death is indicated as cancer, is considered a cancer death.[149] The most recent follow-up for vital status was performed in January 2018.

Population counts for Kuwaiti residents for each year (2000-2013), by age group and sex, were obtained from Kuwait's Statistics Department at the Public Authority of Civil Information.

Complete and accurate data on follow-up for vital status (alive, dead, lost to follow-up) for all registered cancer patients, necessary to estimate the survival probability, were available as at 31 December 2015. Follow-up data were obtained using a combination of passive and active methods that ensured all deaths were included, irrespective of whether deaths were cancer-related.[149]

Incidence and mortality rates were produced by calendar period (2000-2004, 2005-2009, 2010-2013) for each of the index cancers. To avoid having small numbers of patients for analyses, average annual rates were estimated for both sexes combined, and expressed as the number of cancer diagnoses or cancer deaths per 100,000 person-years for adults, and per 1,000,000 person-years for children.

When the number of incident cases or cancer deaths was fewer than 10, rates were not produced. Incidence and mortality rates were age-standardised using the direct method

and the world standard population.[163] For adults, age was categorised into 18 age groups: 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and 85 years and over. For children, the standard weights for the three age groups (0-4, 5-9, 10-14) were scaled up to ensure their sum equals to 1.[164] The 95% confidence intervals (Cls) were also calculated.[165]

Five-year net survival was estimated by calendar period (2000-2004, 2005-2009, 2010-2013) for each index cancer, using the Pohar-Perme estimator,[86] implemented with the program stns[122] in Stata version 14.[154] Survival was not estimated when fewer than 10 patients were available for analysis. For adults, the International Cancer Survival Standard (ICSS) weights[92] were used for age-standardisation, where age at diagnosis was categorised into 5 groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years and, for prostate cancer, 15-54, 55-64, 65-74, 75-84 and 85-99 years. For children, age-standardisation was performed by assigning equal weights to the 3 age-specific estimates: 0-4, 5-9 and 10-14 years. Only unstandardised estimates were reported when standardisation was not possible. The 95% confidence intervals (CI) for all unstandardised and age-standardised estimates were derived assuming a normal distribution, truncated to the range 0-100. Confidence intervals were constructed using standard errors calculated using the Greenwood method.[125] When no deaths or censorings occurred within 5 years, or if all patients died (survival probability 1 or 0), a binomial approximation was obtained for the upper and lower bound of the CI.[88]

Results:

During 2000-2013, survival increased for oesophagus, stomach, liver, pancreas, breast, prostate, brain (adults), lymphoid neoplasms, lymphoma (children), acute lymphoblastic leukaemia (children), and brain (children). Little or no change (less than 2%) was observed for rectal, lung, ovarian and cervical cancer, while survival declined for colon cancer and myeloid neoplasms in adults (Table 7.1 and Figure 7.1).

Considering survival in the context of incidence and mortality, the following patterns were observed: increase in survival combined with decreased incidence and/or mortality (liver cancer and childhood acute lymphoblastic leukaemia and lymphoma); decrease in incidence with little or no change in survival or mortality (lung, cervical and ovarian cancer); increase in survival with increased incidence or mortality (breast, prostate cancer and lymphoid neoplasms); little or no change in incidence, survival or mortality (rectal cancer); decrease in survival with increased incidence or mortality (colon cancer and myeloid neoplasms); and increase in survival with little or no change in incidence or mortality (oesophagus, stomach, pancreatic cancer, and brain tumours in adults and children) (Figure 7.1).

Increase in survival, decreased incidence or mortality

This pattern was illustrated for liver cancer, and for acute lymphoblastic leukaemia (ALL) and lymphoma in children.

For liver cancer, unstandardised five-year net survival increased from 11.4% to 13.4% for patients diagnosed between 2000-2004 and 2010-2013, incidence fell from 5.5 to 3.6 per 100,000 population and mortality decreased slightly (3.9 to 3.0 per 100,000).

For ALL and lymphoma, survival increased from 76.1% to 88.4% and 93.0% to 96.3%, respectively. Incidence rates dropped from 47.3 to 39.9 per 1,000,000 for ALL, and from 25.2 to 20.0 per 1,000,000 for lymphoma. Mortality rates were not available, because deaths due to lymphoblastic leukaemia (ALL) and lymphoma in children were very low (<10 patients).

Decrease in incidence with little or no change in survival or mortality

Between 2000-2004 and 2010-2013, this pattern was illustrated for lung, cervical and ovarian cancer.

For lung and cervical cancer, incidence declined from 10.2 to 7.4 per 100,000 and from 4.9 to 2.4 per 100,000, respectively.

For cervical cancer, survival increased minimally (54.8% to 56.6%) and mortality remained the same, while for lung cancer, both age-standardised five-year survival and mortality rate remained stable (13.3% to 13.4% and 5.1 to 5.5 per 100,000, respectively).

The same pattern was also observed for ovarian cancer between 2005-2009 and 2010-2013, where incidence decreased (5.8 to 4.3 per 100,000), and age-standardised five-year survival and the mortality rate remained stable (35.4% to 35.1% and 2.9 to 2.9 per 100,000, respectively).

Increase in survival, increased incidence or mortality

For breast, age-standardised five-year survival increased from 68.3% to 75.2% between 2000-2004 and 2010-2013, while incidence and mortality also increased, from 45.6 to 58.7 per 100,000, and from 5.8 to 12.8 per 100,000, respectively.

A similar pattern appeared for prostate cancer patients diagnosed between 2005-2009 and 2010-2013, where increases were observed in survival (71.9% to 84.0%) and incidence (16.0 to 21.5 per 100,000); however, unlike for breast cancer, mortality for prostate cancer decreased during 2005-2013 (from 4.9 to 3.4 per 100,000). For lymphoid neoplasms, slight increases between 2000-2004 and 2010-2013 were observed in incidence (15.5 to 16.7 per 100,000) and mortality (3.5 to 4.3 per 100,000), while the increase in survival was more substantial (71.9% to 84.0%).

Little or no change in survival, incidence or mortality

This pattern was reflected for rectal cancer between 2000 and 2013: little change in any of the three age-standardised metrics was observed (1% or less change in survival and 0.5 or less per 100,000).

For melanoma, incidence, survival and mortality were not estimated, due to small numbers of patients or deaths, but the number of incident cases and deaths remained low throughout 2000-2013.

Decrease in survival, increased incidence or mortality

This pattern was most evident in colon cancer and myeloid neoplasms.

For colon cancer, survival decreased (from 64.8% to 58.5%) between 2000-2004 and 2010-2013, and incidence increased slightly (from 11.4 to 12.6 per 100,000), while mortality more than doubled (2.3 to 5.4 per 100,000). In contrast, a different pattern was observed for colon cancer between 2005-2009 and 2010-2013: survival increased (from 50.2% to 58.5%), while incidence and mortality rates increased slightly (from 11.4 to 12.6, and 4.1 to 5.4 per 100,000, respectively).

For myeloid neoplasms in adults, a similar pattern was observed between 2000-2004 and 2010-2013: survival decreased from 38.6% to 25.6%, while incidence and mortality increased slightly (3.5 to 4.3 per 100,000 and 1.4 to 2.2 per 100,000, respectively). Between 2005-2009 and 2010-2013, however, the three metrics changed relatively little: survival changed from 24.0% to 25.6%, incidence from 4.1 to 4.9 per 100,000 and mortality from 1.9 to 2.2 per 100,000.

Increase in survival, little to no change in incidence or mortality

This pattern was observed for oesophagus, stomach, pancreatic cancer, and brain tumours (adults and children). While survival increased between 2000 and 2013, for all these cancers, incidence and mortality rates changed minimally (1 or less per 100,000).

Discussion:

This study presents the first evaluation of trends in survival during 2000-2013 for 18 common cancers in Kuwait, interpreted in the context of incidence and mortality. To evaluate all three metrics simultaneously allows for a more insightful assessment of cancer control strategies, highlighting patterns in incidence, survival and mortality that can show whether progress is truly being achieved.[16,166]

Between 2000-2004 and 2010-2013, survival increased for most cancers: oesophagus, stomach, liver, pancreas, breast, prostate, lymphoid neoplasms, lymphoma (children),

and acute lymphoblastic leukaemia (children). However, survival decreased for patients diagnosed during 2000-2004 and 2005-2009 for all cancers, with the exception of liver, lung, breast, lymphoid neoplasms and brain (children). This decline was attributed primarily to improvements in the registry's data quality.[146] Over the 14-year period (2000-2013), the percentage of patients lost to follow-up, as well as those registered only from a death certificate (DCO) or detected solely at autopsy, gradually decreased, ultimately reaching 0% for almost all cancers by 2010-2013. In survival analyses, DCOs are excluded because follow-up information for these patients is unavailable. DCO registrations also tend to comprise patients diagnosed with more lethal cancers, or with cancers diagnosed at an advanced stage. Therefore, improved registration practices over the years, resulting in fewer exclusion of DCOs, can also lead to an apparent decline in survival.[129]

The increases in survival between 2005-2009 and 2010-2013 for most cancers, despite continual improvement in data quality, could therefore be indicative of advances in the effectiveness of the healthcare system in managing and treating cancer. These increases in survival also coincide with the establishment of the five-year cancer care partnership between the Kuwait Cancer Control Centre (KCCC) and the Toronto University Health Network (UHN). The latter commenced in January 2011, with the goal of improving the health services for cancer patients in Kuwait.[167] To monitor survival of patients diagnosed after the end of the partnership will be critical to assess its effect on the healthcare system.

Mortality rates were relatively stable for most cancers between 2000-2004 and 2010-2013, with the exception of colon and breast cancer, where mortality increased (2.3 to 5.4 per 100,000, and 5.8 to 12.8 per 100,000, respectively). This lack of decrease in cancer deaths over the years, despite increased survival for many cancers, could be indicative of incomplete death registration in earlier years, particularly during 2000-2004. As with the registration of incident cases, the quality and completeness of death registrations at the KCR have improved over time. Death registration practices are now

more standardised and timely, better coordinated with hospitals and vital statistics offices, and less susceptible to variations in attributing the deaths as “due to cancer”. The latter, however, are dependent on whether the selection of causes leading to the death are coded correctly by physicians.[149] Therefore, incomplete death ascertainment, improper sequencing of causes of death, and differences in certification of cancer as the underlying cause, could collectively constitute a problem in calculating cancer mortality rates. This reinforces the argument against using mortality rates as the sole indicator of progress.

The combination of increased survival with decreased incidence and mortality presents an explicit pattern of progress against cancer. This pattern was shown for liver cancer, and childhood acute lymphoblastic leukaemia (ALL) and lymphoma. For liver cancer, some of the main precursors are chronic infections with hepatitis B (HBV) or C virus (HCV).[168] Therefore, this decrease in incidence of liver cancer in Kuwait, and slight increase in survival (2%), could be due to improved vaccination and medical interventions (e.g. new antiviral therapies for acute HCV and chronic HBV or HCV infections),[168,169] increased public health knowledge of preventing transmission and infection, and enhanced detection or access to care.

For lymphoma and acute lymphoblastic leukaemia in children, progress was mainly attributable to the major advances in the treatment of ALL in children, and lymphoma in both adults and children over the past decades.[170,171] However, the same cannot be implied for myeloid neoplasms in adults, where only slight increases in survival were observed between 2005-2013 (24.0% to 25.6%). This could be partly because improved management of ALL pertains mostly to younger patients, where adults with ALL trend to have worse outcomes than children, due to underutilisation of chemotherapy regimens associated with older age.[172,173] Moreover, our definition of myeloid neoplasms in this study includes other subtypes such as acute myeloid leukaemia (AML), which are associated with poorer prognosis.[142]

Decreases in incidence, observed for lung, cervical and ovarian cancer, are also likely to indicate progress. This is primarily due to the fact that although survival increased minimally for cervix (54.8% to 56.6%) and remained relatively constant for lung and ovary, a decline in incidence generally reflects that fewer people are being diagnosed with the disease. This could be due to lower prevalence of risk factors. In the case of lung cancer, introducing tobacco control initiatives such as the implementation of national tobacco control programmes, smoking bans, smoking cessation support, and decreasing the affordability of cigarettes,[174] could have contributed to the decline in incidence rates. For ovarian cancer, the reduced incidence could reflect the uptake of oral contraceptives or the decline in usage of menopausal hormone therapies,[175] both of which are known to reduce the risk of ovarian cancer.[176]

Declines in incidence can also reflect early diagnostic activity. In the case of cervical cancer, cancer precursors or pre-malignant tumours are detected through pap smears, and are subsequently removed. This leads to an increase in *in situ* tumours [data not shown] and fewer invasive malignancies, without necessarily improving survival.

For breast cancer, incidence, survival and mortality increased between 2000-2004 and 2010-2013, while for prostate cancer, incidence and survival increased, but mortality remained relatively constant. Similar increases in incidence and survival for breast and prostate were also observed in Europe,[177] and were partly attributed to early diagnosis: mammography screening programmes for breast cancer, and widespread use of prostate-specific antigen (PSA) testing for prostate cancer. These early diagnostic procedures can sometimes bias survival estimates: lead-time bias (increases survival through bringing forward the time of diagnosis without postponing the time of death), length bias (increases survival by preferential detection of slow-growing tumours or tumours with good prognosis), and “over-diagnosis” (detecting tumours that would never have progressed to cancer during the patient’s expected lifetime, or progressed so slowly that the patient would have died from other causes without experiencing symptoms that could have led to a clinical diagnosis).[166] These biases, however, are more pronounced

for prostate cancer than breast cancer,[104] implying that the increased survival for prostate cancer does not necessarily reflect true progress. However, between 2005-2009 and 2010-2013, increases in prostate cancer survival in Kuwait were coupled with slight decreases in mortality. This decrease, despite a continuous increase in incidence, could suggest possible therapeutic improvements or better management and access to cancer care.

In Kuwait, the national mammography screening programme for breast cancer was not operational for patients diagnosed during 2000-2013. This suggests that, in addition to opportunistic screening, other factors could be responsible for the increasing incidence, such as delayed childbirth, fewer children and increased obesity.[178,179] The obesity epidemic in Kuwait is striking,[180] and could certainly influence the incidence of obesity-related cancers. These factors could also have contributed to the increased mortality rates observed in Kuwait, and most Asian countries, which conflict with the decreases in breast cancer mortality observed in North America, Western Europe and Oceania.[178] In contrast, the increased survival seen in Kuwait could therefore be attributed to an increase in early-stage diagnosis, providing better treatment opportunities and more effective and individualised approach to treatment,[181] and increased awareness and knowledge of Kuwaiti women with regard to breast cancer warning signs.[182]

Between 2000-2004 and 2010-2013, colon cancer incidence increased slightly, survival decreased, and mortality increased substantially. This pattern, however, was not consistent throughout the 14-year period. Between 2005-2009 and 2010-2013, incidence, survival and mortality all increased. The increases in incidence and mortality could be due to higher prevalence of lifestyle-related risk factors (diet high in fat, high meat consumption, physical inactivity, obesity).[183] However, although these factors are highly prevalent in Kuwait,[184] the incidence rates during 2000-2013 increased only slightly (11.4 to 12.6 per 100,000). This could suggest greater early diagnostic activity, for instance, the widespread use of advanced endoscopy procedures – not necessarily as part of a screening programme – that enable the detection and removal of polyps and

benign tumours, and can result in decreased incidence of invasive malignancies. This can counterbalance the high prevalence of risk factors, leading to a minimal increase in incidence. The increased survival for colon cancer in Kuwait could therefore be due to diagnosis of early-stage tumours or better treatment.

For cancers where survival increased but there was no substantial change in incidence or mortality, increases in survival could be due to various reasons: earlier detection via endoscopy (stomach cancer),[185] enhanced diagnostic imaging (pancreatic cancer),[186] better therapeutic practices, or better access to cancer care. Moreover, in Kuwait, more complete death registration since 2000-2004 could have contributed to the lack of decrease in mortality for many cancers between 2000-2004 and 2010-2015, despite increases in survival. Continuous surveillance of incidence, survival and mortality should therefore be maintained in the future, in order to monitor where mortality eventually decreases as a result of increased survival.

Due to Kuwait's small population, small numbers of patients restricted the estimation of some cancer metrics (e.g. melanoma in adults, childhood mortality). Separate analyses by sex, and age-standardisation of all the survival estimates was also not possible for some cancers, hindering our interpretation of trends throughout the period 2000-2013.

Conclusion

This evaluation of survival alongside incidence and mortality has provided a more comprehensive overview of progress against cancer. In Kuwait, the observed progress might be associated with implantation of preventive strategies (e.g., tobacco control initiatives with lung cancer, or improved HBV vaccination for liver cancer), removal of precursor lesions (e.g., pap smears for cervical cancer), early diagnostic activity (e.g., mammography for breast cancer), and better treatment (e.g., lymphoma, childhood ALL and colon cancer). However, the increase in the incidence of lifestyle-related cancers (e.g., breast and colon cancer) suggests the need for more public health prevention campaigns, particularly targeting obesity. Continuous monitoring will also be required to

assess progress against cancers where survival has not improved, or even declined. Finally, this study accentuates the importance of strategic and continuous evaluation of all aspects of the cancer burden, to aid the efforts made against cancer.

Tables

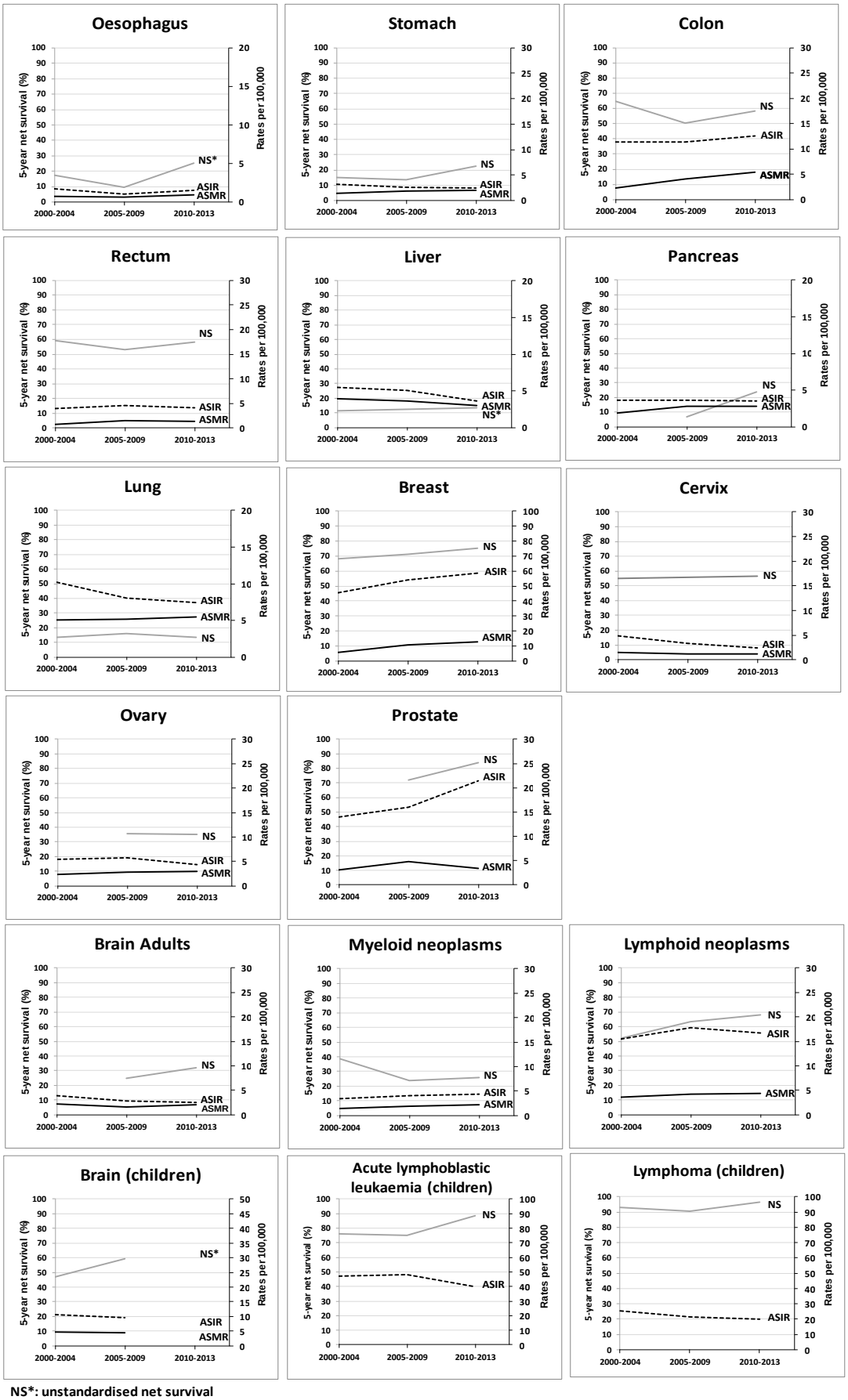
Table 7.1 Age-standardised incidence (ASIR) and mortality rates (ASMR) per 100,000 per years and age-standardised 5-year net survival (NS,%), Kuwaiti adults (0-99 years) and children (0-14 years), 2000-2013

Cancer	Calendar period	No. patients	ASIR rate	ASIR 95% CI	No. patients	Unstandardised NS (%)	Unstandardised NS 95% CI	Standardised NS (%)	Standardised NS 95% CI	Deaths	ASMR rate	ASMR 95% CI
Adults												
Oesophagus	2000-2004	33	**1.7**	1.1 - 2.3	27 §	**17.6**	2.9 - 32.4	..		15	**0.8**	0.4 - 1.2
	2005-2009	25	**1.0**	0.6 - 1.4	24	**9.5**	0.0 - 20.6	..		16	**0.7**	0.3 - 1.0
	2010-2013	39	**1.5**	1.0 - 2.0	39	**25.4**	10.5 - 40.4	..		23	**1.0**	0.6 - 1.4
Stomach	2000-2004	69	**3.2**	2.4 - 4.0	59	**18.9**	8.0 - 29.9	**15.0**	7.2 - 22.8	29	**1.4**	0.9 - 1.9
	2005-2009	81	**2.7**	2.0 - 3.3	79	**15.9**	7.8 - 24.0	**13.4**	7.8 - 19.0	53	**1.9**	1.4 - 2.5
	2005-2009	69	**2.5**	1.9 - 3.1	69	**16.9**	7.4 - 26.4	**22.4**	13.8 - 31.1	53	**2.0**	1.5 - 2.6
Colon	2000-2004	259	**11.4**	10.0 - 12.9	237	**64.8**	57.6 - 72.0	**64.8**	53.1 - 76.5	47	**2.3**	1.6 - 2.9
	2005-2009	332	**11.4**	10.2 - 12.7	325	**57.8**	51.9 - 63.7	**50.2**	42.7 - 57.7	106	**4.1**	3.3 - 4.9
	2010-2013	347	**12.6**	11.2 - 13.9	346	**60.9**	54.5 - 67.2	**58.5**	49.4 - 67.7	141	**5.4**	4.5 - 6.3
Rectum	2000-2004	89	**4.0**	3.2 - 4.9	85	**60.7**	49.2 - 72.3	**59.3**	50.2 - 68.4	15	**0.8**	0.4 - 1.2
	2005-2009	131	**4.5**	3.7 - 5.3	130	**60.8**	51.3 - 70.3	**53.3**	42.4 - 64.2	41	**1.5**	1.0 - 2.0
	2010-2013	115	**4.1**	3.4 - 4.9	115	**63.7**	53.0 - 74.3	**58.2**	48.5 - 67.9	35	**1.3**	0.9 - 1.8
Liver	2000-2004	111	**5.5**	4.4 - 6.5	68 §	**11.4**	3.5 - 19.2	..		78	**3.9**	3.0 - 4.8
	2005-2009	126	**5.0**	4.1 - 5.9	106	**12.4**	5.8 - 19.1	..		87	**3.6**	2.8 - 4.4
	2010-2013	90	**3.6**	2.8 - 4.4	87	**13.4**	6.3 - 20.6	**18.6**	10.0 - 27.2	74	**3.0**	2.3 - 3.7
Pancreas	2000-2004	75	**3.6**	2.7 - 4.4	57 §	**11.2**	3.1 - 19.3	..		37	**1.9**	1.3 - 2.5
	2005-2009	95	**3.7**	2.9 - 4.4	91	**8.2**	2.5 - 13.8	**7.0**	3.1 - 10.9	72	**2.8**	2.1 - 3.4
	2010-2013	95	**3.6**	2.8 - 4.3	92	**13.2**	5.4 - 21.1	**23.6**	12.0 - 35.2	69	**2.8**	2.1 - 3.4
Lung	2000-2004	202	**10.2**	8.8 - 11.6	180	**13.7**	8.2 - 19.2	**13.3**	9.3 - 17.4	103	**5.1**	4.1 - 6.1
	2005-2009	202	**8.0**	6.9 - 9.2	191	**15.7**	10.1 - 21.3	**16.3**	11.1 - 21.5	127	**5.2**	4.3 - 6.1
	2010-2013	189	**7.4**	6.3 - 8.5	188	**13.8**	8.4 - 19.3	**13.4**	8.8 - 18.0	134	**5.5**	4.5 - 6.4
Melanoma (skin)	2000-2004	6 ¥	..		5 ¥	..		..		1 ¥	..	
	2005-2009	7 ¥	..		6 ¥	..		..		4 ¥	..	
	2010-2013	8 ¥	..		7 ¥	..		..		2 ¥	..	
Breast (women)	2000-2004	639	**45.6**	41.9 - 49.3	628	**76.1**	72.3 - 79.8	**68.3**	58.0 - 78.7	78	**5.8**	4.5 - 7.2
	2005-2009	957	**53.9**	50.3 - 57.4	953	**77.8**	74.8 - 80.8	**71.0**	63.8 - 78.2	175	**10.9**	9.2 - 12.6
	2010-2013	989	**58.7**	55.0 - 62.5	987	**80.5**	77.5 - 83.6	**75.2**	66.4 - 83.9	204	**12.8**	11.0 - 14.6
Cervix	2000-2004	64	**4.9**	3.6 - 6.2	62	**57.8**	45.0 - 70.6	**54.8**	45.7 - 63.8	16	**1.5**	0.7 - 2.3
	2005-2009	59	**3.3**	2.4 - 4.2	59	**73.8**	61.7 - 86.0	..		17	**1.2**	0.6 - 1.8
	2010-2013	43	**2.4**	1.7 - 3.2	42	**65.2**	50.1 - 80.3	**56.6**	44.8 - 68.4	18	**1.2**	0.6 - 1.8
Ovary	2000-2004	70	**5.4**	4.0 - 6.7	62	**38.9**	26.3 - 51.5	..		27	**2.4**	1.5 - 3.3
	2005-2009	100	**5.8**	4.6 - 6.9	92	**42.6**	32.0 - 53.3	**35.4**	27.1 - 43.7	44	**2.9**	2.0 - 3.8
	2005-2009	70	**4.3**	3.3 - 5.4	67	**43.3**	31.7 - 54.8	**35.1**	27.5 - 42.8	43	**2.9**	2.0 - 3.8
Prostate	2000-2004	124	**14.0**	11.6 - 16.5	116	**78.8**	66.7 - 90.9	..		27	**3.1**	1.9 - 4.2
	2005-2009	172	**16.0**	13.6 - 18.4	169	**72.1**	62.3 - 81.9	**71.9**	64.1 - 79.6	52	**4.9**	3.5 - 6.2
	2010-2013	226	**21.5**	18.6 - 24.4	224	**85.8**	75.3 - 96.3	**84.0**	74.1 - 94.0	34	**3.4**	2.2 - 4.5
Brain	2000-2004	109	**3.8**	3.0 - 4.6	67 §	**30.3**	19.1 - 41.5	..		56	**2.2**	1.6 - 2.8
	2005-2009	100	**2.7**	2.2 - 3.3	84	**29.0**	19.2 - 38.8	**24.9**	17.4 - 32.5	53	**1.5**	1.1 - 2.0
	2010-2013	87	**2.5**	1.9 - 3.1	79	**38.9**	27.1 - 50.7	**31.8**	23.4 - 40.2	63	**2.0**	1.5 - 2.6
Myeloid neoplasms	2000-2004	115	**3.5**	2.8 - 4.2	84	**55.5**	44.4 - 66.6	**38.6**	29.3 - 47.8	38	**1.4**	0.9 - 1.9
	2005-2009	157	**4.1**	3.4 - 4.8	136	**44.3**	35.6 - 53.0	**24.0**	15.9 - 32.0	60	**1.9**	1.4 - 2.5
	2010-2013	141	**4.3**	3.6 - 5.1	126	**42.0**	32.9 - 51.1	**25.6**	17.7 - 33.6	62	**2.2**	1.6 - 2.8
Lymphoid neoplasms	2000-2004	509	**15.5**	14.0 - 17.0	375	**69.7**	64.5 - 74.9	**52.1**	42.9 - 61.2	89	**3.5**	2.8 - 4.3
	2005-2009	681	**17.7**	16.3 - 19.2	537	**73.3**	69.0 - 77.5	**63.2**	55.8 - 70.7	133	**4.2**	3.5 - 5.0
	2010-2013	601	**16.7**	15.3 - 18.1	493	**77.9**	73.6 - 82.3	**68.2**	59.5 - 76.9	124	**4.3**	3.5 - 5.1
Children*												
Brain children	2000-2004	20	**10.7**	6.0 - 15.4	18	**47.1**	24.4 - 69.8	..		9 ¥	..	
	2005-2009	20	**9.7**	5.5 - 14.0	22	**59.2**	39.2 - 79.1	..		9 ¥	..	
	2010-2013	9 ¥	..		9 ¥	..		..		8 ¥	..	
ALL children	2000-2004	85	**47.3**	37.2 - 57.4	83	**78.5**	69.1 - 87.9	**76.1**	65.7 - 86.5	8 ¥	..	
	2005-2009	99	**48.4**	38.8 - 57.9	98	**79.7**	71.8 - 87.6	**74.9**	65.6 - 84.1	17	**8.0**	4.2 - 11.8
	2010-2013	70	**39.9**	30.5 - 49.2	70	**86.8**	79.1 - 94.4	**88.4**	80.6 - 96.2	3 ¥	..	
Lymphoma children	2000-2004	48	**25.2**	18.0 - 32.3	48	**91.5**	83.5 - 99.6	**93.0**	86.9 - 99.1	3 ¥	..	
	2005-2009	45	**21.3**	15.0 - 27.5	45	**91.0**	82.6 - 99.5	**90.7**	84.3 - 97.1	2 ¥	..	
	2010-2013	36	**20.0**	13.4 - 26.5	36	**94.6**	87.2 - 100.0	**96.3**	91.4 - 100.0	2 ¥	..	

ASIR: age-standardised incidence rate; ASMR: age-standardised mortality rate; NS: net survival; CI: confidence interval; § Survival estimates considered less reliable due to greater than 15% of patients lost to follow-up or registered only from a death certificate or at autopsy; ¥ Number of patients/deaths <10; * Incidence and mortality rates for childhood cancers are presented per 1,000,000

Figures

Figure 7.1 Age-standardised incidence rate (ASIR), age-standardised 5-year net survival (NS,%) and age-standardised mortality rate (ASMR), 2000-2013



NS*: unstandardised net survival

Chapter 8: Discussion, perspectives and conclusion

8.1 Summary

Evaluation of population-based cancer survival is crucial to assess the effectiveness of the cancer care system in a country or region. In Kuwait, population-based cancer survival has never been evaluated. In this thesis, a new approach was implemented to obtain reliable and complete follow-up data on the last known vital status for all Kuwaiti cancer patients. This is essential to obtain robust estimates of population-based survival. Net survival was then estimated up to 5 years after diagnosis for 18 common cancers. Further analyses of survival by stage at diagnosis were performed, to provide a deeper understanding of cancer survival in Kuwait. Finally, an overall assessment of progress against cancer was performed, using the three main cancer control metrics: incidence, survival and mortality.

8.1.1 First objective

To enable the estimation of population-based survival in Kuwait for the first time, the initial objective was to obtain reliable and complete follow-up data on the last known vital status for all Kuwaiti cancer patients registered in the Kuwait Cancer Registry (KCR) during 2000-2013. To achieve this, the implementation of a novel approach to obtain follow-up data on vital status was required. Unlike the traditional method used by the Kuwait cancer registry, this new approach ensured that all deaths among registered cancer patients were ascertained, irrespective of the cause of death.

This approach proved to be highly effective, resolving the vital status and, if dead, the date of death, for almost all (98.3%) patients whose vital status had previously been unknown. This allowed complete data on follow-up for vital status to become available for all Kuwaiti cancer patients, for the first time.

Implications and perspectives

The Kuwait cancer registry is a long-standing registry, established in 1971,[15] that maintains high-quality data on cancer patients.[107] However, since the registry's establishment, the mechanism available for following up and updating the patients' vital

status has been restricted to deaths due to cancer. This meant that information on patients who died due to other causes was not captured. Therefore, these patients were considered to be alive. While it is plausible that most cancer patients' deaths would be due to their cancer - especially those diagnosed with more lethal types of cancer - many patients die from causes other than cancer. This is particularly important in our case, where about 40% of the cancer patients included in this thesis are diagnosed with breast and prostate cancer, which generally entails a good prognosis. Moreover, in Kuwait, injuries primarily from car accidents account for almost as many deaths as cancer.[94] Therefore, there is a great chance that cancer patients in Kuwait could die from other causes, and those deaths would not be recorded by the registry.

Our approach was implemented with the coordination of different ministerial agencies and departments. Electronic linkages were not possible, since this required formal ministerial agreements, which it has not yet been possible to obtain. We therefore used semi-manual methods whereby employees at the Central Record Department for Birth and Death of the Ministry of Health, manually entered each patient's national identification (Civil ID) number into the databases to extract the desired information. However, although the sources of information utilised were considered reliable, and the process proved to be highly effective in obtaining data on follow-up for vital status, the whole process was very time-consuming and required numerous data quality checks. For this reason, the recommendation is for this approach to be performed electronically and routinely in the future, through a series of steps:

1) Submission of a proposal to the Director of the Kuwait Cancer Control Center (KCCC), highlighting the results of this research (Chapter 4) and requesting systematic provision (preferably annual) of follow-up data to the Kuwait Cancer registry (KCR).
2) Attainment of approval by the Minister of Health in Kuwait.
3) Establishment of a formal agreement between the Ministry of Health and the Public Authority for Civil Information (PACI), to allow the Civil ID numbers for

all patients registered in the KCR by the end of a given year to be electronically linked with the vital status information available in the PACI database. The date of death for the deceased, as well as additional variables, such as sex and date of birth, should be retrieved to confirm that correct linkages were performed.

The most evident benefits of implementing this approach would be gained by the KCR. For instance, from a practical perspective, this approach can substantially decrease the cancer registry's workload, thus enabling the staff to focus their efforts elsewhere. The KCR's current procedures to obtain data on follow-up for vital status involve manual scanning of all death announcements in a given year for the entire country. This process is time-consuming and prone to human error. With the electronic implementation of this approach, the cancer registry staff's time could be better spent on improving the quality of the data, as well as the variables included in their data base, by collecting additional information, such as TNM (Tumor, Nodes, Metastasis) stage, treatment and comorbidities.

As the KCR is a major source of information on cancer patients in the country, the implementation of this approach will enable accurate and prompt production of reports on cancer patients' vital statistics at any given time. Many researchers, clinicians, organisations and policy-makers also use data from the cancer registry for different reasons. Therefore, the data provided on vital status must be complete and up to date, in order to be utilised and interpreted correctly.

In terms of international impact, this approach can offer guidance to other registries, particularly those in neighbouring countries with similar administrative systems. To use the same concepts and framework adopted in Kuwait could help them to update and improve their procedures to collect data on follow-up for vital status.

It is important to note, however, that without the systematic implementation of this method, in the future it will not be possible to produce population-based net survival for

Kuwait. The systematic implementation of this approach is therefore crucial to allow continuous monitoring and evaluation of the healthcare system in the country.

8.1.2 Second objective

Upon obtaining all the required data, the second objective of this thesis was to produce net survival estimates up to 5 years since diagnosis, for 18 common cancers, that can be monitored and compared internationally, in order facilitate the assessment of cancer control in Kuwait.

An overview of trends in population-based cancer survival was presented for Kuwaiti patients diagnosed during 2000-2013, with the following index cancers: oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast (women), cervix, ovary, prostate and melanoma of the skin in adults, in addition to brain tumours, leukaemias and lymphomas in both adults and children.

Although population-based 5-year net survival estimates for the same time period were also published for Kuwait in the third cycle of the CONCORD programme,[81] it is important to note that this was due to the work of this thesis (first objective), which made complete data on follow-up for vital status available, and therefore enabled Kuwait to participate for the first time. The inclusion of the Kuwaiti data in the CONCORD programme has benefited this thesis, allowing survival estimates in Kuwait to be compared with other high-income countries.

Through this objective, survival estimates beyond those published in CONCORD-3 for Kuwait were presented and discussed. For instance, estimates by sex were produced, as well as shorter-term survival estimates (at 1 and 3 years), which are important for more lethal cancers. The results revealed that cancer survival improved for most Kuwaiti adults and children during 2000-2013, with women generally having a more favourable prognosis than men. The discussion, however, did point towards the need for further investigation of the effects of screening and differences in stage at diagnosis, to help

explain Kuwait's generally low survival in comparison with other high-incomes countries included in CONCORD-3.

Implications and perspectives

Cancer survival is crucial to measure how the healthcare system manages cancer in a specific region and calendar period. Survival in Kuwait was estimated by using complete and high-quality data, as well as the most up-to-date, unbiased, non-parametric methods. These results can therefore be of use to various groups: academics and researchers, governmental organisations, health awareness campaigns, cancer charities and health policy-makers, as well as the general public.

These estimates can also contribute to the planning of cancer care services, and feed in to the national cancer plans. In Kuwait, the KCCC has implemented a strategic cancer plan for 2013-2018. One of its long-term goals is to "measure and improve outcomes", which is proposed to be assessed through measuring "disease control rates and survival". Age-standardised net survival estimates up to 5 years for 2010-2013 could serve as the basis to achieve this goal. Survival estimates for patients diagnosed during 2014-2018 can subsequently be obtained and compared with those for patients diagnosed in 2010-2013. These survival estimates can also serve as a basis for more specific goals targeting survival in future cancer control plans; for example, using the results to target certain cancers where no improvements have been observed, or to help specify a survival target to be reached, based on the most recent survival estimate for that cancer.

Moreover, the survival estimates published in this thesis can be used to assess interventions aimed at improving cancer care services, such as the KCCC's 5-year partnership with the Toronto University Health Network (UHN), initiated in 2011.[187] One of the primary goals of this partnership was to improve clinical management and services through the creation of specialised multidisciplinary teams for the delivery of disease-specific care, and to strengthen clinical services providing high-quality care, according

to the best international guidelines. The increase in survival observed for most cancers between 2005-2009 and 2010-2013 could therefore point towards improvements resulting from this partnership. However, further monitoring of survival is essential for a more comprehensive evaluation of the success of this partnership, through comparing the cancer control metrics and survival of patients diagnosed before and after the launch of this partnership.

The ability for Kuwaiti cancer patients to receive cancer treatment abroad also suggests the need to quantify the proportion of patients who travel abroad in order to understand the effect of different therapeutic geographies on the cancer care system in Kuwait. Further sub-group analyses comparing patients who stay in Kuwait for the totality of their treatment to patients who receive partial or complete treatment abroad should also aid the interpretation of the healthcare system in Kuwait. Assessment of the differences in the healthcare systems is also crucial in interpreting the findings.

8.1.3 Third objective

The third objective was to assess the distribution of stage at diagnosis and stage-specific survival for 12 cancers in Kuwait, for which Surveillance Epidemiology and End Results (SEER) Summary Stage data were available. According to the results corresponding to my second objective, improvements were shown for many cancers in Kuwait, but differences in survival were observed between Kuwait and other high-income countries. In order to understand these disparities better, the stage distribution and stage-specific survival for colon, lung and breast cancer were compared between Kuwait and the United States.

This objective aimed to illustrate, for the first time in Kuwait, the diagnostic activity for 12 cancers over a 14-year period. The results revealed that early diagnosis was generally low, and that survival was progressively lower with more advanced stage. However, the difference between earlier and more advanced stages was more substantial for some cancers. The differences in stage-specific survival between Kuwait and the US also

indicated that late-stage diagnoses are a major contributing factor to lower survival in Kuwait.

Implications and perspectives

Stage at diagnosis is a major determinant of cancer outcome. The pattern of survival by stage at diagnosis can illustrate where improvements and investments can and should be made. The results of this objective, therefore, not only provide a more thorough evaluation of survival in Kuwait, but may also have wider uses and implications, as explained below.

A major outcome was highlighting Kuwait's cancer diagnostic activity. Early diagnosis was generally less common than in the US for all cancers, including those for which early diagnostic tests are available. However, via comparing stage-specific survival between Kuwait and the US, the results showed that survival could be improved if more cancers were diagnosed at an earlier stage. This highlights the urgent need for initiatives aiming to improve early detection in Kuwait. Including early diagnosis as a goal in the KCCC's future cancer control strategic cancer plan, where changes can be assessed and monitored, should be the first step towards improvement.

Introducing national screening programmes for a few cancers could also substantially improve early diagnosis. While Kuwait has the financial resources to implement such programmes, further assessments are necessary to determine whether the health infrastructure and the diagnostic capabilities are adequate to enable the implementation of successful long-term screening programmes. Currently, there is only one national screening programme available in Kuwait, for breast cancer, initiated in 2014.[140] Results on the uptake of screening have not yet been reported, but the distribution of stage-specific survival would provide a valuable assessment of its success. Breast cancer survival should be continually monitored over the next 5-10 years, in order to evaluate the effects of early diagnosis on ultimately improving outcomes.

Furthermore, Kuwait's low level of activity to achieve early diagnosis also suggests the need for future investigations to identify other factors contributing to delayed diagnosis. For instance, low early detection could be due to Kuwaiti women's lack of awareness of cancer risk factors or the early symptoms of cancer, or even due to the cultural stigma and perception of being diagnosed with cancer. All these factors should be addressed in order to understand better their impact on early diagnosis. It is also crucial that the results presented in this objective are shared beyond the context of KCCC and academia, reaching cancer awareness organisations in the country, such as Cancer Awareness Nation (CAN).[188] Increased awareness and promotion of earlier diagnosis of cancers for which screening is available could be achieved through CAN's initiatives.

Finally, in addition to the importance of diagnosis at an early stage, the results also revealed that incomplete data on stage present a major limitation to monitoring trends in cancer survival by stage in Kuwait. The proportion of patients with unknown stage at diagnosis has actually increased in recent years, reaching about 40% during 2010-2013. This restricted the evaluation of trends in survival by stage during 2000-2013, and will probably prevent future evaluations, unless the recording of stage at diagnosis is improved. Further enhancement in the collection of stage data is therefore crucial. This can be achieved through encouraging clinicians to systematically record TNM stage at diagnosis, investing in the KCR, improving the management of patients' files, and allowing better access to patients' data via the implementation of an electronic medical record system in the KCCC.

In conclusion, although late stage at diagnosis partly explains the lower survival in Kuwait than in other high-income countries, it is undoubtedly not the only factor. The prevalence of comorbidities, outmoded attitudes and behaviours towards treatment, differences in primary care systems, delays in diagnosis or treatment, as well as the efficacy of treatment, constitute additional factors that have not been explored in this thesis.

8.1.4 Fourth objective

The fourth and final objective of this thesis was to evaluate the overall health care system in Kuwait in managing cancer patients, using the three major cancer control metrics: incidence, survival and mortality.

A comprehensive overview of the progress against cancer in Kuwait was presented for the first time, for all Kuwaiti cancer patients diagnosed with one of 18 common cancers over a 14-year period. The results revealed patterns of progress for the majority of cancers in Kuwait. The observed progress was probably due to the following factors: implementation of prevention strategies, removal of cancer precursors, early diagnostic activity, and better treatment and access to care.

Implications and perspectives

Cancer control initiatives generally focus on three main goals: a) reducing the number of people diagnosed with cancer (incidence); b) extending the length of cancer patients' lives following diagnosis (survival); and c) reducing the number of cancer deaths (mortality).

Throughout the thesis, emphasis was placed on the importance of population-based survival as a means of assessing improvements in cancer care. Evidence against the use of mortality rates as the sole indicator of progress was as also given (Section 1.5). While working on this fourth objective, the reliability of the mortality rates in Kuwait was found to be affected by several issues, such as incomplete death ascertainment, improper sequencing of causes of death, and differences in selection of cancer as the underlying cause. The results, therefore, are in agreement with the current literature, which supports the use of survival as the best evaluator of the healthcare system.[21,83]

The results of this objective have also provided examples supporting the use of all three cancer metrics simultaneously to evaluate cancer progress. For instance, progress would not have been inferred for some cancers in Kuwait where survival did not increase. However, when assessing the trends of incidence and mortality alongside survival, a

more comprehensive evaluation of progress was obtained, providing information on whether the number of people diagnosed with the disease decreased or fewer patients were dying from it.

In the case of Kuwait, these results have revealed that progress has been achieved for many cancers over the years. Progress was more clearly illustrated in the most recent years (2010-2013), coinciding with the country's increased investment in improving cancer care services through international collaborations. The results also point towards improvements in reducing risk factors and providing earlier diagnosis for some cancers. However, the results also showed that for some cancers, increased risk factors could be contributing to more people being diagnosed. This, therefore, points to the need of more public health intervention and awareness programmes targeting specifically those cancers.

The results presented here, as well as the method used to evaluate progress, should also be implemented in Kuwait in a systematic manner. For instance, in the KCCC's strategic plan 2013-2018, measuring "disease control rates and survival" is included as a method of evaluating one of the long-term goals of improving outcome. However, currently, cancer incidence is the only metric systematically produced and assessed by the KCR. While mortality rates are produced annually by the National Centre for Health Information for Kuwaitis, they are currently reported for all cancers combined, and they cannot be used to assess changes in cancer control for each type of cancer. However, population-based survival had not previously been reported for the major cancers, apart from the publications arising from this research (Chapter 5). This indicates that, although the need to measure and assess the cancer metrics is included in the national cancer control plans, the necessary procedures to ensure their production are not yet in place. In order for all three metrics to be assessed, legislative regulations need to be established that would ensure the systematic production of these metrics. Their evaluation would then need to be performed using the same methods performed in this thesis.

8.2 Limitations

The main limitation affecting most of our objectives was the small number of patients available, predominantly due to Kuwait's low population. This limited the production of more detailed survival estimates for all cancers, such as survival by sex, or long-term survival, for example at 10 years. The small number of patients also led to less reliable estimates for the rarer cancers, and prevented age-standardisation of some estimates, particularly for stage-specific analyses.

In terms of mortality, the small number of diagnoses also implied a low number of deaths; this inhibited the production of mortality rates for some cancers, particularly for children. Incomplete death registration in the early calendar periods in Kuwait also inhibited robust evaluation of mortality trends for all cancers. That said, mortality rates were used as a supplement to survival in evaluating trends, and not as the main measure of interest. However, the completeness of death registrations has improved over the years, both in the cancer registry and in the country's civil registration and vital statistics sytem,[189] and therefore, mortality rates presented for the most recent years (2005-2013) were more robust.

The inability to include in this thesis data for non-Kuwaiti cancer patients residing in Kuwait also presented a limitation. While most non-Kuwaiti patients would be diagnosed in Kuwait, and therefore should have complete diagnosis information, data on follow-up for their vital status would be substantially incomplete. That is because non-Kuwaitis primarily consist of expatriate labourers employed with short contracts who would generally return home upon becoming critically ill. The Public Authority for Civil Information, where vital status was ascertained for Kuwaiti patients, cannot be used to track the vital status of persons who have left the country. Thus, to obtain complete and reliable data on follow-up for vital status of all non-Kuwaitis would not have been possible.

8.3 Action plan

Based on the evidence provided in the thesis, the following actions are required:

ACTION PLAN	
1) Improving data:	a) To establish an electronic linkage between the Kuwait Cancer Registry (KCR) and the Public Authority of Civil Information (PACI) in order to enable the ascertainment of all deaths among registered cancer patients, regardless of the cause of death, and the systematic update of vital status for cancer patients in Kuwait. b) To implement an electronic health record system in the Kuwait Cancer Control Centre (KCCC) to improve the completeness of ascertainment of data on stage at diagnosis in the KCR. c) To introduce new policies and procedures to ensure patients' information and medical history is sent to the KCCC after the patient returns from having had cancer treatment abroad.
2) Potential cancer policy developments:	a) To introduce a bowel cancer screening programme into Kuwait, to improve early diagnosis. b) To investigate reasons for delays in diagnosis in Kuwait through conducting a case-control study, comprising 'late'-diagnosed patients and controls 'non-late' diagnosed patients (controls). c) To develop a questionnaire to explore relevant explanatory factors such as ignorance, fears, cultural barriers, promptness in receiving early diagnostic procedures and social perceptions of the effectiveness of treatment and level of adherence.

8.4 Conclusion

Cancer is a major cause of death in Kuwait and the measures involved in the fight against it are numerous and complicated, ranging from prevention and diagnosis, to prompt and effective treatment and care. Population-based cancer survival is a valuable measure of the effectiveness of the health system in managing cancer, and improvement in survival is vital for extending patients' lives. However, in order to make valid assessments of survival, complete and high-quality data on diagnosis and follow-up are required on all cancer patients.

This thesis has, for the first time, outlined and implemented an effective method to obtain complete data on follow-up for vital status, for all cancer patients in Kuwait, enabling robust estimation of population-based net survival for 18 cancers. This also enabled Kuwait to participate in the CONCORD programme, the largest programme for surveillance of population-based cancer survival world-wide, allowing international comparisons between survival in Kuwait and other countries.

Survival estimates up to 5 years after diagnosis were produced for patients diagnosed over a period of 14 years, 2000-2013, using appropriate statistical methods that allow comparisons to be made over time and between different populations. A more detailed assessment of survival was also performed, evaluating Kuwait's diagnostic activity, examining stage-specific survival for 10 cancers, and comparing stage-specific survival between Kuwait and in the US. Finally, this thesis offered a comprehensive evaluation of the Kuwaiti cancer care system, using the three major cancer control metrics (incidence, survival and mortality), thus assessing progress. The findings showed that survival has improved for many cancers during 2000-2013. However, they have also highlighted the importance of more complete collection of stage data, the necessity of improving early detection, and the need for systematic production and assessment of cancer control measures in Kuwait.

While this thesis presents a broad overview of the current cancer care system in Kuwait, further research is required, based on the recommendations provided here. This will

allow the efforts in collecting and analysing data performed as part of this thesis to be continued, and for more factors to be addressed and evaluated to improve cancer outcomes in the future.

References

1. Central Intelligence Agency. The World Facebook. United States of America, 2018.
2. International Relations and Security Network. Charter of the Gulf Cooperation Council (GCC). https://www.files.ethz.ch/isn/125347/1426_GCC.pdf.
3. The World Bank. Data- High income. United States of America, 2018.
4. WHO. Country Cooperation Strategy for WHO and Kuwait 2012–2016. WHO Regional Office for the Eastern Mediterranean, 2014.
5. The Public Authority for Civil Information. Population Pyramid. 2017. http://stat.paci.gov.kw/englishreports/#DataTabPlace:PopulationPyramid.
6. The Public Authority for Civil Information. Size and Structure Of the Community Population by Gender And Nationality groups. Kuwait: Government of the State of Kuwait,2017. http://stat.paci.gov.kw/englishreports/#DataTabPlace:ColumnChartGendrAge.
7. MOH. World Health Survey in Kuwait: Main Report 2013. Kuwait, 2013.
8. Gulseven O. Forecasting population and demographic composition of Kuwait until 2030. *International Journal of Economics and Financial Issues* 2016; **6**(4).
9. Rabah K, Cox C. How does health spending in the US compare to other countries? *Health Spending.* Kaiser Family Foundation. https://www.healthsystemtracker.org/chart-collection/how-do-healthcare-prices-and-use-in-the-u-s-compare-to-other-countries/#item-start (accessed May 2019).
10. Kuwait Life Sciences Company. Market Overview 2016 Kuwait. Kuwait, 2016.
11. Union for International Cancer Control. World Cancer Declaration 2013. Geneva: UICC, 2013. http://www.uicc.org/world-cancer-declaration (accessed 25 September 2017).
12. KCCC. Kuwait Cancer Control Centre Strategic Plan 2013-2018. Kuwait, 2013.
13. Elbasmi A, Alawadhi A. Kuwait cancer registry annual report. Kuwait: Kuwait Cancer Control Center, 2013.
14. MOH. Kuwait Cancer Control Center. Kuwait: Minisitry of Health. http://www.kuwaitcancercenter.com/Kuwait-Cancer-Registry.php (accessed 4th April 2016).
15. International Association of Cancer Registries (IACR). Kuwait Cancer Registry Profile Page. Lyon, France. http://www.iacr.com.fr/index.php?option=com_comprofiler&task=userprofile&user=978&Itemid=498.
16. Ellis L, Woods LM, Estève J, Eloranta S, Coleman MP, Rachet B. Cancer incidence, survival and mortality: explaining the concepts. *Int J Cancer* 2014; **135**: 1774-82.
17. Parkin DM. The role of cancer registries in cancer control. *Int J Clin Oncol* 2008; **13**(2): 102-11.
18. Parkin DM. The evolution of the population-based cancer registry. *Nat Rev Cancer* 2006; **6**: 603-12.
19. Dos Santos Silva I. The role of cancer registries. In Cancer epidemiology: Principles and methods: International Agency for research on cancer.
20. Allemani C, Coleman MP. Public health surveillance of cancer survival in the US and world-wide: the contribution of the CONCORD programme. *Cancer* 2017; **123**: 4977-81.
21. Allemani C. The importance of global surveillance of cancer survival for cancer control: the CONCORD programme. *Cancer Control* 2017: 19-22.
22. Katchy KC, Alexander S, Al-Nashmi NM, Al-Ramadan A. Epidemiology of primary brain tumors in childhood and adolescence in Kuwait. *Springerplus* 2013; **2**.
23. Katchy KC, Mallik AA, Al-Nashmi NM, Joseph E, Alexander S, Al-Ramadan A. Intracranial tumors in Kuwait: a 15-year survey. *J Neurooncol* 2011; **104**(1): 271-7.

24. Katchy KC, Ziad F, Alexander S, Gad H, Mota'al MA. Malignant bone tumors in Kuwait - A 10-year clinicopathological study. *Int Orthop* 2005; **29**(6): 406-11.
25. Abuzallouf S, Vasishta S, Ragheb A, Varghese A, El-Hattab O. Prognostic value of hemoglobin levels prior to radiotherapy for cervical cancer--Kuwait experience. *The Gulf journal of oncology* 2008; (3): 41-5.
26. Siddique I, El-Naga HA, Memon A, Thalib L, Hasan F, Al-Nakib B. CLIP score as a prognostic indicator for hepatocellular carcinoma: experience with patients in the Middle East. *Eur J Gastroenterol Hepatol* 2004; **16**(7): 675-80.
27. El-Ghamrawi KA, Khalifa MS. Thyroid cancer in Kuwait: review of 117 cases. *Br J Surg* 1979; **66**(2): 139-42.
28. Morris RE, Al Mahmeed BE, Gjorgov AN, Al Jazzaf HG, Al Rashid B. The epidemiology of lip, oral cavity and pharyngeal cancers in Kuwait 1979-1988. *Br J Oral Maxillofac Surg* 2000; **38**(4): 316-9.
29. Al-Bahar S, Pandita R, Al-Muhannaha A, Al-Bahar E. The epidemiology of leukemia in Kuwait. *Leuk Res* 1994; **18**(4): 251-5.
30. Parikh SD, El-Ghamrawi KA. Cancer of the naso-pharynx in Kuwait. *J Laryngol Otol* 1978; **92**(8): 681-91.
31. El-Basmy A, Shihab A-M, Ahmed A-A. Profile of Lung Cancer in Kuwait. *Asian Pac J Cancer Prev* 2013; **14**(10): 6181-4.
32. Al-Hamdan N, Al-Jarallah M, Ravichandran K, Al-Sayyad J, Al-Lawati J, Khazal Z, Al-Khateeb F, Abdulwahab A, Al-Mulla A, Al-Asfour A, Bazarbashi S. The incidence of lung cancer in the Gulf Cooperation Council countries. *Ann Saudi Med* 2006; **26**(6): 433-8.
33. Al Ramadhan MA. Eradicating Breast Cancer: Longevity Impact on Kuwaiti Women. *Asian Pac J Cancer Prev* 2017; **18**(3): 803-9.
34. Al-Majed HT, El-Basmi AA, Al-Mohannadi SH, Govindan R, Rajakumari GB. Pancreatic cancer: Incidence, clinical profile, and frequency of associated factors in Kuwait. *Alexandria Journal of Medicine* 2013; **49**(1): 75-80.
35. Alshemmari S, Sajnani KP, Refaat S, Albassami A. Population-based study of Hodgkin's lymphoma in Kuwait. *The Gulf journal of oncology* 2011; **1**(9): 20-6.
36. Ameen R, Sajnani KP, Albassami A, Refaat S. Frequencies of non-Hodgkin's lymphoma subtypes in Kuwait: comparisons between different ethnic groups. *Ann Hematol* 2010; **89**(2): 179-84.
37. AlBahar S, Pandita R, AlBahar E, AlMuhana A, AlYaseen N. Recent trends in the incidence of lymphomas in Kuwait. *Neoplasma* 1996; **43**(4): 253-7.
38. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, Ferlay J. Cancer Incidence in Five Continents, Vol. XI. Lyon: International Agency for Research on Cancer. http://ci5.iarc.fr (accessed 11/3/2019).
39. Elbasmi A, Alawadi A. Kuwait cancer registry annual report. Kuwait: Kuwait Cancer Control Center, 2015.
40. Elbasmi A, Al-Asfour A, Al-Nesf Y, Al-Awadi A. Cancer in Kuwait: magnitude of the problem. *The Gulf journal of oncology* 2010; (8): 7-14.
41. El-Basmy A, Al-Mohannadi S, Al-Awadi A. Some Epidemiological Measures of Cancer in Kuwait: National Cancer Registry Data from 2000-2009. *Asian Pac J Cancer Prev* 2012; **13**(7): 3113-8.
42. Aziz MM. Spatial patterns of major mortality causes in Kuwait. *Geographical Review of Japan, Series B* 1989; **62**(1): 1-13.
43. Al-Ramadhan MA, Al-Hajji RM. Elimination life tables of malignant neoplasm and their impact on life expectancy at birth in Kuwait. *Eastern Mediterranean health journal* 2014; **19 Suppl 3**: S45-54.
44. Ashley J. The International Classification of Diseases: the structure and content of the Tenth Revision. *Health Trends* 1990; **22**: 135-7.
45. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**(6): 394-424.

46. Mittal R, Khalifa N, Khalifa S. Pediatric solid tumors: Kuwait experience. *Pediatric Blood and Cancer* 2009; **53 (5)**: 848.
47. Mottl H, Bajciova V, Nemec J, Al Shemmari S, Al Awadi S. High survival rate in childhood non-Hodgkin lymphoma without CNS involvement: Results of BFM 95 study in Kuwait. *Pediatr Hematol Oncol* 2003; **20**(2): 103-10.
48. Awwad AH, Omar YT, Abouna GM. Cancer of pancreas and periampullary region in Kuwait. *J Kuwait Med Assoc* 1981; **15**(4): 207-15.
49. Krishnan Y, Al Awadi S, Sreedharan PS, Sujith Nair S, Thuruthel S. Analysis of neoadjuvant therapies in breast cancer with respect to pathological complete response, disease-free survival and overall survival: 15 years follow-up data from Kuwait. *Asia Pac J Clin Oncol* 2013.
50. Motawy M, El Hattab O, Fayaz S, Oteifa M, Ali J, George T, Barghash I, Abuzallouf S, El Jarallah M. Multidisciplinary approach to breast cancer management in Kuwait, 1993-1998. *J Egypt Natl Canc Inst* 2004; **16**(2): 85-91.
51. Krishnan Y, Al Awadi S, Sreedharan PS, Sujith Nair S, Thuruthel S. Analysis of neoadjuvant therapies in breast cancer with respect to pathological complete response, disease-free survival and overall survival: 15 years follow-up data from Kuwait. *Asia Pac J Clin Oncol* 2016; **12**(1): e30-7.
52. Fayaz S, Gerges AD, El-Sherify M, Eissa H, Aziz M, Abuzallou S. Triple Negative Breast Cancer: 10-Year Survival Update of The Applied Treatment Strategy in Kuwait. *The Gulf Journal of Oncology* 2019; **1**(29): 53-9.
53. A. ASK, Safwat R, Gaber A, Hattab O. Analysis of the outcome of treatment for squamous cell carcinoma of the oral cavity: Retrospective study of 180 patients. *J Clin Oncol* 2011; **29**(15 SUPPL. 1).
54. Mittal R, Khalifa NM, Khalifa SO, Ragheb AM, Ali J. Outcome of children with Hodgkin's disease A 10-year experience from a single institution in Kuwait. *Saudi Med J* 2010; **31**(1): 69-73.
55. Motawy MS, Omar YT. Hodgkin's disease in children in Kuwait. *Cancer* 1986; **57**(11): 2255-9.
56. Alshemmari SH, Elhagracy RS, Elbasmy A. Treatment of early stage classic hodgkin's lymphoma outcome: Kuwait experience. *Blood Conference: 53rd Annual Meeting of the American Society of Hematology, ASH* 2011; **118**(21).
57. Mittal R, Khalifa NM, Khalifa SO, Bedair R. Profile of pediatric non hodgkins lymphomas in Kuwait: A 10 year analysis from kuwait cancer control centre, Kuwait. *Pediatric Blood and Cancer* 2011; **57 (5)**: 870.
58. Al-Shemmari SH, Sajnani KP, Ameen RM, Ragheb AM. Primary gastrointestinal non-Hodgkin's lymphoma: Treatment outcome. *Clin Lymphoma* 2003; **4**(2): 99-103.
59. Al Shemmari SH, Ameen RM, Sajnani KP. Extranodal lymphoma: a comparative study. *Hematology* 2008; **13**(3): 163-9.
60. Vasishta S, Varghese A, Ragheb A. Patterns of failure in cervical carcinoma and outcome of salvage therapy: a retrospective study. *The Gulf journal of oncology* 2007; **1**(1): 43-9.
61. Al Wakiel H, Ragheb AM, Varghese A, Juzeer A, Vashista S, Albasmy A. Uterine sarcoma: 14 years experience in KCCC. *The Gulf journal of oncology* 2008; (4): 45-51.
62. Motawy M, Abuzallouf S, El-Hattab O, Thomas G, Fayaz S, Murray A. Treatment outcome of rectal and rectosigmoid cancer in Kuwait - A retrospective analysis. *Klinicka Onkologie* 2007; **20**(2): 231-4.
63. Thotathil ZS, Varghese A, Ragheb A. Renal cell carcinoma: The experience of Kuwait Cancer Control Center, Kuwait. *Med Princ Pract* 2005; **14**(1): 1-5.
64. Awadh-Behbehani N, Al-Humood K, Ayed A, Memon A, Ali A. Comparison between young and old patients with bronchogenic carcinoma. *Acta Oncol* 2000; **39**(8): 995-9.
65. Fayaz MS, Eissa HES, Demian GA, Samir S, George T, Abuzalouf S, Juma HM. Colon cancer in patients below age of 50 years: Kuwait cancer control center eight

years case series. *Journal of Clinical Oncology Conference* 2015; **33**(15 SUPPL. 1).
66. Fayaz MS, El-Sherify MS, El-Basmy A, Zlouf SA, Nazmy N, George T, Samir S, Attia G, Eissa H. Clinicopathological features and prognosis of triple negative breast cancer in Kuwait: A comparative/perspective analysis. *Rep Pract Oncol Radiother* 2014; **19**(3): 173-81.
67. Samir SM, Fayaz MS, Elbasmi A, Motawy MM, Abuzallouf S, George T, Abdelhady M, Bedair A. Medullary carcinoma of the breast: ten year clinical experience of the Kuwait cancer control centre. *The Gulf journal of oncology* 2011; (10): 45-52.
68. AlShemmari SH, Ameen RM, Sajnani KP. Extranodal lymphoma: a comparative study. *Hematology* 2008; **13**(3): 163-9.
69. Al-Shemmari SH, Al-Humood S, Ameen R, Kamlesh S, Nemec J, Varghese A. Hodgkin's disease: Kuwait experience. *Med Princ Pract* 2004; **13**(4): 201-5.
70. Omar YT, Al-Nakib B, Jacob GS, Ali SM, Temmim L, Radhakrishnan S, Fayaz MS. Primary gastrointestinal lymphoma in Kuwait. An 11-yr retrospective analysis of 108 cases. *Eur J Cancer Clin Oncol* 1985; **21**(5): 573-7.
71. Demian GA, Fayaz S, El-Sayed Eissa H, Nazmy N, Samir S, George T, El-Sherify M, Abuzalouf S. Phyllodes tumors of the breast: Analysis of 35 cases from a single institution. *J Egypt Natl Canc Inst* 2016; **28**(4): 243-8.
72. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
73. Rich JT, Neely JG, Paniello RC, Voelker CC, Nussenbaum B, Wang EW. A practical guide to understanding Kaplan-Meier curves. *Otolaryngol Head Neck Surg* 2010; **143**(3): 331-6.
74. Percy CL, Dolman AB. Comparison of the coding of death certificates related to cancer in seven countries. *Public Health Rep* 1978; **93**: 335-50.
75. Laurenti R, Coleman MP, Aylin P. Accuracy of statements of the cause of death on death certificates and the international comparability of mortality statistics. In: Coleman MP, Aylin P, eds. Death certification and mortality statistics: an international perspective. London: Office for National Statistics; 2000: 1-9.
76. Percy CL, Miller BA, Gloeckler Ries LA. Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. *Annals of the New York Academy of Science* 1990; **609**: 87-97.
77. Percy CL, Muir CS. The international comparability of cancer mortality data: results of an international death certificate study. *Am J Epidemiol* 1989; **129**: 934-46.
78. Percy CL, Stanek E, Gloeckler Ries LA. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 1981; **71**: 242-50.
79. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, Azevedo e Silva G, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL, CONCORD Working Group. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; **9**: 730-56.
80. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X-S, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen W-Q, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP, CONCORD Working Group. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015; **385**: 977–1010.
81. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, Bonaventure A, Valkov M, Johnson CJ, Esteve J, Ogunbiyi OJ, Azevedo ESG, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK, Coleman MP, Group CW. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients

diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391**: 1023-75.
82. Mariotto AB, Noone A-M, Howlader N, Cho H, Keel GE, Garshell J, Woloshin S, Schwartz LM. Cancer Survival: An Overview of Measures, Uses, and Interpretation. *JNCI Monographs* 2014; **49**: 145-86.
83. Coleman MP. Cancer survival: global surveillance will stimulate health policy and improve equity. *Lancet* 2014; **383**: 564-73.
84. Coleman MP. Why we need global surveillance of cancer survival: the CONCORD programme. In: McGrath I, ed. Cancer care in emerging health systems. Oxford: International Network for Cancer Treatment and Research; 2013: 60-5.
85. Cutler SJ, Ederer F. Maximum utilisation of the life table method in analyzing survival. *J Chronic Dis* 1958; **8**: 699-712.
86. Pohar Perme M, Stare J, Estève J. On estimation in relative survival. *Biometrics* 2012; **68**: 113-20.
87. Pohar Perme M, Estève J, Rachet B. Analysing population-based cancer survival - settling the controversies. *BMC Cancer* 2016; **16**(1): 933.
88. Estève J, Benhamou E, Raymond L. Statistical methods in cancer research, volume IV. Descriptive epidemiology. (IARC Scientific Publications No. 128). Lyon: International Agency for Research on Cancer; 1994.
89. Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. *J Clin Epidemiol* 1997; **50**: 211-6.
90. Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. *Eur J Cancer* 2004; **40**(3): 326-35.
91. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996; **78**: 2004-10.
92. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer* 2004; **40**(15): 2307-16.
93. Woods LM, Rachet B, Ellis L, Coleman MP. Full dates (day, month, year) should be used in population-based cancer survival studies. *Int J Cancer* 2012; **131**: E1120-E4.
94. Health Vital Statistics Division. Health, Kuwait 2014. Kuwait: Department of Statistics & Medical Records, Ministry of Health, 2015.
95. Allemani C, Harewood R, Johnson CJ, Carreira H, Spika D, Bonaventure A, Ward K, Weir HK, Coleman MP. Population-based cancer survival in the United States: Data, quality control, and statistical methods. *Cancer* 2017; **123**: 4982-93.
96. Office for National Statistics. Guidance for doctors completing Medical Certificates of Cause of Death in England and Wales. In: Service HOIaP, editor.; 2010. p. 1-15.
97. World Health Organisation. International statistical classification of diseases and related health problems. Tenth revision. Geneva: World Health Organization; 1994.
98. Schaffar R, Rachet B, Belot A, Woods LM. Estimation of net survival for cancer patients: Relative survival setting more robust to some assumption violations than cause-specific setting, a sensitivity analysis on empirical data. *Eur J Cancer* 2017; **72**: 78-83.
99. Schaffar R, Rachet B, Belot A, Woods L. Cause-specific or relative survival setting to estimate population-based net survival from cancer? An empirical evaluation using women diagnosed with breast cancer in Geneva between 1981 and 1991 and followed for 20 years after diagnosis. *Cancer Epidemiology* 2015; **39**(3): 465-72.
100. Ederer F, Axtell LM, Cutler SJ. The relative survival: a statistical methodology. *Natl Cancer Inst Monogr* 1961; **6**: 101-21.
101. Baili P, Micheli A, De Angelis R, Weir HK, Francisci S, Santaquilani M, Hakulinen T, Quaresma M, Coleman MP, CONCORD Working Group. Life-tables for world-wide comparison of relative survival for cancer (CONCORD study). *Tumori* 2008; **94**: 658-68.

102. Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. *Stat Med* 1990; **9**: 529-38.
103. Spika D, Bannon F, Bonaventure A, Woods LM, Harewood R, Carreira H, Coleman MP, Allemani C. Life tables for global surveillance of cancer survival (the CONCORD programme): data sources and methods. *BMC Cancer* 2017; **17**: 159-73.
104. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. *J Intern Med* 2006; **260**: 103-17.
105. Rachet B, Woods LM, Mitry E, Riga M, Cooper C, Quinn MJ, Steward JA, Brenner H, Estève J, Sullivan R, Coleman MP. Cancer survival in England and Wales at the end of the 20th century. *Br J Cancer* 2008; **99 (Suppl. 1)**: 2-10.
106. Health System Strengthening and Breast Cancer Care in the Middle East: Results of the Harvard Research Study. 2018 21-23 January; Dubai: Harvard Medical School Center for Global Health Delivery–Dubai; 2018.
107. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-86.
108. Hashim D, Boffetta P, La Vecchia C, Rota M, Bertuccio P, Malvezzi M, Negri E. The global decrease in cancer mortality: trends and disparities. *Ann Oncol* 2016; **27**(5): 926-33.
109. Mortality GBD, Causes of Death C. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**(9963): 117-71.
110. Moussa MA, Shafie MZ, Khogali MM, el-Sayed AM, Sugathan TN, Cherian G, Abdel-Khalik AZ, Garada MT, Verma D. Reliability of death certificate diagnoses. *J Clin Epidemiol* 1990; **43**(12): 1285-95.
111. Ohmi K, Yamamoto A. Changes in mortality statistics in Japan, 1995: the effect of implementation of ICD-10 and revision of the death certificate. In: Coleman MP, Aylin P, eds. Death certification and mortality statistics: an international perspective. London: Office for National Statistics; 2000: 21-7.
112. Hoyert DL, Rosenburg HM, MacDorman MF. Effects of changes in death certificate format on cause-specific mortality trends, United States, 1970-1992. In: Coleman MP, Aylin P, eds. Death certification and mortality statistics: an international perspective. London: Office for National Statistics; 2000: 47-58.
113. Haghighi MH, Dehghani M, Teshizi SH, Mahmoodi H. Impact of documentation errors on accuracy of cause of death coding in an educational hospital in Southern Iran. *The HIM journal* 2014; **43**(2): 35-42.
114. Whelan SL, Parkin DM, Masuyer E, editors. Patterns of cancer in five continents (IARC Scientific Publications No. 102). Lyon: International Agency for Research on Cancer; 1990.
115. Fritz AG, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL, editors. International Classification of Diseases for Oncology (ICD-O). 3rd ed. Geneva: World Health Organization; 2000.
116. Fritz AG, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL, editors. International Classification of Diseases for Oncology (ICD-O). First revision of 3rd ed. Geneva: World Health Organisation; 2013.
117. Sant M, Karjalainen-Lindsberg ML, Maynadié M, Raphael M, Ferretti S, Giacomin A, Tereanu C, Giraldo P, Marcos-Gragera R, Martos C, Lutz JM, Visser O, HAEMACARE Working Group. Manual for coding and reporting haematological malignancies. *Tumori* 2010; **96**: i-A32.
118. Turner JJ, Morton LM, Linet MS, Clarke CA, Kadin ME, Vajdic CM, Monnereau A, Maynadie M, Chiu BC, Marcos-Gragera R, Costantini AS, Cerhan JR, Weisenburger DD. InterLymph hierarchical classification of lymphoid neoplasms

for epidemiologic research based on the WHO classification (2008): update and future directions. *Blood* 2010; **116**: e90-8.
119. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer* 2005; **103**: 1457-67.
120. Johnson CJ, Weir HK, Yin D, Niu X. The impact of patient follow-up on population-based survival rates. *J Registry Manage* 2010; **37**: 86-103.
121. Pohar Perme M, Henderson R, Stare J. An approach to estimation in relative survival regression. *Biostatistics* 2009; **10**: 136-46.
122. Clerc-Urmès I, Grzebyk M, Hédelin G. Net survival estimation with stns. *Stata J* 2014; **14**: 87-102.
123. Corazziari I, Quinn MJ, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer* 2004; **40**: 2307-16.
124. Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971-85. *Br J Cancer* 1990; **62**: 806-15.
125. Greenwood M. The natural duration of cancer. (Report on Public Health and Medical Subjects No. 33). London: HMSO; 1926.
126. Albreht T, McKee CM, Alexe DM, Coleman MP, Martín-Moreno JM. Making progress against cancer in Europe in 2008. *Eur J Cancer* 2008; **44**: 1451-6.
127. Department of Health. The NHS Outcomes Framework. Department of Health: London, UK., 2017.
128. Rossi S, Baili P, Capocaccia R, Caldora M, Carrani E, Minicozzi P, Pierannunzio D, Santaquilani M, Trama A, Allemani C, Belot A, Buzzoni C, Lorez M, De Angelis R. The EUROCARE-5 study on cancer survival in Europe 1999–2007: Database, quality checks and statistical analysis methods. *Eur J Cancer* 2015; **51**(15): 2104-19.
129. Holleczek B, Brenner H. Reduction of population-based cancer survival estimates by trace back of death certificate notifications: an empirical illustration. *Eur J Cancer* 2012; **48**: 797-804.
130. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. *Cancer Epidemiol Biomarkers Prev* 2011; **20**(8): 1629-37.
131. Ellison LF. Differences in cancer survival in Canada by sex. *Health Rep* 2016; **27**(4): 19-27.
132. Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, Zambon P, Gatta G, De Angelis R, EUROCARE Working Group. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. *Eur J Cancer* 2009; **45 (Suppl. 6)**: 1017-27.
133. Jung KW, Park S, Shin A, Oh CM, Kong HJ, Jun JK, Won YJ. Do female cancer patients display better survival rates compared with males? Analysis of the Korean National Registry data, 2005-2009. *PLoS One* 2012; **7**(12): e52457.
134. White A, Ironmonger L, Steele RJC, Ormiston-Smith N, Crawford C, Seims A. A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. *BMC Cancer* 2018; **18**(1): 906.
135. Goto R, Hamashima C, Mun S, Lee WC. Why screening rates vary between Korea and Japan--differences between two national healthcare systems. *Asian Pac J Cancer Prev* 2015; **16**(2): 395-400.
136. Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N, Tomatis M, Žakelj MP, Dillner J, Fernan M, Elfström KM, Lönnberg S, Soerjomataram I, Sankaranaryanan R, Vale D. Cancer Screening in the European Union. Lyon, France, 2017.
137. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, Brawley OW, Wender RC. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin* 2018.
138. Marcus PM, Prorok PC, Miller AB, DeVoto EJ, Kramer BS. Conceptualizing overdiagnosis in cancer screening. *J Natl Cancer Inst* 2015; **107**(4).

139. Matz M, Coleman MP, Carreira H, Salmerón D, Chirlaque López MD, Allemani C, the CONCORD Working Group. World-wide comparison of ovarian cancer survival: morphological group and stage at diagnosis (CONCORD-2). *Gynecol Oncol* 2017; **144**: 396-404.
140. Ministry of Health. Kuwait National Mammography Screening Program. Kuwait: Government of Kuwait, 2015. https://www.moh.gov.kw/knmsp/index-en.html#Mammogram.
141. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin* 2016; **66**(4): 337-50.
142. De Angelis R, Minicozzi P, Sant M, Dal Maso L, Brewster DH, Osca-Gelis G, Visser O, Maynadié M, Marcos-Gragera R, Troussard X, Agius D, Roazzi P, Meneghini E, Monnereau A. Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000–2007: Results of EUROCARE-5 population-based study. *Eur J Cancer* 2015; **51**(15): 2254-68.
143. Yadav S, Sharma P, Zakalik D. Comparison of Demographics, Tumor Characteristics, and Survival Between Pancreatic Adenocarcinomas and Pancreatic Neuroendocrine Tumors: A Population-based Study. *Am J Clin Oncol* 2018; **41**(5): 485-91.
144. Brierley J, Gospodarowicz M, O'Sullivan B. The principles of cancer staging. *Ecancermedicalscience* 2016; **10**: ed61.
145. Brierley JD, Srigley JR, Yurcan M, Li B, Rahal R, Ross J, King MJ, Sherar M, Skinner R, Sawka C. The value of collecting population-based cancer stage data to support decision-making at organizational, regional and population levels. *Healthcare quarterly (Toronto, Ont)* 2013; **16**(3): 27-33.
146. Alawadhi E, Al-Awadi A, Elbasmi A, Coleman MP, Allemani C. Cancer survival trends in Kuwait, 2000-2013: A population-based study. *The Gulf Journal of Oncology* 2019; **1**(29): 39-52.
147. Maringe C, Walters S, Rachet B, Butler J, Fields T, Finan PJ, Maxwell R, Nedrebø B, Påhlman L, Sjövall A, Spigelman A, Engholm G, Gavin A, Gjerstorff ML, Hatcher J, Johannesen TB, Morris EJ, McGahan CE, Tracey E, Turner D, Richards MA, Coleman MP, ICBP Module 1 Working Group. Stage at diagnosis and colorectal cancer survival in six high-income countries: a population-based study of patients diagnosed during 2000-7. *Acta Oncol* 2013; **52**: 919-32.
148. CONCORD Working Group. CONCORD Programme. 2018. http://csg.lshtm.ac.uk/research/themes/concord-programme/.
149. Alawadhi E, Al-Awahi A, Elbasmi A, Coleman MP, Allemani C. A Novel Approach to Obtain Follow-up Data on the Vital Status of Registered Cancer Patients: The Kuwait Cancer Registry Experience. *The Gulf Journal of Oncology* 2019; **1**(29): 31-8.
150. Young JL, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA. SEER Summary Staging Manual - 2000: Codes and Coding Instructions. NIH Pub. No. 01-4969. Bethesda, MD: National Cancer Institute; 2001.
151. White A, Rim SH, Joseph C, Johnson CJ, Coleman MP, Allemani C. Colon cancer survival in the United States by race and stage (2001–2009): findings from the CONCORD–2 study. *Cancer* 2017; **123**: 5014-36.
152. Richards TB, Henley SJ, Puckett MC, Weir HK, Huang B, Tucker TC, Allemani C. Lung cancer survival in the United States by race and stage (2001–2009): findings from the CONCORD–2 study. *Cancer* 2017; **123**: 5079-99.
153. Miller JW, Lee Smith J, Ryerson AB, Tucker TC, Allemani C. Disparities in breast cancer survival in the United States (2001–2009): findings from the CONCORD-2 study. *Cancer* 2017; **123**: 5100-18.
154. StataCorp. STATA statistical software. 14 ed. College Station TX: Stata Corporation; 2015.
155. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, Nur U, Tracey E, Coory M, Hatcher J, McGahan CE, Turner D, Marrett L, Gjerstorff ML, Johannesen TB, Adolfsson J, Lambe M, Lawrence G, Meechan D, Morris EJ,

Middleton R, Steward J, Richards MA, ICBP Module 1 Working Group. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* 2011; **377**: 127-38.
156. Butler J, Foot C, Bomb M, Hiom S, Coleman MP, Bryant H, Vedsted P, Hanson J, Richards M. The International Cancer Benchmarking Partnership: an international collaboration to inform cancer policy in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom. *Health Policy* 2013; **112**: 148-55.
157. AlSharafi G. Sector Report -Healthcare sector, Kuwait. Kuwait: British Embassy, 2010.
158. Wakelee H, Kelly K, Edelman MJ. 50 Years of progress in the systemic therapy of non-small cell lung cancer. *Am Soc Clin Oncol Educ Book* 2014: 177-89.
159. Albaba H, Lim C, Leighl N. Economic considerations in the use of novel targeted therapies for lung cancer: Review of current literature. *Pharmacoeconomics* 2017; **35**(12): 1195-209.
160. Karim-Kos HE, Kiemeney LA, Louwman MW, Coebergh JW, de Vries E. Progress against cancer in the Netherlands since the late 1980s: an epidemiological evaluation. *Int J Cancer* 2012; **130**(12): 2981-9.
161. Extramural Committee to Assess Measures of Progress Against Cancer. Measurement of progress against cancer. *J Natl Cancer Inst* 1990; **82**: 825-35.
162. Mathers CD, Fat DM, Inoue M, Rao C, López AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005; **83**(3): 171-7.
163. Doll R, Payne P, Waterhouse J A H. Cancer Incidence in Five Continents, Volume 1, Geneva, UICC; . Berlin, Springer; 1966.
164. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, Hesseling P, Shin HY, Stiller CA. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol* 2017.
165. Cochran WG. Sampling techniques: John Wiley & Sons; 1977.
166. Cho H, Mariotto AB, Schwartz LM, Luo J, Woloshin S. When do changes in cancer survival mean progress? The insight from population incidence and mortality. *Journal of the National Cancer Institute Monographs* 2014; **2014**: 187-97.
167. Health Innovation Forum. The University Health Network's partnership with the Kuwait Cancer Control Centre. https://www.healthinnovationforum.org/article/the-university-health-networks-partnership-with-the-kuwait-cancer-control-centre/.
168. Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. *Best Pract Res Clin Gastroenterol* 2014; **28**(5): 753-70.
169. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. *Lancet* 2015; **385**(9973): 1124-35.
170. Pui CH, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol* 2013; **50**: 185-96.
171. Heyman B, Yang Y. New developments in immunotherapy for lymphoma. *Cancer Biol Med* 2018; **15**(3): 189-209.
172. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J* 2017; **7**(6): e577.
173. Yilmaz M, Kantarjian H, Jabbour E. Treatment of acute lymphoblastic leukemia in older adults: now and the future. *Clin Adv Hematol Oncol* 2017; **15**(4): 266-74.
174. World Health Organization. WHO report on the global tobacco epidemic, 2017; Country profile: Kuwait, 2017.
175. Collaborative Group On Epidemiological Studies Of Ovarian Cancer, Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet* 2015; **385**: 1835–42.
176. Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives:

collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 2008; **371**(9609): 303-14.
177. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JWW. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008; **44**: 1345-89.
178. Kim Y, Yoo KY, Goodman MT. Differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. *Asian Pac J Cancer Prev* 2015; **16**(7): 2857-70.
179. Ravichandran K, Al-Zahrani AS. Association of reproductive factors with the incidence of breast cancer in Gulf Cooperation Council countries. *Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit* 2009; **15**(3): 612-21.
180. Collaborators GBDO, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Arnlov J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Furst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabares-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017; **377**(1): 13-27.
181. Tong CWS, Wu M, Cho WCS, To KKW. Recent Advances in the Treatment of Breast Cancer. *Front Oncol* 2018; **8**: 227.
182. Al-Sejari MM, Al-Kandari YY. Breast Cancer Knowledge and Awareness among Kuwaiti Women. *Journal of the Gulf & Arabian Peninsula Studies* 2014; **40**(153).
183. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg* 2009; **22**(4): 191-7.
184. MOH. STEPS Survey of Risk Factors for Chronic Non Communicable Diseases. Ministry of Health, Kuwait, 2015.
185. Yao K. The endoscopic diagnosis of early gastric cancer. *Ann Gastroenterol* 2013; **26**(1): 11-22.
186. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. *World J Gastroenterol* 2014; **20**(24): 7864-77.
187. Ladha-Waljee N, McAteer S, Nickerson V, Khalfan A. Using the accreditation journey to achieve global impact: UHN's experience at the Kuwait Cancer Control Center. *Healthcare quarterly (Toronto, Ont)* 2014; **17**(2): 33-7.
188. CAN campaign. Cancer Aware Nation. Kuwait. http://cancampaignkw.com/.

189. Mikkelsen L, Phillips DE, AbouZahr C, Setel PW, de Savigny D, Lozano R, López AD. A global assessment of civil registration and vital statistics systems: monitoring data quality and progress. *Lancet* 2015; **386**: 1395-406.

Appendices

Original Article

A Novel Approach to Obtain Follow–up Data on the Vital Status of Registered Cancer Patients: The Kuwait Cancer Registry Experience

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Abstract

Objective: We present an approach to obtain accurate and complete data on the last known vital status, and the date of last known vital status of all Kuwaiti cancer patients. These data are essential for robust estimation of population–based cancer survival.

Methods: Government–issued Civil ID numbers (IDs) of patients registered during 2000–2013 were obtained from the Kuwait Cancer Registry. Missing IDs were traced using the Ministry of Health's Information System or the patient's medical records. IDs were manually entered in the Public Authority of Civil Information (PACI) database to ascertain vital status for patients whose vital status was not known in the registry. To obtain the date of death for deceased patients, IDs were then manually entered and searched in the electronic archive of "Death Announcements" at the Ministry of Health's Central Records Department of Births and Deaths. Patients not found in the "Death Announcements" archive were considered alive as on 31 December 2015.

Results: The traditional method to obtain data on cancer patients' vital status, restricted to patients whose death was certified as due to cancer, had captured only 62% of all patients' deaths. This new approach resolved the vital status for 98.3% of patients for whom it was previously unknown. The impact was substantial: the proportion of patients known to be dead rose from 27.9% to 45.0%, while the proportion presumed alive dropped from 72.1% to 53.7%. Only 1.3% of the patients remained lost to follow–up.

Conclusion: This approach substantially improved the quality and completeness of follow–up data for all Kuwaiti cancer patients. We recommend that this approach should be performed routinely in Kuwait to enable accurate estimation and monitoring of population–based survival trends.

Keywords: population–based cancer registry, net survival, vital status, date of last known vital status

Introduction

Cancer is the second most common cause of death in Kuwait, following diseases of the circulatory system.[1] Reducing cancer–related deaths can be achieved primarily in two ways: by reducing cancer risk, or by improving the health–care system in terms of management and treatment of cancer patients.[2] Population–based cancer survival is a key measure of the effectiveness of a health system in managing cancer.[2,3] Monitoring survival over time, between sub–populations and between countries, is also crucial for assessing inequalities and driving policies for cancer control.[4, 5]

The aim of population–based survival analysis is to estimate net survival, which represents the cumulative probability for cancer patients to survive their cancer up to a given time (say, 5 years) since diagnosis, after controlling for competing risks of death (background mortality).[6] Net survival can be measured in two contexts: a cause–specific setting, when the exact cause of death is known and accurately reported, or a relative survival setting, when the exact cause of death is unknown, unreliable or inaccessible.

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Cause–specific survival estimation requires information on the underlying cause of death, and uses as an end–point those deaths that were attributed to cancer. Patients who die from other causes are censored, in order to estimate the cancer–specific hazard of death (excess hazard). This approach relies on the assumption that the death certification and the coding of the underlying cause of death are accurate. However, due to the variability in determining the cause of death accurately between physicians, hospitals, and countries, cause–specific survival estimates are not considered suitable for comparisons between countries or over time.[7–9]

The procedure for coding the underlying cause of death also differs between countries. For example, the procedures are different in Kuwait and the United Kingdom (Figure 1). In Kuwait, the "Death Announcement" is similar to the Medical Certificate of Cause of Death (MCCD) used in the UK,[10] which includes a section on the cause of death. Both are completed by physicians or hospital authorities, in accordance with the World Health Organisation (WHO) recommendations in the International Statistical Classification of Diseases and Related Health Problems (ICD).[11] However, the categories used to report cancer as the underlying cause of death differ in the two countries (Figure 1). The Kuwait Cancer Registry (KCR) reports the cause of death as "due to cancer" if either the first line (a) of the Death Announcement (the so–called "immediate cause" of death) or the third and last line (c) of the Death Announcement (the so–called "original or underlying cause" of death) is a cancer–related condition. The second line (b) of the Death Announcement is not coded, and will not be considered as the underlying cause of death even if the last line is not completed. In the UK, all three lines (Ia, Ib, Ic) of the sequence of events leading to death on the MCCD are taken into account to determine the underlying cause of death. This difference in coding the underlying cause of death may lead to under–estimation of cancer mortality rates in Kuwait, compared to the UK. Even minor misclassifications of the underlying cause of death have been shown to result in large changes in net survival estimates.[12] In addition, cause–specific estimates tend to be higher than relative survival estimates,[12, 13] therefore overemphasising the effectiveness of the health system in dealing with cancer.

Medical Certificate of Cause of Death in the UK

Cause of death the disease or condition thought to be the underlying cause should appear in the lowest completed line of part I

I	(a) disease or condition leading directly to death	Intraperitoneal haemorrhage
	(b) other disease or condition, if any, leading to I(a)	Ruptured metastatic deposit in liver
	(c) other disease or condition, if any, leading to I(b)	Primary adenocarcinoma of colon
II	Other significant conditions contributing to death but not related to the disease or condition causing it	Non–insulin dependent diabetes mellitus

Death Announcement in Kuwait

Deaths in less than a week old children ☐☐☐☐	Deaths in more than a week olds K 6 6 1
(a) Basic disease or condition in child	(a) Immediate cause: Intraperitoneal Haemorrhage
(b) Other disease or condition in child	(b) Secondary cause: Ruptured metastatic deposit in liver
(c) Disease or condition in mother that led to child's death ☐☐☐☐	(c) Original/ Underlying cause: Primary adenocarcinoma of colon C 1 8 9

Figure 1: An example of the "cause of death" sections of the UK's Medical Certificate of Cause of Death (MCCD) and Death Announcement in Kuwait, used in determining the underlying cause of death

*Death Announcements in Kuwait are completed in Arabic with exception to the codes.

Estimating cancer survival within a relative survival framework eliminates any differences or inaccuracies in certifying or coding the underlying cause of death, because the cause of death is not required for analysis. Relative survival is estimated as the ratio of the cancer patients' all–cause survival, where the endpoint is death from all causes, to the survival that the patients would have experienced if they had had the same background mortality as the general population (expected survival).[14, 15] Expected survival is estimated from population life tables that adequately represent the all–cause mortality experience of the population under study.[16–18] The relative survival framework is more appropriate for the estimation and comparison of net survival.[12, 19–21]

To produce reliable and accurate population–based survival estimates, it is necessary to have complete, reliable and long–term data for all patients diagnosed with cancer in a defined geographical area. It is thus imperative to have accurate and complete data on the date of diagnosis, the last known vital status and the date of last known vital status. When the patient has died, it is essential to know the date of death, regardless of the cause.

Many countries are able to maintain long–standing, high–quality population–based cancer registries and provide accurate incidence data. However, it is becoming increasingly difficult to obtain follow–up data and ascertain complete vital status for all patients. Many countries, including high–income countries such as Canada and Saudi Arabia, have reported difficulties in accessing this information for all cancer patients, due

to technical, legal or administrative barriers.[21] A recent international meeting on strengthening the health system and breast cancer care in the Middle Eastern countries, organised by the Harvard Medical School Center for Global Health Delivery in Dubai,[22] highlighted the fact that even in high–income Middle Eastern countries, efficient civil registration and availability of unique identification codes, both crucial to obtain the follow–up data, are still problematic. Such difficulties hinder robust survival estimation and, in many cases, prevent survival estimates from being produced at all.

An example of a national population–based registry that maintains high–quality cancer incidence data for the whole country is the Kuwait Cancer Registry (KCR), a department of the Kuwait Cancer Control Centre (KCCC).[23] However, complete data on vital status for all registered cancer patients are not available, since the registry has only been able to capture information on deaths due to cancer.

This study presents a novel approach to obtain accurate and complete follow–up data on the last known vital status and the date of last known vital status, as on 31 December 2015, of all Kuwaiti cancer patients registered between 2000 and 2013; thus enabling robust estimation of population–based survival in Kuwait.

Materials and Methods

Data on 12,469 patients diagnosed during 2000–2013 were obtained from the KCR database, including the patient's hospital file number, the Civil ID number where available, and the date of diagnosis (Figure 2, step 1). The Civil ID number was missing for 2,026 patients, and it was necessary to obtain these numbers, either electronically from the Health Information System or manually through the medical records (Figure 2, step 2), so that the records for all patients could then be manually linked with the Public Authority of Civil Information (PACI) database. The PACI database is considered to be the most reliable and up–to–date source to obtain the last known vital status, and the date of last known vital status, of any person resident in Kuwait, provided that their Civil ID number is known.

Only Kuwaiti patients were included in this study since vital status information for non–Kuwaitis is relatively inaccurate. Non–Kuwaiti residents are mostly expatriate labourers employed with short contracts (e.g. two–year contracts) who generally choose to return home upon completion of their contracts or when they become terminally ill. Although the vital status (alive or dead) of non–Kuwaitis in Kuwait is also recorded in the PACI database, it cannot be used to track the vital status of persons who have left the country. Therefore, the vital status data for non–Kuwaitis are incomplete.

Tracing of Civil ID numbers

To obtain the Civil ID number for Kuwaiti patients for whom it was not available, an "electronic search" using the patient's hospital file number was queried from the Health Ministry's Health Information System (HIS) database. If the Civil ID number was not available in the HIS system, a "manual search" was performed: the patient's hospital file number was used to locate and check the physical medical file in the Medical Records Department at the KCCC, in order to identify the Civil ID number of each patient. This step was performed twice (once at the beginning of this tracing process and once after 6 months), to increase the prospect of locating patients' files that might previously have been misplaced.

If the Civil ID number could not be traced, but a date of last known vital status earlier than 31 December 2015 was available in the medical records, this date was extracted to update the database. These patients were considered lost to follow–up and will contribute to survival analysis until that date.

Vital status and date of last known vital status update

To obtain follow–up data on last known vital status and date of last known vital status, a list of Civil ID numbers, sorted by year of diagnosis, was printed. Direct linkage with the PACI database was not permitted, therefore indirect access was granted through the Central Records Department of Births and Deaths at the Ministry of Health. Employees from this Department who have access to the PACI database manually entered the Civil ID numbers to determine each patient's vital status. If the patient was alive, the employee recorded the status as "alive" on the printed sheet. If the patient was dead, the employee used the patient's Civil ID number to access the Central Records Department's computerised database in order to obtain the exact date of death from the electronic archive of "Death Announcements", which is updated on a continuous basis. Each cancer patient's updated vital status was then entered manually into our existing cancer dataset, matched to the patient's record with the corresponding Civil ID and file numbers. The vital status was recorded as alive at 31 December 2015 for patients who were alive, or dead, with the date of death, for deceased patients.

Quality control

To ensure the correct transfer of vital status data from hard copy to the electronic database, data entry was verified by checking every 10th record on the hard copy with the vital status data that had been entered. This

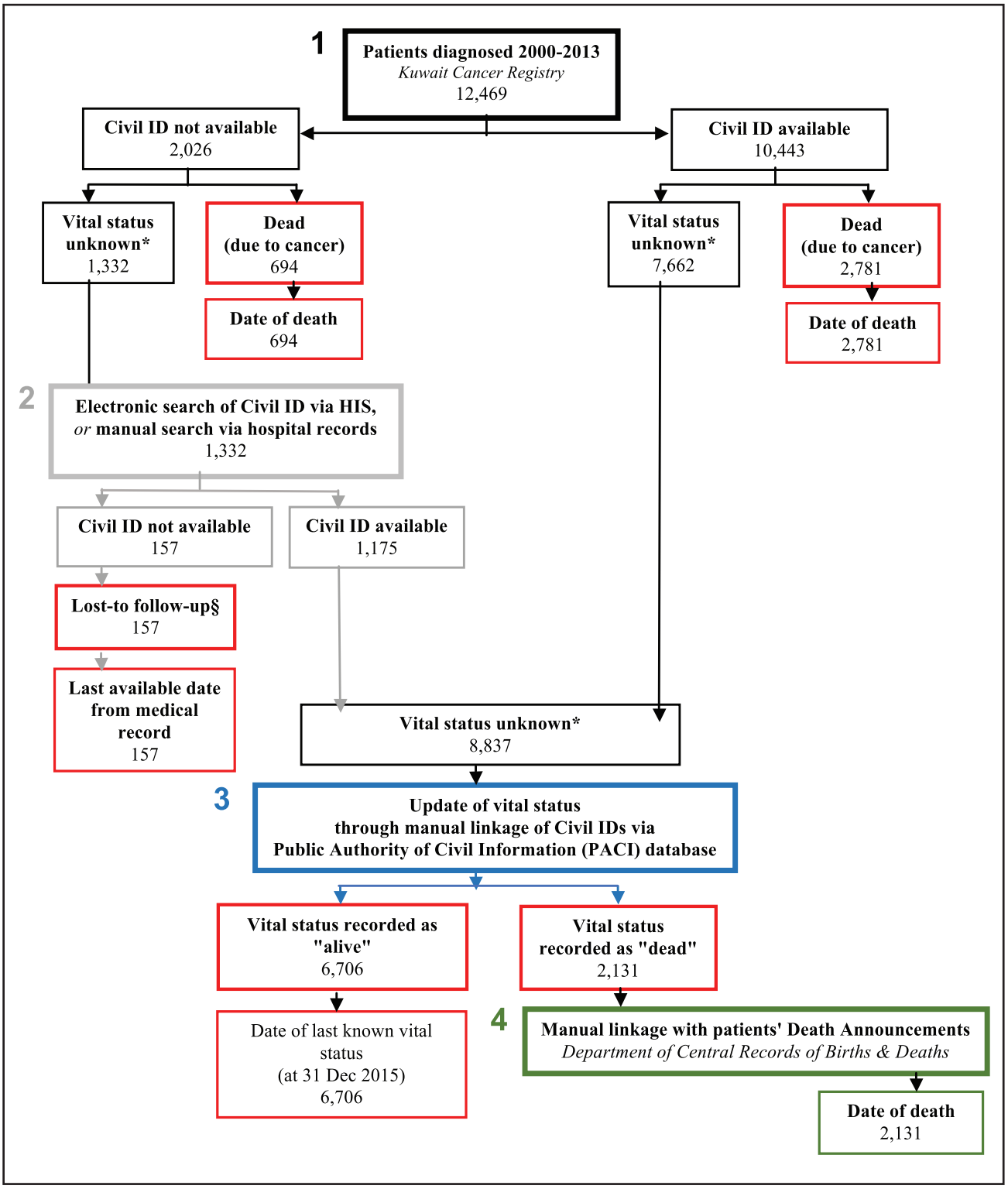

Figure 2: Process flow diagram of updating patients' vital status

*Unknown vital status: patients not reported as dead due to cancer; HIS: Health Information System

§Patients reported alive in medical records, at a specific date prior to 31 December 2018

process was performed on all the records that had been linked with the PACI database, and errors were corrected. All dates of death entered manually were also double–checked, to ensure correct transfer from the hard copy to the electronic database.

Results

During 2000–2013, Civil ID numbers were available in the registry for 10,443 (83.7%) of 12,469 Kuwaiti cancer patients registered (Table 1; Figure 2, step 1). Among these patients, 2,781 were known to be "dead", with the

cause of death attributed to cancer, while the vital status was unknown for the remaining 7,662 patients (61.4%).

The Civil ID number was not available for 2,026 patients (16.3%). Of these, 694 were known to be dead due to cancer, while the vital status of the remaining 1,332 (10.7%) patients was not known and needed to be traced and updated.

Most of the patients with unknown vital status and without Civil IDs had been diagnosed during 2000–2004; the proportion dropped from 35.4% to 0.5% for those diagnosed during 2010–2013 (Table 2; Figure 2, step 2). This combination of manual and electronic search enabled tracing of 1,175 out of 1,332 Civil ID numbers; 157 Civil ID numbers remained unavailable. However, for these patients, a date of last known vital status earlier than 31 December 2015 was available from the medical records. Therefore, these patients were considered lost to follow–up at that date. The overall proportion of patients without a Civil ID who would be considered lost to follow–up decreased from 10.7% to 1.3%. The impact of this tracing was most marked for patients diagnosed during 2000–2004, among whom the percentage whose Civil IDs were not available fell from 35.4% to 3.7%.

Tracing the Civil ID numbers enabled the vital status to be reliably ascertained through the PACI database, and updated for 8,837 (98.3%) of 8,994 of patients for whom it was initially unknown (Table 3; Figure 2, step 3). As a result, the number known to be dead rose by 2,131. The proportion of total deaths increased from 27.9% (3,475 patients, of which 2,781 had Civil ID numbers and 694 did not) to 45.0% (5,606 patients, including 3,475 known to be dead due to cancer and 2,131 known to be dead due to other causes). About 54% (6,706) out of the 12,469 patients were shown to be alive, leaving only 157 classified as lost to follow–up.

	Calendar period of diagnosis							
	No.	%	No.	%	No.	%	No.	%
	2000–04		2005–09		2010–13		All periods	
All patients	3,489		4,545		4,435		12,469	
Civil ID number available	1,656	47.5	4,402	96.9	4,385	98.9	10,443	83.7
Dead (due to cancer)	496	14.2	1,400	30.8	885	20.0	2,781	22.3
Unknown vital status	1,160	33.3	3,002	66.1	3,500	78.9	7,662	61.4
Civil ID number not available	1,833	52.5	143	3.1	50	1.1	2,026	16.3
Dead (due to cancer)	597	17.1	69	1.5	28	0.6	694	5.6
Unknown vital status	1,236	35.4	74	1.6	22	0.5	1,332	10.7

Table 1: Number of Kuwaiti cancer patients, with and without Civil ID numbers, by period of diagnosis

Unknown vital status	Calendar period of diagnosis							
	No.	%	No.	%	No.	%	No.	%
	2000–04		2005–09		2010–13		All periods	
Before Tracing								
Civil ID number not available	1,236	35.4	74	1.6	22	0.5	1,332	10.7
After tracing								
Civil ID number traced	1,107	31.7	49	1.1	19	0.4	1,175	9.4
Civil ID number not available	129	3.7	25	0.5	3	0.1	157	1.3

Table 2: Kuwaiti patients with unknown vital status* and Civil ID numbers not available, before and after the tracing:

*unknown vital status: patients not reported as dead to cancer

	Pre–update		Post update	
Vital Status	**No.**	**%**	**No.**	**%**
Dead (due to cancer)	3,475	27.9	–	–
Dead (due to any cause)	–	–	5,606	45.0
Alive	–	–	6,706	53.7
Lost to follow–up	–	–	157	1.3
Unknown*	8,994	72.1	–	–
Total	**12,469**	**100.0**	**12,469**	**100.0**

Table 3: Vital status, pre– and post–update: Kuwaiti cancer patients diagnosed during 2000–2013

* These patients were presumed alive (not known to be dead) in the KCR before applying our approach to update the follow–up data

Discussion

We present a novel approach to obtain complete follow–up data on the vital status of all Kuwaiti cancer patients. This approach enabled us to update the vital status for most (98.3%) Kuwaiti cancer patients registered during the period 2000 to 2013.

Of the deaths occurring by 31 December 2015 among cancer patients registered during 2000–2013, only 62.0% (3,475 of 5,606) had initially been recorded in the KCR database through the traditional follow–up method, relying solely on deaths that had been certified as due to cancer.

The process of tracing Civil ID numbers enabled ascertainment of the vital status for almost all registered cancer patients, including all deaths, regardless of the cause. This had a substantial impact on the proportion of cancer patients who were known to be dead, which rose from 27.9% to 45.0%, while the proportion considered to be alive at the end of follow–up dropped from 72.1% to 53.7%.

The most evident changes resulting from tracing the Civil ID numbers occurred during 2000–2004, where the proportion of patients without Civil IDs and with unknown vital status was much greater (52.5%) than in 2005–2009 (3.1%) and in 2010–2014 (1.1%). This difference was probably due to several improvements in KCR registration practices, implemented over the years: the routine practice of obtaining the patients' Civil ID during registration was progressively enforced, resulting in lower numbers of patients without ID numbers. The availability of Civil IDs is crucial to the implementation of our approach: a higher proportion of IDs made linkage between the cancer registry data and the patients' vital status records more effective. Complete and accurate data on follow–up for vital status are essential to enable robust estimation of population–based cancer survival.

Observed survival (also called all–cause survival) can be useful in predictive tools and cost–effectiveness analyses,[24] but it cannot be used to provide information on the probability of surviving a specific cancer, or to examine cancer survival trends within a given country, because its estimation also includes deaths from causes other than cancer (competing risks of death), which are likely to be decreasing over time due to continuous medical advancement. Similarly, observed survival estimates cannot be used for international comparisons of cancer survival, since background mortality also varies very widely between countries.[18, 25, 26] Estimates of observed survival can also substantially over–estimate the true observed survival if based only on deaths that were certified or coded as due to cancer, because deaths from causes other than cancer are not included in the computation.

The accuracy of death certification and of the coding of the underlying cause of death can vary between countries and over time within a country. These can arise from inaccuracies in the certification of death when compared with autopsy findings and clinical data, differences among physicians in completing the death certificates, and variations in coding the underlying the cause of death.[7–9] Inaccuracies in certifying the cause of death have been found in Kuwait when original death certificates were compared with the patients' medical records, indicating poor agreement in the certification of death between the original and revised certificates.[27]

Other differences in death registration practices can arise from changes to the death certificate forms used in a country, when coding rules are updated or revisions of the ICD are introduced, from changes in diagnostic terminology and measurement, or when there is a lack of training in certifying the cause of death.[28–30]

For all these reasons, international comparisons of population–based cancer survival require statistical methods that do not rely on the cause of death (net survival). By eliminating the effect of background mortality, differences and trends in net survival reflect differences in cancer outcome, rather than differences in competing causes of death. Net survival estimates are thus better suited for international comparisons and to evaluate the impact of changes in health policy over time.

Our approach to obtain follow–up data through individual record linkage between the KCR database and the PACI database provides the most complete and up–to–date information on the vital status for almost all Kuwaiti cancer patients. However, to conduct this update manually is labour–intensive and time–consuming, and requires extensive quality checks on the manual entry and extraction of data. If performed efficiently, electronic linkage between the cancer registry database and the vital status data stored in the PACI database would be more accurate and timelier, but it is more complex and requires ministerial agreement and collaboration.

The use of this novel approach will provide the Kuwait Cancer Registry with more accurate and complete information on Kuwaiti cancer patients' vital status, on a routine basis. It will allow clear distinction between patients who are alive and patients who are dead from any cause (i.e. not just those who have died from cancer). These data, together with the use of appropriate life tables of background mortality, would enable Kuwait to monitor routinely net survival trends and to compare cancer survival in Kuwait with survival in other countries.

Conclusion

Robust estimates of population–based cancer survival are crucial to assess the effectiveness of the health system in managing cancer. Complete and reliable follow–up data on the vital status of all cancer patients, regardless of the cause of death, are essential to produce robust cancer survival estimates that can be monitored over time and compared internationally.

Prior to this study, there was no system to update the vital status for all Kuwaiti cancer patients. With support from the Kuwait Ministry of Health and the Ministry of Interior/PACI this approach could be performed routinely by the KCR to ensure (a) that virtually all deaths of Kuwaiti cancer patients, regardless of the cause, are systematically recorded; and (b) that the follow–up on the vital status of all cancer patients is accurately updated through record linkage between the KCR database and the PACI database.

The ultimate goal would be to establish routine electronic linkages with the PACI system, making the process more efficient and timely.

Several countries in the Gulf Cooperation Council (e.g. Qatar, Bahrain and United Arab Emirates) have an administrative system similar to the one in Kuwait. This study may assist cancer registries in these countries to integrate the conceptual framework in their administrative system, to improve their follow–up procedures and to enhance the quality of cancer patients' vital statistics.

Ethical Approval

Ethical approval [2015/276] was granted by the Standing Committee for Coordination of Health and Medical Research at Kuwait's Ministry of Health.

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References

1. Health Vital Statistics Division. Health, Kuwait 2014. Kuwait: Department of Statistics & Medical Records, Ministry of Health, 2015.
2. Coleman MP. Cancer survival: global surveillance will stimulate health policy and improve equity. Lancet. 2014;383:564–73
3. Coleman MP. Why we need global surveillance of cancer survival: the CONCORD programme. In: McGrath I, editor. Cancer care in emerging health systems. Oxford: International Network for Cancer Treatment and Research; 2013. p. 60–5.
4. Allemani C, Harewood R, Johnson CJ, Carreira H, Spika D, Bonaventure A, et al. Population–based cancer survival in the United States: Data, quality control, and statistical methods. Cancer. 2017 December 15, 2017;123: 4982–93
5. Allemani C. The importance of global surveillance of cancer survival for cancer control: the CONCORD programme. Cancer Control. 2017:19–21
6. Perme MP, Stare J, Esteve J. On estimation in relative survival. Biometrics. 2012 Mar;68(1):113–20
7. Laurenti R, Coleman MP, Aylin P. Accuracy of statements of the cause of death on death certificates and the international comparability of mortality statistics. In: Coleman MP, Aylin P, editors. Death certification and mortality statistics: an international perspective. London: Office for National Statistics; 2000. p. 1–9.
8. Percy CL, Muir CS. The international comparability of cancer mortality data: results of an international death certificate study. Am J Epidemiol. 1989;129:934–46
9. Percy CL, Dolman AB. Comparison of the coding of death certificates related to cancer in seven countries. Public Health Rep. 1978;93:335–50
10. Office for National Statistics. Guidance for doctors completing Medical Certificates of Cause of Death in England and Wales. In: Service HOlaP, editor. 2010. p. 1–15.
11. World Health Organisation. International statistical classification of diseases and related health problems. Tenth revision. Geneva: World Health Organization; 1994.
12. Schaffar R, Rachet B, Belot A, Woods LM. Estimation of net survival for cancer patients: Relative survival setting more robust to some assumption violations than cause–specific setting, a sensitivity analysis on empirical data. Eur J Cancer. 2017 Feb;72:78–83
13. Schaffar R, Rachet B, Belot A, Woods L. Cause–specific or relative survival setting to estimate population–based net survival from cancer? An empirical evaluation using women diagnosed with breast cancer in Geneva between 1981 and 1991 and followed for 20 years after diagnosis. Cancer Epidemiology. 2015;39(3):465–72
14. Ederer F, Axtell LM, Cutler SJ. The relative survival: a statistical methodology. Natl Cancer Inst Monogr. 1961;6:101–21
15. Cutler SJ, Ederer F. Maximum utilisation of the life table method in analyzing survival. J Chronic Dis. 1958;8: 699–712
16. Baili P, Micheli A, De Angelis R, Weir HK, Francisci S, Santaquilani M, et al. Life–tables for world–wide comparison of relative survival for cancer (CONCORD study). Tumori. 2008;94:658–68
17. Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. Stat Med. 1990;9:529–38
18. Spika D, Bannon F, Bonaventure A, Woods LM, Harewood R, Carreira H, et al. Life tables for global surveillance of cancer survival (the CONCORD programme): data sources and methods. BMC Cancer. 2017 27 Feb 2017;17:159–73
19. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. J Intern Med. 2006;260:103–17
20. Rachet B, Woods LM, Mitry E, Riga M, Cooper C, Quinn MJ, et al. Cancer survival in England and Wales at the end of the 20th century. Br J Cancer. 2008;99 (Suppl. 1):2–10
21. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD–3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population–based registries in 71 countries. Lancet. 2018 Jan 30;391:1023–75
22. Health System Strengthening and Breast Cancer Care in the Middle East: Results of the Harvard Research Study, 2018 21–23 January; Dubai: Harvard Medical School Center for Global Health Delivery–Dubai.

23. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136:E359–86

24. Mariotto AB, Noone AM, Howlader N, Cho H, Keel GE, Garshell J, et al. Cancer survival: an overview of measures, uses, and interpretation. J Natl Cancer Inst Monogr. 2014 Nov;2014(49):145–86

25. Hashim D, Boffetta P, La Vecchia C, Rota M, Bertuccio P, Malvezzi M, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol. 2016 May;27(5): 926–33

26. Mortality GBD, Causes of Death C. Global, regional, and national age–sex specific all–cause and cause–specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Jan 10;385(9963):117–71

27. Moussa MA, Shafie MZ, Khogali MM, el–Sayed AM, Sugathan TN, Cherian G, et al. Reliability of death certificate diagnoses. J Clin Epidemiol. 1990;43(12):1285–95

28. Ohmi K, Yamamoto A. Changes in mortality statistics in Japan, 1995: the effect of implementation of ICD–10 and revision of the death certificate. In: Coleman MP, Aylin P, editors. Death certification and mortality statistics: an international perspective. London: Office for National Statistics; 2000. p. 21–7.

29. Hoyert DL, Rosenburg HM, MacDorman MF. Effects of changes in death certificate format on cause–specific mortality trends, United States, 1970–1992. In: Coleman MP, Aylin P, editors. Death certification and mortality statistics: an international perspective. London: Office for National Statistics; 2000. p. 47–58.

30. Haghighi MH, Dehghani M, Teshizi SH, Mahmoodi H. Impact of documentation errors on accuracy of cause of death coding in an educational hospital in Southern Iran. The HIM journal. 2014;43(2):35–42

Original Article

Cancer survival trends in Kuwait, 2000–2013: A population–based study

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Abstract

Objective: To examine population–based cancer survival trends in Kuwait; to facilitate public assessment of cancer control.

Methods: Data were obtained from the Kuwait Cancer Registry for Kuwaiti adults (15–99 years) and children (0–14 years) diagnosed with one of 18 common cancers during 2000–2013 and followed up to 31 December 2014. Net survival was estimated at 1, 3, and 5 years by sex. To control for background mortality, life tables of all–cause mortality in the general population were constructed by single year of age, sex, and calendar year of death ("complete" life tables). Net survival estimates were age–standardised using the International Cancer Survival Standard weights.

Results: Cancers with the highest net survival throughout the 14–year period were prostate, breast (women) and rectum in adults, and lymphoma in children. Survival was lowest for liver, pancreas and lung cancer in adults, and brain tumours in children. During 2010–2013, one–year survival was over 80% for cancers of the prostate, breast, rectum, cervix and colon. Five–year survival was above 80% only for prostate cancer. For children, one– and five–year survival was above 80% only for acute lymphoblastic leukaemia (ALL) and lymphoma. Survival was generally higher for women than men, and declined faster in women than men between 1 and 3 years after diagnosis. Differences between boys and girls were small.

Conclusion: Cancer survival improved for most Kuwaiti adults and children over the 14–year period, with women generally having a more favourable prognosis than men. Continuous surveillance is required to monitor cancers for which survival did not improve, and to dissect the underlying causes for the differences in survival between Kuwait and other countries.

Keywords: population–based, net survival, cancer registries, Kuwait

Introduction

Cancer is the second most common cause of death in Kuwait after cardiovascular diseases.[1] To evaluate the effectiveness of health systems in controlling the cancer burden and prevent cancer–related deaths, three population–based metrics need to be assessed: incidence, survival and mortality.[2] Population–based metrics are obtained using data on all cancer patients residing in a defined geographic area. These data are collected by population–based cancer registries. While trends in cancer incidence and mortality are routinely monitored in Kuwait, population–based cancer survival trends are not.

Because survival time is dependent on two events, diagnosis and death, complete data on the eventual death of all cancer patients, regardless of the cause of death, are required to produce reliable and accurate survival estimates.[3] Producing population–based cancer survival estimates from complete and good–quality data for Kuwait is important for several reasons. Firstly, population–based survival represents a reliable measure for assessing the effectiveness of all aspects of the health system, from awareness and diagnosis to the system's ability to treat and cure cancer. Age–standardised survival estimates are essential for making valid comparisons over time, between sub–populations and countries, to guide cancer control policies.[4] To understand fully the progress against cancer, therefore, it is essential to assess survival estimates alongside incidence and mortality.

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This study aims to produce a comprehensive profile of population–based cancer survival in Kuwait: robust estimates of net survival up to 5 years for 18 common cancers that can be monitored and compared internationally to facilitate assessment of cancer control in Kuwait.

Material and methods

The data used in this study were obtained from the Kuwait Cancer Registry (KCR). Cancer notification in Kuwait is mandatory by ministerial regulation. The KCR is considered to be a comprehensive source of information for all cancer patients diagnosed or treated in Kuwait. Kuwait incidence data on patients diagnosed since 1979 have been published in "Cancer Incidence in Five Continents",[5] which is generally considered an imprimatur of high–quality data.

The KCR maintains an index of all cancer patients through collecting information on malignant neoplasms according to the International Association of Cancer Registries (IACR) guidelines (www.iarc.fr). Since January 2000, the registry has adopted the third edition of the International Classification of Diseases for Oncology (ICD–O–3)[6] for all clinical coding, including topography, morphology and behaviour.

Data were obtained for Kuwaiti adults (age 15–99 years) and children (age 0–14 years) diagnosed between 1 January 2000 and 31 December 2013 with one of 18 cancers or groups of cancers: oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast (women), cervix, ovary, prostate and melanoma of the skin in adults, together with brain tumours, leukaemias and lymphomas in both adults and children.

Data were collected according to the CONCORD protocol.[7] Topography and morphology were coded to the International Classification of Diseases for Oncology (third edition, ICD–O–3),[6] including its first revision.[8] Solid tumours were defined by anatomical site (topography), while leukaemias, lymphomas and melanoma of the skin were defined by morphology (Table 1).

The KCR provided data for all haematopoietic malignancies (ICD–O–3 morphology codes in the range 9590–9992) in adults and children. For adults, we analysed "lymphoid (HAEMACARE groups 1–19)" or "myeloid (HAEMACARE groups 20–25)" malignancies, in consultation with specialists in the HAEMACARE9 and InterLymph10 working groups (Table 2). For children, we analysed survival for acute lymphoblastic leukaemia (ALL) and lymphomas, based on the International Classification of Childhood Cancer 3rd edition (ICCC–3)[11] (Table 3).

Malignancy	Topography or morphology codes*	Description
Oesophagus	C15.0–C15.5; C15.8–C15.9	Oesophagus
Stomach	C16.0–C166; C168–C16.9	Stomach
Colon	C18.0–C18.9; C19.9	Colon and rectosigmoid junction
Rectum †	C20.9; C21.0–C21.2, C21.8	Rectum, anal canal and anorectal junction
Liver	C22.0–C22.1	Liver and intrahepatic bile ducts
Pancreas	C25.0–C25.4; C25.7–C25.9	Pancreas
Lung‡	C34.0–C34.3; C34.8–C34.9	Lung and bronchus
Breast (women) †	C50.0–C50.6; C50.8–C50.9	Breast
Cervix	C53.0–C53.1; C53.8–C53.9	Cervix uteri
Ovary	C48.0–C48.2; C56.9; C57.0–C57.4; C57.7–C57.9	Ovary, fallopian tube and uterine ligaments, other and unspecified female genital organs, peritoneum and retroperitoneum
Prostate	C61.9	Prostate gland
Brain (adults and children)	C71.0–C71.9	Brain
Melanoma of the skin	M8720–8790	Melanoma of the skin, with skin of labia majora, vulva, penis and scrotum
Haematological malignancies (adults and children) ¥	M9590–9992	Myeloid and lymphoid neoplasms (adults); Acute lymphoblastic leukaemia and lymphoma (children)

Table 1: Definition of malignancies

* International Classification of Diseases for Oncology 3rd edn (ICD–O–3. † Excludes skin of anus, perianal skin, and skin of breast(C44.5). ‡ Excludes trachea (C39.9). ¥ Grouping of leukaemias and lymphomas is based on HAEMACARE groups and the InterLymph recommendations for adults, and on the ICCC–3 (3rd edn) group I & II for children (Tables 2 and 3)

Only primary, invasive malignancies (ICD–O behaviour code 3) were included in survival analyses. The only exception was brain tumours, where tumours of benign or uncertain behaviour (code 0 or 1) were also included (Table 4). Other ineligibilities included records that were incomplete or outside the age range specified in the CONCORD protocol, as well as tumours that were metastatic from another primary site, or were unknown whether primary or metastatic.

Follow–up data on each patient's vital status (alive, dead, lost to follow–up), at 31 December 2014, were obtained through a mixture of passive and active methods, to include all deaths regardless of the cause of death. Passive follow–up is the term used when

HAEMACARE groups		ICD–O–3 morphology codes	
No.	Description	Lymphoid neoplasms	Myeloid neoplasms
1	Lymphoma NOS	9590	
2	NH Lymphoma NOS	9591, 9597	
3	Composite HL and NHL	9596	
4	HL nodular lymphocyte predominance	9659	
5	Classical HL	9650, 9661, 9662, 9651, 9663, 9664, 9665, 9667, 9652, 9653, 9654, 9655	
6	CLL/SLL	9670, 9823	
7	Immunoproliferative diseases	9760, 9671, 9761, 9762	
8	Mantle cell/centrocytic lymphoma	9673	
9	Follicular B lymphoma	9690, 9691, 9695, 9698	
10	Diffuse B lymphoma	9675, 9678, 9679, 9680, 9684, 9688, 9712, 9735, 9737, 9738	
11	Burkitt's leukaemia/lymphoma	9687, 9826	
12	Marginal zone lymphoma	9689, 9699, 9764	
13	T lymphoma cutaneous	9700, 9701, 9709, 9718, 9708, 9726	
14	Other T cell lymphoma	9702, 9705, 9714, 9716, 9717, 9725, 9948, 9719, 9827, 9831, 9834	
15	Lymphoblastic lymphoma/acute (precursor cell) lymphoblastic leukaemia	9727, 9728, 9729, 9811, 9812, 9813, 9814, 9815, 9816, 9817, 9818, 9835, 9836, 9837	
16	Plasma cell neoplasms	9731,9732, 9733, 9734	
17	Mature B cell leukaemia	9833	
18	Mature B–cell leukaemia, hairy cell	9940	
19	Lymphatic leukaemia NOS	9820, 9832	
20	Leukaemia NOS		9800, 9801, 9805, 9806, 9807, 9808, 9809
21	Myeloid leukaemia NOS		9860, 9898
22	Acute myeloid leukaemia		9840, 9861, 9865, 9866, 9867, 9869, 9870, 9871, 9872, 9873, 9874, 9891, 9895, 9896, 9897, 9910, 9911, 9920, 9930, 9931, 9984, 9987
23	Myeloproliferative neoplasms*		9740, 9741, 9742, 9863, 9875, 9950, 9960, 9961, 9962, 9963, 9964
24	Myelodysplastic syndrome		9980, 9982, 9983, 9985, 9986, 9989, 9991, 9992
25	Myelodysplastic/myeloproliferative neoplasms**		9945, 9876, 9946, 9975

Table 2: Definition of adult haematological malignancies

NOS: Not otherwise specified, * this group includes chronic myeloid leukaemias (several morphology codes), ** Note: this group includes chronic myelomonocytic leukaemia (M–9945) and Juvenile Myelomonocytic leukaemia (M–9946)

cancer registries routinely receive notification of deaths from a vital statistics office, or when they link cancer registrations to vital statistics records at routine intervals, using unique identifiers such as name or identity numbers. Active follow–up refers to the process whereby a registry actively seeks data on the vital status for each patient via direct contact with hospitals, the patient's family or local authorities.[3,12] The follow–up procedures in this study involved a series of steps that included identifying the unique national identification numbers (Civil ID numbers) of all the Kuwaiti patients, and manually linking them to the country's centralised registration database, the Public Authority of Civil Information (PACI). This provided accurate information on all deaths, irrespective of whether the cause of death was cancer–related. The dates of death for deceased patients were obtained by manual search of the Civil ID numbers from the electronically archived "Death Announcements" at the Central Records Department of Births and Deaths. In cases where the patient's vital status could not be ascertained, the date when the patient was last known to be alive was extracted from the patient's medical hospital files: the tumour registry record was

ICCC–3 groups		ICD–O–3 morphology codes	
No.	Description	Acute lymphoblastic leukaemia	Lymphomas & RE neoplasms
Ia	Lymphoid leukaemias	9835, 9836, 9837	
IIa	Hodgkin lymphomas		9650–9655, 9659, 9661–9665, 9667
IIb	Non Hodgkin lymphomas (except Burkitt lymphoma)		9591, 9597, 9670, 9671, 9673, 9675, 9678–9680, 9684, 9688, 9689–9691, 9695, 9698–9702, 9705, 9708, 9709, 9712, 9714, 9716–9719, 9725, 9726, 9727–9729, 9731–9734, 9735, 9737, 9738, 9760–9762, 9764–9769, 9970, 9971
			and 9811, 9812, 9813, 9814, 9815, 9816, 9817, 9818 only if topography is NOT in C42.0, C42.1, C42.3, C42.4, C80.9
IIc	Burkitt lymphoma		9687
IId	Miscellaneous lymphoreticular neoplasms		9740–9742, 9750, 9751, 9752, 9753, 9754–9758, 9759
IIe	Unspecified lymphomas		9590, 9596

Table 3: Definition of childhood haematological malignancies

updated, the vital status was recorded as "lost to follow–up", and the patient was censored from analysis at the date he or she was last known to be alive.

Quality control

Quality and completeness were assessed using the standardised quality–control procedures from the CONCORD programme for global surveillance of cancer survival.[7]

The data quality checks were performed in three consecutive phases. Phase one, protocol adherence, examines each individual variable within a given record for compliance with the CONCORD protocol. Phase two, exclusions, assesses logical coherence between the variables in each tumour record, and excludes records, such as tumours known to the registry only from a death certificate, or detected solely through autopsy. These records must be excluded from survival analyses since follow–up time is not available. Other exclusions are related to records with vital status unknown, or an invalid date sequence, or inconsistencies between sex and site, site and morphology, age and site, or age and site and morphology.

Duplicate registrations were also excluded. When two or more primary, invasive malignancies with the same site existed in the same person and the records had the same date of diagnosis, the record with the most complete information was retained. If these records presented different dates of diagnosis, the record with the earliest date of diagnosis was retained.

Phase three, editorial, evaluates, for each cancer, the distribution of key data quality indicators. Table 4 provides a summary of the records that were excluded from survival analysis, and the number of patients included in analyses, together with the distribution of the quality indicators.

Statistical analysis

We estimated net survival for patients diagnosed with one of 18 malignancies during 2000–2004, 2005–2009 and 2010–2013. Survival was estimated at 1, 3 and 5 years after diagnosis, for males, females and both sexes combined.

For patients diagnosed in 2000–2004 and in 2005–2009, for whom follow–up was available for the full duration of the survival analysis (either one, three or five years), estimates were produced using the cohort approach. The cohort approach is considered the gold standard,[13] because it provides a survival estimate for a cohort of patients who were all diagnosed during the same year or calendar period and followed up for at least the duration for which survival estimates are required, in this case 1, 3 or 5 years. For 2010–2013, we applied the "period" approach,[14] which offers reliable prediction of the eventual survival of recently diagnosed patients who have not all been followed up for the whole time of analysis.

Net survival is the term used to describe the probability that cancer patients survive their cancer up to a given time (e.g. five years) following diagnosis, after controlling for competing causes of death (background mortality).[15] To control for background mortality, we used life tables of all–cause mortality in the general population.[16] Life tables were constructed by single year of age ("complete" life tables), sex, calendar year of death and ethnicity (Kuwaiti, non–Kuwaiti).

To estimate net survival, we used the Pohar–Perme estimator,[15] implemented with the program stns[17] in Stata version [14] (StataCorp LP, College Station, TX). This estimator accounts for the fact that competing risks of death are higher in older cancer patients.

For each cancer, calendar period and sex, we present age–standardised net survival estimates up to 5 years after diagnosis. For adults, we used the International Cancer Survival Standard (ICSS) weights,[18] in which age at diagnosis is categorised into 5 groups: 15–44, 45–54, 55–64, 65–74 and 75–99 years and, for prostate cancer, 15–54, 55–64, 65–74, 75–84 and 85–99 years. Of the

	Patients Submitted	Ineligible		Eligible patients	Exclusions‖		2000–2004		No of cases 2005–2009		2010–2013		Total	††MV (%)	Non–specific morphology (%)	Lost to followup (%)
		In situ (%)	Other (%)		DCO (%)	Other (%)	M	F	M	F	M	F				
Adult cancers																
Oesophagus	97	0.0	0.0	97	7.2	0.0	12	15	12	12	26	13	90	100.0	0.0	2.2
Stomach	233	0.0	6.4	218	5.0	0.0	35	24	48	31	36	33	207	100.0	0.0	1.0
Colon	938	0.1	0.3	934	2.8	0.0	106	131	165	160	172	174	908	100.0	0.0	2.2
Rectum	335	0.0	0.3	334	1.2	0.0	37	48	64	66	60	55	330	100.0	0.0	0.9
Liver	303	0.0	0.3	302	13.2	0.3	48	20	75	31	62	25	261	100.0	0.4	1.1
Pancreas	265	0.0	0.4	264	8.3	0.8	31	26	54	37	46	46	240	100.0	0.4	0.8
Lung	586	0.2	0.2	584	4.3	0.0	131	49	142	49	135	53	559	100.0	0.2	1.3
Melanoma	21	0.0	14.3	18	0.0	0.0	2	3	2	5	4	2	18	100.0	0.0	0.0
Breast	2,698	3.6	0.2	2,595	0.5	0.6	0	628	0	953	0	987	2,568	100.0	0.1	0.4
Cervix	183	9.8	0.0	165	1.2	0.0	0	62	0	59	0	42	163	100.0	0.0	0.6
Ovary	279	0.0	17.6	230	2.6	1.3	0	62	0	92	0	67	221	99.5	0.9	0.5
Prostate	521	0.6	0.0	518	1.7	0.0	116	0	169	0	224	0	509	100.0	0.0	0.8
Brain	259	0.0	0.0	259	8.9	2.3	42	25	50	34	42	37	230	96.5	3.9	0.9
Myeloid neoplasms	350	0.0	0.6	348	0.6	0.0	44	40	77	59	68	58	346	98.8	2.6	0.9
Lymphoid neoplasms	1,409	0.0	0.1	1,407	0.1	0.0	208	167	330	207	271	222	1,405	99.6	0.8	1.6
Total	**8,477**	**1.4**	**1.0**	**8,273**	**2.3**	**0.3**	**812**	**1,300**	**1,188**	**1,795**	**1,146**	**1,814**	**8,055**	**99.8**	**0.4**	**1.0**
Childhood cancers																
Brain	57	0.0	0.0	57	8.8	5.3	13	5	16	6	5	4	49	100.0	0.0	2.0
ALL	251	0.0	0.0	251	0.0	0.0	54	29	55	43	40	30	251	100.0	0.0	5.2
Lymphoma	146	0.0	11.6	129	0.0	0.0	35	13	29	16	23	13	129	100.0	1.6	4.7
Total	**454**	**0.0**	**3.7**	**437**	**1.1**	**0.7**	**102**	**47**	**100**	**65**	**68**	**47**	**429**	**100.0**	**0.5**	**4.7**

Table 4. Data quality indicators for patients diagnosed during 2000–2013, for adults and children by cancer site

¶ In situ malignant disease (ICD–O–3 behaviour code 2). Other: records with incomplete data; or tumours that are benign (behaviour code 0), of uncertain behaviour (1), metastatic from another organ (6), or unknown if primary or metastatic (9); or patients falling outside the age range 0–14 years (children) or 15–99 years (adults); or other conditions. ‖DCO=tumours registered from a death certificate only or detected solely at autopsy. Other: vital status or sex unknown; or invalid sequence of dates; or inconsistency of sex–site, site–morphology, age–site, age–morphology, or age–sitemorphology. †† MV=microscopically verified. Non–specific morphology (solid tumours only): ICD–O–3 morphology code in the range 8000–8005.

three sets of ICSS weights, we used group 2 (cancers for which incidence does not increase steeply with age) for melanoma of the skin, cervix uteri and brain (adults), and group 1 (cancers for which incidence does increase steeply with age) for oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast, ovary and prostate, and both groups of haematopoietic malignancies. For children, we estimated survival for the age groups 0–4, 5–9 and 10–14 years; age–standardised estimates were obtained by assigning equal weights to the three age–specific estimates.[18,19] Cumulative survival probabilities in the range 0–1 are presented for convenience as percentages in the range 0–100%.

Survival was not estimated if fewer than ten patients were available for analysis. When the total number of available patients was fewer than 50, unstandardised estimates were produced for all ages combined. When the number of patients was 50 or more, age–specific estimates were produced where possible and an age–standardised summary estimate was derived. Where an age–specific estimate could not be obtained, the data from adjacent age groups were merged, and a combined estimate was assigned to both age groups. If two or more age–specific estimates could not be produced, only the unstandardised estimates for all ages combined were presented. 95% confidence intervals (CI) for both unstandardised and standardised survival estimates were derived assuming a normal distribution, truncated to the range 0–100. Standard errors to construct the CIs were calculated using the Greenwood method.[20] If no death or

		Males						Females						Both sexes					
		2000–2004		2005–2009		2010–2013		2000–2004		2005–2009		2010–2013		2000–2004		2005–2009		2010–2013	
		NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI
Adults																			
Oesophagus	1 year	*56.0*	*27.9 – 84.1*	*30.6*	*5.0 – 56.1*	*53.1*	*31.9 – 74.4*	*34.4*	*11.6 – 57.3*	*26.2*	*3.0 – 49.4*	*45.3*	*20.6 – 70.0*	*44.2 §*	*25.3 – 63.1*	*28.4*	*10.3 – 46.5*	*50.3*	*33.6 – 66.9*
	3 years	*21.8*	*0.0 – 44.7*	*0.1*	*0.0 – 0.3*	*32.0*	*11.7 – 52.3*	*14.4*	*0.0 – 31.0*	*17.7*	*0.0 – 37.3*	*15.2*	*0.0 – 32.2*	*17.6 §*	*2.9 – 32.4*	*9.5*	*0.0 – 20.6*	*25.0*	*10.3 – 39.8*
	5 years	*21.8*	*0.0 – 44.7*	..		*32.3*	*11.8 – 52.8*	*14.4*	*0.0 – 31.0*	*17.7*	*0.0 – 37.3*	*15.7*	*0.0 – 33.3*	*17.6 §*	*2.9 – 32.4*	*9.5*	*0.0 – 20.6*	*25.4*	*10.5 – 40.4*
Stomach	1 year	*53.6*	*36.5 – 70.8*	*57.2*	*43.1 – 71.2*	**49.0**	35.0 – 63.1	*46.6*	*27.0 – 66.2*	*45.5*	*28.2 – 62.7*	**51.4**	41.4 – 61.3	**45.8**	32.5 – 59.2	**47.4**	37.7 – 57.2	**50.5**	39.2 – 61.8
	3 years	*29.6*	*13.7 – 45.4*	*21.3*	*9.8 – 32.9*	**23.7**	11.1 – 36.4	*17.1*	*2.7 – 31.6*	*19.8*	*6.3 – 33.4*	**15.4**	7.2 – 23.5	**20.3**	11.0 – 29.5	**16.1**	10.1 – 22.1	**27.9**	16.0 – 39.8
	5 years	*19.9*	*5.2 – 34.6*	*13.1*	*3.7 – 22.5*	*14.5*	*2.9 – 26.2*	*17.1*	*2.7 – 31.6*	*19.8*	*6.3 – 33.4*	**15.5**	7.3 – 23.7	**15.0**	7.1 – 22.9	**13.4**	7.1 – 19.7	**22.4**	12.6 – 32.3
Colon	1 year	**86.1**	78.0 – 94.2	**73.2**	64.0 – 82.5	**86.4**	79.5 – 93.3	**85.4**	80.6 – 90.2	**79.0**	70.4 – 87.6	**77.0**	68.0 – 86.1	**85.8**	79.0 – 92.5	**76.1**	69.6 – 82.6	**82.6**	76.7 – 88.4
	3 years	**73.1**	61.1 – 85.0	**59.3**	48.7 – 69.8	**76.6**	66.0 – 87.1	**70.1**	62.9 – 77.2	**60.2**	50.5 – 69.9	**60.3**	50.2 – 70.4	**72.7**	63.0 – 82.3	**59.5**	52.1 – 66.9	**68.9**	61.0 – 76.7
	5 years	**62.6**	48.6 – 76.5	**48.0**	37.9 – 58.0	**58.8**	45.0 – 72.6	**59.6**	51.0 – 68.3	**51.8**	41.7 – 62.0	**54.1**	42.8 – 65.3	**64.8**	53.1 – 76.5	**50.2**	42.7 – 57.7	**58.5**	49.4 – 67.7
Rectum	1 year	*90.4*	*80.0 – 100.0*	**93.4**	88.3 – 98.4	**86.0**	77.1 – 95.0	**86.4**	79.1 – 93.7	*90.6*	*83.2 – 98.0*	**93.5**	84.9 – 100.0	**87.0**	81.6 – 92.4	**92.3**	86.5 – 98.2	**87.9**	80.5 – 95.3
	3 years	*69.1*	*52.7 – 85.6*	**64.2**	55.6 – 72.8	**66.0**	54.5 – 77.4	**74.2**	63.6 – 84.8	*78.6*	*67.7 – 89.5*	**69.1**	55.2 – 82.9	**70.6**	62.5 – 78.7	**67.1**	55.9 – 78.3	**67.0**	57.6 – 76.4
	5 years	*59.3*	*41.6 – 77.0*	**54.0**	44.9 – 63.1	**55.1**	42.4 – 67.8	**60.2**	47.8 – 72.7	*66.1*	*53.5 – 78.8*	**56.7**	41.4 – 72.0	**59.3**	48.1 – 70.4	**53.3**	42.4 – 64.2	**58.2**	48.5 – 67.9
Liver	1 year	*37.2*	*23.4 – 51.1*	*38.3*	*27.1 – 49.5*	*31.1*	*19.6 – 42.6*	*27.2*	*8.1 – 46.2*	*32.8*	*16.6 – 48.9*	*52.4*	*34.7 – 70.1*	*34.3 §*	*22.8 – 45.8*	*36.8*	*27.4 – 46.1*	**37.6**	27.8 – 47.3
	3 years	*13.6*	*3.8 – 23.5*	*15.9*	*7.4 – 24.4*	*9.8*	*2.8 – 16.9*	*16.3*	*0.9 – 31.8*	*17.5*	*4.4 – 30.6*	*27.8*	*12.3 – 43.3*	*14.6 §*	*5.9 – 23.2*	*16.5*	*9.2 – 23.8*	**19.4**	11.5 – 27.4
	5 years	*8.6*	*0.5 – 16.7*	*10.9*	*3.6 – 18.3*	*7.9*	*1.6 – 14.2*	*16.3*	*0.9 – 31.8*	*15.2*	*2.6 – 27.7*	*26.7*	*10.2 – 43.2*	*11.4 §*	*3.5 – 19.2*	*12.4*	*5.8 – 19.1*	**18.6**	9.8 – 27.3
Pancreas	1 year	*24.0*	*9.2 – 38.9*	*20.7*	*10.0 – 31.3*	*33.7*	*19.9 – 47.4*	*32.3*	*14.5 – 50.0*	*38.3*	*22.8 – 53.7*	*48.9*	*34.2 – 63.6*	*27.8 §*	*16.0 – 39.5*	**24.3**	17.2 – 31.4	**40.9**	30.1 – 51.8
	3 years	*10.1*	*0.5 – 19.8*	*3.8*	*0.0 – 8.4*	*13.9*	*3.3 – 24.4*	*16.2*	*2.6 – 29.9*	*22.5*	*9.3 – 35.8*	*19.0*	*7.0 – 30.9*	*12.9 §*	*4.3 – 21.6*	**10.6**	5.2 – 16.0	**22.3**	12.5 – 32.2
	5 years	*10.1*	*0.5 – 19.8*	*1.9*	*0.0 – 5.0*	*10.9*	*1.1 – 20.7*	*12.3*	*0.3 – 24.3*	*17.3*	*5.1 – 29.6*	*16.4*	*4.8 – 28.0*	*11.2 §*	*3.1 – 19.3*	**7.0**	3.0 – 11.0	**23.6**	12.0 – 35.2
Lung	1 year	**37.7**	29.6 – 45.9	**43.9**	35.5 – 52.4	**41.0**	32.8 – 49.2	*33.2*	*20.1 – 46.3*	*49.5*	*35.4 – 63.6*	**58.7**	49.5 – 68.0	**35.9**	28.4 – 43.4	**46.4**	39.2 – 53.7	**46.3**	39.4 – 53.1
	3 years	**14.2**	9.6 – 18.8	**26.0**	18.0 – 34.0	**16.6**	10.4 – 22.7	*20.7*	*9.1 – 32.2*	*22.1*	*10.1 – 34.0*	**23.2**	13.7 – 32.8	**15.1**	10.3 – 19.9	**25.1**	18.5 – 31.8	**19.9**	14.4 – 25.5
	5 years	**14.5**	7.8 – 21.2	**15.7**	9.9 – 21.6	**10.4**	5.8 – 15.0	*11.6*	*2.5 – 20.6*	*17.5*	*6.5 – 28.5*	**23.5**	13.8 – 33.2	**13.3**	8.9 – 17.7	**16.3**	11.1 – 21.5	**13.4**	8.8 – 18.0
Melanoma of the skin	1 year	..		..		..		..		..		..		..		..		*67.5*	*32.8 – 100.0*
	3 years	..		..		..		..		..		..		..		..		*71.0*	*34.4 – 100.0*
	5 years	..		..		..		..		..		..		..		..		*49.0*	*0.0 – 98.4*
Breast (women)	1 year	..		..		..		**95.1**	91.5 – 98.7	**92.2**	88.4 – 95.9	**93.3**	89.9 – 96.7	..		..		..	
	3 years	..		..		..		**82.5**	74.4 – 90.6	**76.7**	70.7 – 82.7	**83.2**	77.0 – 89.4	..		..		..	
	5 years	..		..		..		**68.3**	58.0 – 78.7	**71.0**	63.8 – 78.2	**75.2**	66.4 – 83.9	..		..		..	

Table 5. One–, three– and five–year age–standardised net survival (NS, %), Kuwaiti adults (15–99 years) and children (0–14 years) diagnosed during 2000–2013, followed to 31 December 2014

§ Survival estimate considered less reliable (i.e. proportion of patients lost to follow–up or registered only from a death certificate or at autopsy is greater than 15%); Italics denote survival estimates that are not age–standardised; ALL, Acute lymphoblastic leukaemia

		Males						Females						Both sexes					
		2000–2004		2005–2009		2010–2013		2000–2004		2005–2009		2010–2013		2000–2004		2005–2009		2010–2013	
		NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI	NS(%)	95% CI
Adults																			
Cervix	1 year	..		..		..		**79.0**	73.7 – 84.3	*88.7*	*80.4 – 97.0*	**85.7**	77.3 – 94.2	..		..		..	
	3 years	..		..		..		**57.9**	49.1 – 66.6	*79.9*	*69.1 – 90.7*	**60.5**	48.3 – 72.7	..		..		..	
	5 years	..		..		..		**54.8**	45.2 – 64.3	*73.8*	*61.7 – 86.0*	**56.6**	44.2 – 69.0	..		..		..	
Ovary	1 year	..		..		..		*73.4*	*62.2 – 84.5*	**72.6**	65.5 – 79.7	**75.6**	68.5 – 82.6	..		..		..	
	3 years	..		..		..		*60.5*	*47.8 – 73.2*	**43.4**	34.4 – 52.4	**43.0**	34.6 – 51.3	..		..		..	
	5 years	..		..		..		*38.9*	*26.3 – 51.5*	**35.4**	25.2 – 45.6	**35.1**	25.6 – 44.7	..		..		..	
Prostate	1 year	*88.8*	*82.0 – 95.5*	**91.0**	86.6 – 95.4	**98.0**	94.3 – 100.0	..		..		..		..		..		..	
	3 years	*79.9*	*70.3 – 89.6*	**79.1**	72.6 – 85.7	**93.4**	87.3 – 99.5	..		..		..		..		..		..	
	5 years	*78.8*	*66.7 – 90.9*	**71.9**	63.7 – 80.0	**84.0**	74.1 – 94.0	..		..		..		..		..		..	
Brain	1 year	*50.2*	*35.2 – 65.3*	*60.7*	*47.1 – 74.3*	*81.3*	*69.3 – 93.2*	*59.7*	*40.7 – 78.8*	*67.9*	*52.3 – 83.5*	*70.3*	*55.5 – 85.1*	*53.7 §*	*41.7 – 65.6*	**59.1**	50.6 – 67.6	**68.0**	60.9 – 75.2
	3 years	*30.4*	*16.5 – 44.3*	*26.7*	*14.5 – 38.8*	*50.4*	*35.0 – 65.8*	*34.2*	*15.8 – 52.7*	*44.6*	*28.1 – 61.2*	*38.6*	*22.6 – 54.5*	*31.7 §*	*20.4 – 43.0*	**29.4**	21.4 – 37.5	**37.3**	28.5 – 46.1
	5 years	*28.0*	*14.4 – 41.6*	*20.2*	*9.1 – 31.3*	*42.3*	*25.8 – 58.8*	*34.2*	*15.8 – 52.7*	*41.9*	*25.4 – 58.3*	*34.6*	*18.5 – 50.8*	*30.3 §*	*19.1 – 41.5*	**24.9**	17.3 – 32.6	**31.8**	23.2 – 40.4
Myeloid neoplasms	1 year	*61.9*	*47.5 – 76.4*	**33.1**	23.4 – 42.8	**49.5**	35.6 – 63.4	*80.1*	*67.8 – 92.5*	*71.5*	*60.0 – 83.0*	**58.5**	49.6 – 67.4	**55.0**	46.8 – 63.3	**42.2**	31.2 – 53.3	**50.2**	40.1 – 60.3
	3 years	*53.1*	*38.0 – 68.2*	**23.0**	14.5 – 31.5	**17.9**	9.4 – 26.5	*67.6*	*53.0 – 82.3*	*59.9*	*47.3 – 72.4*	**39.2**	30.2 – 48.3	**44.3**	35.3 – 53.3	**27.9**	19.1 – 36.8	**28.6**	20.2 – 37.0
	5 years	*48.5*	*33.1 – 64.0*	**17.0**	11.0 – 23.0	**15.3**	7.9 – 22.8	*63.1*	*47.8 – 78.4*	*58.7*	*45.9 – 71.5*	**40.5**	31.1 – 49.9	**38.6**	27.1 – 50.0	**24.0**	15.9 – 32.0	**25.6**	17.7 – 33.6
Lymphoid neoplasms	1 year	**69.7**	60.0 – 79.5	**77.7**	70.9 – 84.5	**77.3**	68.5 – 86.1	**71.1**	60.7 – 81.6	**72.1**	62.0 – 82.2	**78.9**	70.1 – 87.8	**70.8**	63.4 – 78.1	**76.7**	71.1 – 82.4	**78.5**	72.2 – 84.8
	3 years	**52.4**	41.5 – 63.4	**67.0**	58.5 – 75.5	**74.6**	64.5 – 84.7	**61.4**	49.4 – 73.5	**67.6**	55.7 – 79.6	**72.0**	61.5 – 82.5	**56.7**	48.4 – 65.0	**68.4**	61.5 – 75.4	**74.1**	66.7 – 81.5
	5 years	**45.3**	34.5 – 56.2	**59.9**	50.8 – 69.0	**65.5**	54.4 – 76.6	**54.1**	41.9 – 66.3	**65.8**	53.7 – 77.8	**73.8**	62.0 – 85.5	**52.1**	42.9 – 61.2	**63.2**	55.8 – 70.7	**68.2**	59.5 – 76.9
Children																			
Brain	1 year	*75.0*	*51.7 – 98.4*	*81.3*	*62.8 – 99.7*	*48.0*	*12.5 – 83.5*	..		..		*50.0*	*9.2 – 90.8*	*82.4*	*64.8 – 99.9*	*77.3*	*60.2 – 94.4*	**45.2**	23.9 – 66.6
	3 years	*41.7*	*15.7 – 67.7*	*62.6*	*39.8 – 85.3*	*24.0*	*0.0 – 50.5*	..		..		*25.0*	*0.0 – 56.9*	*53.0*	*30.2 – 75.8*	*63.7*	*44.1 – 83.2*	**20.7**	3.3 – 38.0
	5 years	*33.4*	*8.8 – 58.0*	*56.4*	*33.0 – 79.7*	*20.6*	*0.0 – 44.0*	..		..		*25.0*	*0.0 – 56.9*	*47.1*	*24.4 – 69.8*	*59.2*	*39.2 – 79.1*	**18.4**	2.6 – 34.3
ALL	1 year	**88.42**	81.7 – 95.2	**80.0**	68.5 – 91.5	**95.1**	88.5 – 100.0	*100.0*	*87.7 – 100.0*	**90.5**	85.0 – 95.9	**96.9**	92.9 – 100.0	**89.8 §**	81.7 – 97.9	**85.7**	77.9 – 93.4	**95.7**	91.2 – 100.0
	3 years	**82.6**	74.5 – 90.69	**73.4**	60.9 – 85.9	**90.1**	80.6 – 99.7	*95.7*	*87.6 – 100.0*	**84.3**	77.8 – 90.8	**94.4**	89.5 – 99.3	**84.5 §**	75.1 – 93.8	**78.4**	69.5 – 87.2	**91.0**	84.1 – 98.0
	5 years	**71.26**	61.6 – 80.9	**70.1**	57.2 – 82.9	**88.9**	79.1 – 98.7	*90.7*	*78.6 – 100.0*	**81.2**	73.8 – 88.5	**91.7**	84.7 – 98.7	**76.1 §**	65.7 – 86.5	**74.9**	65.6 – 84.1	**88.4**	80.6 – 96.2
Lymphoma	1 year	**98.3**	95.0 – 100.0	**96.3**	91.6 – 100.0	**100.0**	87.2 – 100.0	*92.3*	*78.4 – 100.0*	*93.8*	*82.3 – 100.0*	**96.7**	90.8 – 100.0	**97.5**	94.3 – 100.0	**95.6**	90.8 – 100.0	**98.3**	95.2 – 100.0
	3 years	**94.1**	88.1 – 100.0	**96.3**	91.6 – 100.0	**100.0**	80.5 – 100.0	*92.3*	*78.4 – 100.0*	*87.5*	*71.8 – 100.0*	**96.7**	90.8 – 100.0	**94.4**	88.9 – 99.9	**93.1**	87.4 – 98.8	**98.4**	95.3 – 100.0
	5 years	**92.1**	85.0 – 99.2	**92.7**	86.1 – 99.3	**96.7**	90.8 – 100.0	*92.3*	*78.4 – 100.0*	*87.5*	*71.8 – 100.0*	**96.7**	90.8 – 100.0	**93.0**	86.2 – 99.8	**90.7**	83.2 – 98.2	**96.3**	91.4 – 100.0

Table 5 (continued). One–, three– and five–year age–standardised net survival (NS, %), Kuwaiti adults (15–99 years) and children (0–14 years) diagnosed during 2000–2013, followed to 31 December 2014

§ Survival estimate considered less reliable (i.e. proportion of patients lost to follow–up or registered only from a death certificate or at autopsy is greater than 15%); Italics denote survival estimates that are not age–standardised; ALL, Acute lymphoblastic leukaemia

censoring occurred within 5 years, or if all patients died within 5 years (survival probability 1 or 0), we obtained a binomial approximation for the lower or upper bound respectively, of the CI.

Results

Of 8,931 tumour records for adults (8,477) and children (454) diagnosed during 2000–2013, 8,484 (95.0%) were included in the survival analyses (Table 4). Of the 8,273 eligible adults and 437 children, 2.6% adults and 1.8% children were excluded, mainly because the tumour was registered from a death certificate only or detected solely at autopsy (DCO) (2.3% and 1.1%, respectively). The proportion of tumours that were microscopically verified by histology or cytology, or had a specific morphology code, was 99.8% in adults and 100% in children. Only 1.0% of adults and 4.7% of children were lost to follow–up.

Cancers with the highest net survival over the 14 years (2000–2013) were prostate, breast (women), and rectum in adults, and lymphoma in children. Survival was lowest for liver, pancreas, and lung cancer in adults, and for brain tumours in children (Table 5).

During 2010–2013, one–year age–standardised net survival in adults was lowest for liver cancer at 37.6% (95% CI 27.8–47.3%) and highest for prostate cancer at 98.0% (94.0–100.0%) (Figure 1). Survival was over 80% for five adult cancers (prostate, breast, rectum, cervix and colon). In children, one–year net survival for lymphoma and acute lymphoblastic leukaemia (ALL) was greater than 80% over the whole period (2000–2013), reaching 98.3% (95.2–100.0%) and 95.7% (91.2–100.0%) respectively, by 2010–2013. During 2010–2013, however, one–year survival for children with brain tumours was 45.2% (23.9–66.0%).

Five–year survival in adult patients diagnosed during 2010–2013 was lowest for lung cancer at 13.4% (95% CI 8.8–18.0%) and highest for prostate cancer at 84.0% (74.1–94.0%) (Figure 1). Prostate was the only cancer for which 5–year survival exceeded 80%. During this period, 5–year survival improved for lethal cancers, with four cancers showing survival below 25% (stomach, liver, pancreas and lung) compared to five in 2000–2004 (oesophagus, stomach, liver, pancreas and lung) and seven in 2005–2009 (oesophagus, stomach, liver, pancreas, lung, brain and myeloid neoplasms).

In children, the highest 5–year survival observed during 2010–2013 was for lymphoma (96.3%, 95% CI 91.4–100.0%), followed by ALL (88.4%; 80.6–96.2%). The largest improvement in survival in children over the 14–year period (2000–2013) was, however, for ALL: a 12.3% increase versus 6.3% for lymphoma.

For women, 1– and 5–year net survival for all cancers was between 1% and 25% higher than in men, with the exception of oesophagus, colon, and brain tumours, where survival was 5–18% higher in men. The most notable differences in age–standardised five–year net survival between men and women were observed for myeloid neoplasms and lung cancer, which had a 25.1% and 13.1% difference between men (15.3%, 10.4%) and women (40.8%, 23.5%), respectively. Survival among boys and girls was generally similar (differences less than 5%).

For almost all cancers, larger differences were observed between survival at 1 and 3 years since diagnosis than between 3 and 5 years; reductions between 1– and 3–year survival ranged from 4–26% (for lymphoid neoplasms– lung) versus 1–10% (liver – colon) between 3– and 5–year survival. Greater reductions were seen between 1– and 3–year survival estimates among women than men (Figure 2).

Over the 14–year period (2000–2013), 5–year survival increased for most adult cancers (Figure 3). The largest increase in age–standardised survival was for lymphoid neoplasms (16.1%), followed by cancers of the stomach (7.4%) and breast (6.9%). Five–year survival from cancers of the lung, rectum, ovary and cervix remained stable (less than 2% change), while survival declined for myeloid neoplasms and colon cancer in adults (13.0% and 6.3% respectively).

Discussion

This study presents a comprehensive profile of trends in population–based cancer survival up to five years for Kuwaiti patients diagnosed with one of 18 common cancers, by sex. It is the first study reporting cancer survival for males and females separately, allowing gender differences to be addressed. It is also the first to include shorter–term survival (1 and 3 years), which is particularly useful for the more lethal cancers. The survival estimates presented here are crucial for healthcare managers and policymakers to assess the effectiveness of healthcare delivery for cancer, and to plan future strategies for cancer control.[21,22]

Our study estimated population–based survival, which is a key measure of the effectiveness of the health system in dealing with cancer.[23] Survival estimates derived from hospital–based registries or clinical trials are likely to be restrictive in their selection of patients, accessibility to healthcare services, and availability of treatments. By contrast, population–based survival estimates include all patients diagnosed in a particular region. Patients are included irrespective of their age, stage at diagnosis, comorbidities, socio–economic status or any other factor.

These estimates, therefore, constitute the gold standard for evaluating the overall effectiveness of any given health care system.[24]

Obtaining high–quality, complete and reliable incidence and follow–up data on vital status for all cancer patients was necessary to produce robust population–based survival estimates.[25] In this study, the proportion of DCO cases among Kuwaiti patients was only 2.3% in adults and 1.1% in children, reducing the chance of survival overestimation.[26] The total proportion of loss to follow–up was also low (1.2%), illustrating the efficacy of the new follow–up procedure performed ["A Novel Approach to Obtain Follow–up Data on the Vital Status of Registered Cancer Patients: The Kuwait Cancer Registry Experience" E. Alwadhi et. al., also published in this issue]. This new approach enabled follow–up data on vital status to be updated for all Kuwaiti cancer patients, using a mixture of both active and passive follow–up procedures, thus ensuring that all deaths were included in the survival analyses, regardless of the cause of death. While passive follow–up is a very powerful tool, in Kuwait this procedure did not allow reliable capture of information on the deaths of all Kuwaiti registered cancer patients. Before this study, only deaths due to cancer were known to the KCR, and survival estimates for Kuwait were therefore likely to have been overestimated.

Our analyses show that survival for many cancers increased during 2000–2013. However, survival for some cancers remained static, or declined slightly, with an apparent drop in survival between 2000–2004 and 2005–2009. This pattern is probably due to improvements in data quality over the 14–year period; the proportions of DCO and loss to follow–up were highest during 2000–2004 and eventually both fell to 0% for all cancers diagnosed between 2010–2013 (except for pancreatic cancer and lymphoid neoplasms in adults, which remained at 1% DCO). The increases in survival observed between 2005–2009 and 2010–2013, despite improvements in data quality, may therefore be indicative of true advances in survival.

In this study, differences in net survival by sex in Kuwait were consistent with findings from the United States,[27] Canada,[28] Europe[29] and Korea,[30] with women generally having an advantage over men. For colon cancer, however, higher survival was seen in Kuwait for men that women. This may be due to women having more aggressive forms of neoplasia, and presenting at a more advanced stage than men.[31] Our study also suggested a more favourable prognosis for men than women with oesophageal and brain tumours, however, a larger cohort is required to understand better these disparities between men and women.

For some cancers, mostly those diagnosed during 2000–2004, sparse data restricted interpretation of survival estimates for Kuwait. For melanoma, survival could not be estimated for patients diagnosed during 2000–2009, due to the small number of cases. This was also observed in neighbouring Gulf Arab countries (www.globocan.iarc.fr). The low incidence of melanoma could be attributable to the population's skin colour, conservative traditional wear and limited exposure to sunlight due to high temperatures in the country. Pooling data over longer periods could enable more robust estimates to be produced, but this would hinder the examination of trends.

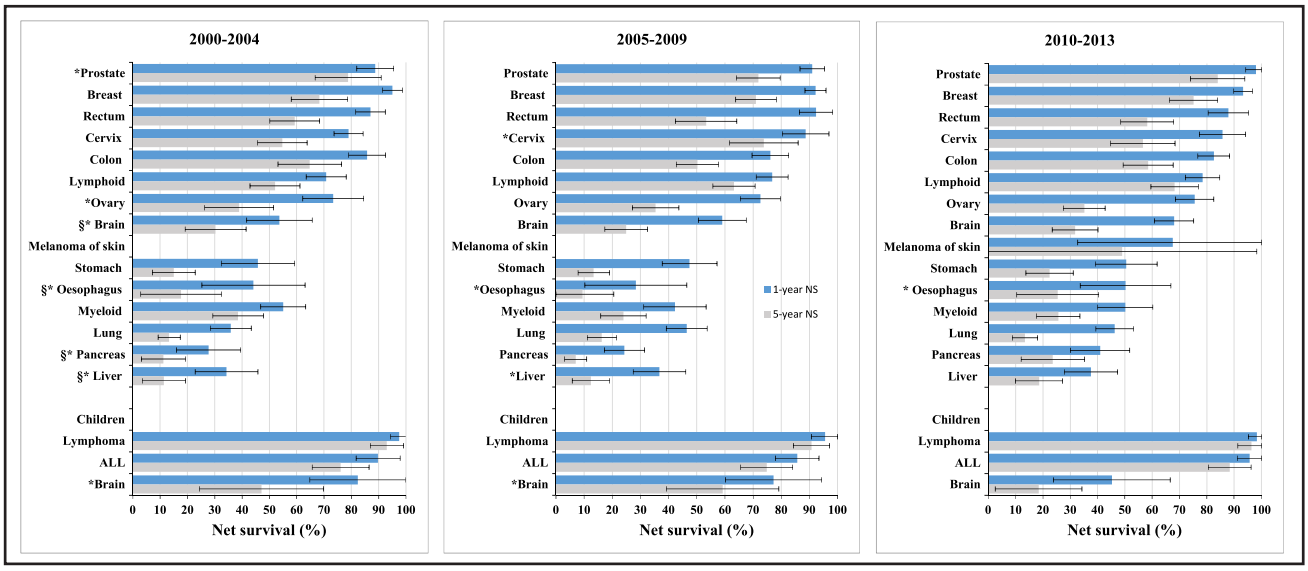

Figure 1. Age–standardised 1–and 5–year net survival (%) in adults (15–99 years) and children (0–14 years); Kuwait, patients diagnosed during 2000–2013

ALL: Acute lymphoblastic leukaemia; § Survival estimate considered less reliable (i.e. proportion of lost to follow–up within five years ≥ 15%); * Survival estimates not age–standardised

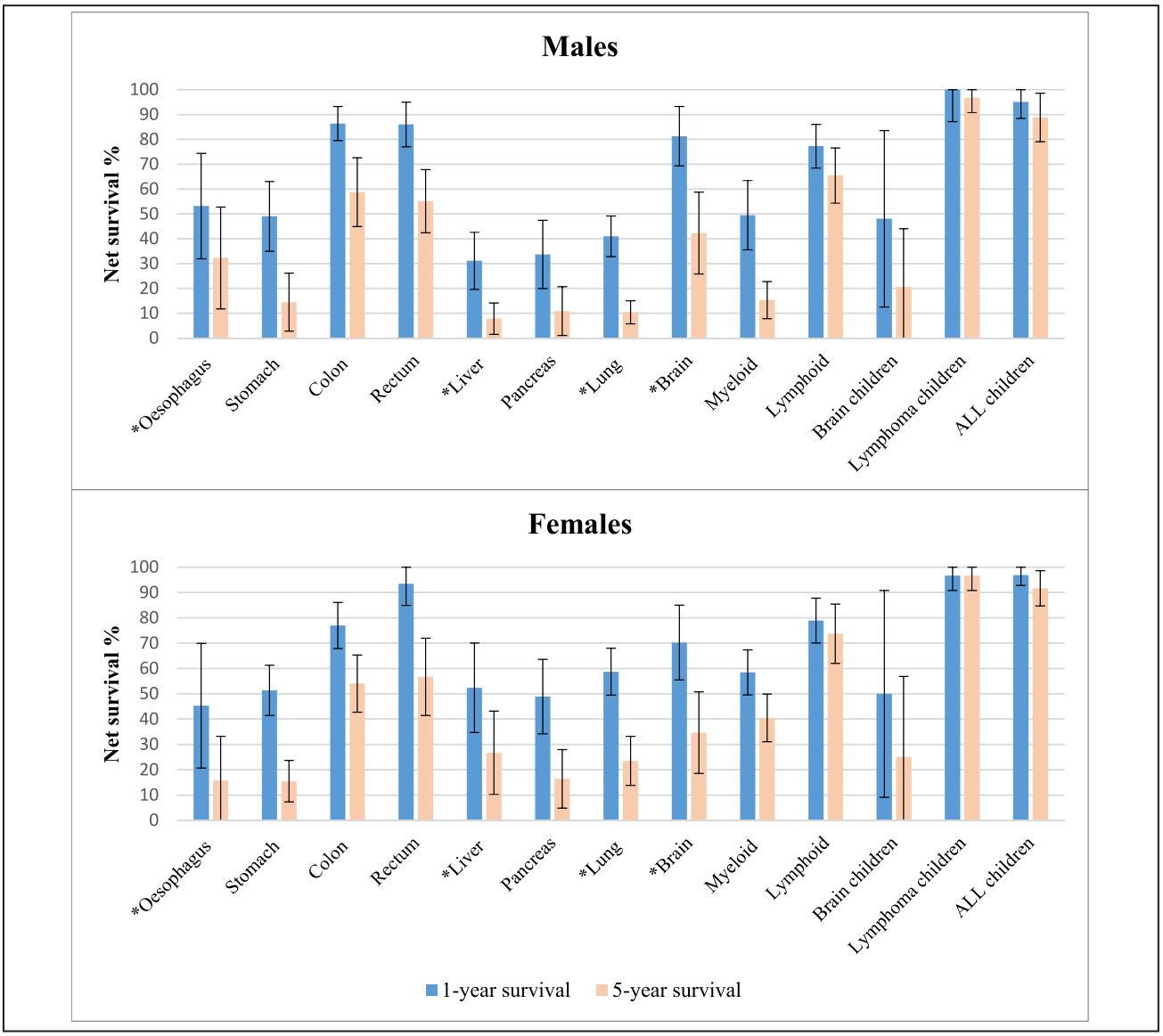

Figure 2. Age–standardised 1– and 5–year net survival (%) in adults (15–99 years) and children (0–14 years); Male and female patients diagnosed during 2010–2013

*One or both survival estimates are not age–standardised

The availability of updated data on follow–up for vital status allowed, for the first time, the inclusion of Kuwaiti data in the third cycle of the CONCORD programme, the largest and most up–to–date global surveillance study of cancer survival.[7] The CONCORD programme uses the same data quality control procedures and the same statistical methods for all participating countries. This means that the same time periods, cancer definitions, data preparation, exclusions, and analytical methods were used for all datasets. Consequently, this enables appropriate and robust survival comparisons to be made between results from this study in Kuwait and results for over 70 other countries included in CONCORD–3.

In particular, during 2010–2013, age–standardised 5–year net survival for adult patients diagnosed with cancer in Kuwait was generally lower than survival for patients diagnosed during 2010–2014 in 40 high–income non–Arab countries included in CONCORD–3.7 Differences ranged from as little as 3–5% (compared to the average survival of the high–income countries) for rectum, colon, lung and ovarian cancer, and from 6–19% for prostate, stomach, cervix and breast cancer and myeloid malignancies. By contrast, survival for children diagnosed with lymphoma or acute lymphoblastic leukaemia (ALL) in Kuwait was similar to that of other high–income countries.

The fact that survival for adults in Kuwait is generally lower than in other high–income countries, particularly for stomach, prostate, breast and cervical cancer, may be partially explained by differences in diagnostic activity. With screening programmes available in most high–income countries,[32–34] diagnosing asymptomatic or less aggressive and non–lethal tumours that do not necessarily progress to symptomatic

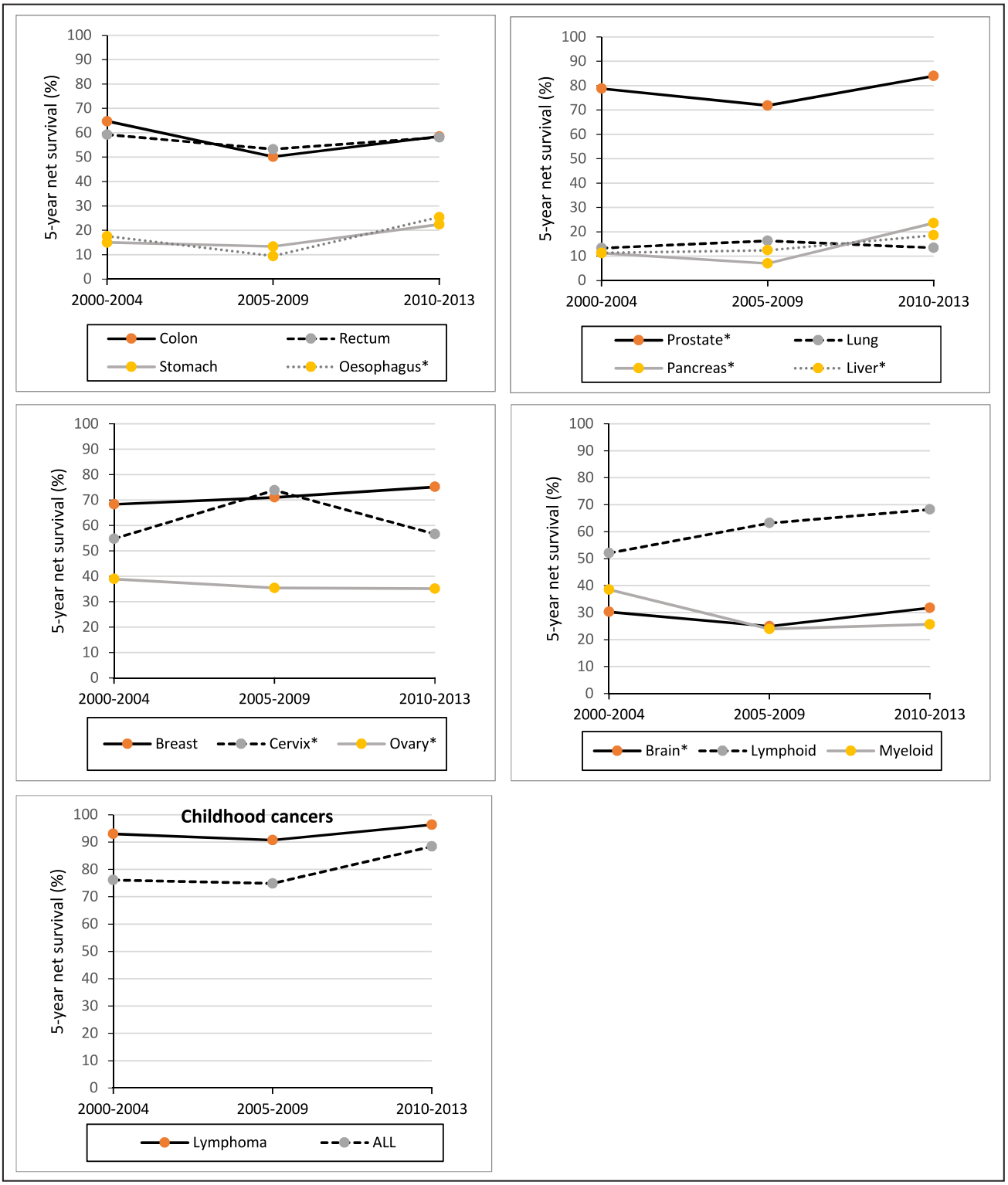

Figure 3. Trends in age–standardised five–year net survival (%) in Kuwaiti adults (15–99 years) and children (0–14 years) during 2000–2013, Kuwait

* denotes not all estimates are age–standardised, ALL: Acute lymphoblastic leukaemia

diagnoses or death is more likely, thus raising survival.[35] Screening can also lead to prolonged survival time and improvements of outcome due to early–stage diagnosis.[36] Kuwait only has one breast cancer screening programme established in 2014,[37] and in the process of implementing a cervical cancer screening programme in 2018. It is thus necessary to evaluate whether the implementation of screening programmes could reduce some of the survival deficit between Kuwait and other high–income countries. Assessing the comorbidity of cancer patients in Kuwait, which tends to compromise the effectiveness and compliance of treatment,[38] could also further help explain these differences.

For myeloid neoplasms, survival in Kuwait during 2010–2013 (25.6%) was considerably lower than in other high–income countries (e.g. 45–57% in the US, UK, Korea, Canada, Australia and Sweden). This may be due to differences in the subtypes of myeloid malignancies, which in our definition included myelodysplastic syndromes and refractory anaemias. These morphologies usually entail better prognosis than the more lethal subtype: acute myeloid leukaemia (AML).[39] The lower survival in Kuwait, therefore, could be due to a higher proportion of patients with AML (almost 50% during this period compared to 36% reported in other European countries),[39] reducing the pooled estimate for all myeloid malignancies combined. Additional comparisons of subtypes, and possibly treatment modalities, are thus also required to understand these differences.

For pancreatic cancer, survival in Kuwait during 2010–2013 (23.6%) was much higher than in other high–income countries for which reliable estimates were available (e.g. 6–12 % in the US, UK, Korea, Canada, Australia and Sweden). Due to the lethal nature of the disease, many countries had unreliable estimates, attributable to high proportions of DCOs. However, for Kuwait, the proportion of DCOs during this period was very low, as was the percentage of patients lost to follow–up (2.1% and 0% respectively; data not shown). It is thus unlikely that poor data quality is the cause of the high survival observed in Kuwait, although the relatively small number of patients (92 patients) may limit the interpretability of the estimates. The higher survival from pancreatic cancer may also be attributable to earlier stage at diagnosis or a higher proportion of neuroendocrine tumours, which are generally considered indolent and have a more favourable prognosis than adenocarcinomas of the pancreas.[40] Supplementary assessments on patients' stage at diagnosis and the distribution of morphologies are needed in order to identify the underlying cause for this difference.

Survival estimates for other Arab countries in CONCORD–3 with similar income and health care systems were only available for Qatar. However, most of the estimates were considered less reliable, due to the high proportion of patients censored within 5 years, preventing robust conclusions. Further comparisons with neighbouring countries, using complete and high–quality data, are therefore necessary to determine whether differences between regions that share similar culture, tradition, climate, income and healthcare systems do in fact reflect true inequalities in cancer care.

Conclusion

During the 14–year period up to 2013, cancer survival improved for most Kuwaiti adults and children. Survival for some cancers remained static or even declined, and this requires continuous surveillance and monitoring. Women generally have a more favourable prognosis than men, with a faster decline in survival following the initial years since diagnosis.

These results should prompt ministerial health planners and politicians in Kuwait to allow robust estimates to be produced through continuous surveillance of population–based cancer survival, and the systematic provision of cancer data and follow–up information on vital status for all cancer patients. The data presented here should assist policymakers and practitioners investing in the Kuwaiti healthcare system to achieve optimal outcomes by promoting early diagnosis and screening programmes, and detecting and treating cancer more efficiently.

Further research is required to help dissect the underlying causes for the differences in survival between Kuwait and other countries with comparable income and health systems, in order to investigate whether the differences are attributable to late diagnosis, treatment, or pathological characteristics of the tumours.

Ethical Approval

Ethical approval [2015/276] was granted by the Standing Committee for Coordination of Health and Medical Research at Kuwait's Ministry of Health.

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References

1. Health Vital Statistics Division. Health, Kuwait 2014. Kuwait: Department of Statistics & Medical Records, Ministry of Health, 2015.
2. Ellis L, Woods LM, Estève J, Eloranta S, Coleman MP, Rachet B. Cancer incidence, survival and mortality: explaining the concepts. Int J Cancer 2014; 135: 1774–82.
3. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X–S, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos–Gragera R, Stiller C, Azevedo e Silva G, Chen W–Q, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska–Lasota M, Storm H, Tucker TC, Coleman MP, CONCORD Working Group. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population–based registries in 67 countries (CONCORD–2). Lancet 2015; 385: 977–1010.
4. Coleman MP. Cancer survival: global surveillance will stimulate health policy and improve equity. Lancet 2014; 383: 564–73.

5. Whelan SL, Parkin DM, Masuyer E, editors. Patterns of cancer in five continents (IARC Scientific Publications No. 102). Lyon: International Agency for Research on Cancer; 1990.

6. Fritz AG, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL, editors. International Classification of Diseases for Oncology (ICD–O). 3rd ed. Geneva: World Health Organization; 2000.

7. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, Bonaventure A, Valkov M, Johnson CJ, Esteve J, Ogunbiyi OJ, Azevedo ESG, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK, Coleman MP, Group CW. Global surveillance of trends in cancer survival 2000–14 (CONCORD–3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population–based registries in 71 countries. Lancet 2018; 391:1023–75.

8. Fritz AG, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL, editors. International Classification of Diseases for Oncology (ICD–O). First revision of 3rd ed. Geneva: World Health Organisation; 2013.

9. Sant M, Karjalainen–Lindsberg ML, Maynadié M, Raphael M, Ferretti S, Giacomin A, Tereanu C, Giraldo P, Marcos–Gragera R, Martos C, Lutz JM, Visser O, HAEMACARE Working Group. Manual for coding and reporting haematological malignancies. Tumori 2010; 96: i–A32.

10. Turner JJ, Morton LM, Linet MS, Clarke CA, Kadin ME, Vajdic CM, Monnereau A, Maynadie M, Chiu BC, Marcos–Gragera R, Costantini AS, Cerhan JR, Weisenburger DD. InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions. Blood 2010; 116: e90–8.

11. Steliarova–Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer 2005; 103: 1457–67.

12. Johnson CJ, Weir HK, Yin D, Niu X. The impact of patient follow–up on population–based survival rates. J Registry Manage 2010; 37: 86–103.

13. Estève J, Benhamou E, Raymond L. Statistical methods in cancer research, volume IV. Descriptive epidemiology. (IARC Scientific Publications No. 128). Lyon: International Agency for Research on Cancer; 1994.

14. Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up–to–date' cancer survival data: theory, empirical evaluation, computational realisation and applications. Eur J Cancer 2004; 40(3): 326–35.

15. Pohar Perme M, Henderson R, Stare J. An approach to estimation in relative survival regression. Biostatistics 2009; 10: 136–46.

16. Spika D, Bannon F, Bonaventure A, Woods LM, Harewood R, Carreira H, Coleman MP, Allemani C. Life tables for global surveillance of cancer survival (the CONCORD programme): data sources and methods. BMC Cancer 2017; 17: 159–73.

17. Clerc–Urmès I, Grzebyk M, Hédelin G. Net survival estimation with stns. Stata J 2014; 14: 87–102.

18. Corazziari I, Quinn MJ, Capocaccia R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer 2004; 40: 2307–16.

19. Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971–85. Br J Cancer 1990; 62: 806–15.

20. Greenwood M. The natural duration of cancer. (Report on Public Health and Medical Subjects No. 33). London: HMSO; 1926.

21. Albreht T, McKee CM, Alexe DM, Coleman MP, Martín–Moreno JM. Making progress against cancer in Europe in 2008. Eur J Cancer 2008; 44: 1451–6.

22. Department of Health. The NHS Outcomes Framework. Department of Health: London, UK., 2017.

23. Allemani C. The importance of global surveillance of cancer survival for cancer control: the CONCORD programme. Cancer Control 2017: 19–22.

24. Allemani C, Coleman MP. Public health surveillance of cancer survival in the US and world–wide: the contribution of the CONCORD programme. Cancer 2017; 123: 4977–81.

25. Rossi S, Baili P, Capocaccia R, Caldora M, Carrani E, Minicozzi P, Pierannunzio D, Santaquilani M, Trama A, Allemani C, Belot A, Buzzoni C, Lorez M, De Angelis R. The EUROCARE–5 study on cancer survival in Europe 1999–2007: Database, quality checks and statistical analysis methods. Eur J Cancer 2015; 51(15): 2104–19.

26. Holleczek B, Brenner H. Reduction of population–based cancer survival estimates by trace back of death certificate notifications: an empirical illustration. Eur J Cancer 2012; 48: 797–804.

27. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev 2011; 20(8): 1629–37.

28. Ellison LF. Differences in cancer survival in Canada by sex. Health Rep 2016; 27(4): 19–27.

29. Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, Zambon P, Gatta G, De Angelis R, EUROCARE Working Group. The advantage of women in cancer survival: an analysis of EUROCARE–4 data. Eur J Cancer 2009; 45 (Suppl. 6): 1017–27.

30. Jung KW, Park S, Shin A, Oh CM, Kong HJ, Jun JK, Won YJ. Do female cancer patients display better survival rates compared with males? Analysis of the Korean National Registry data, 2005–2009. PLoS One 2012; 7(12): e52457.

31. White A, Ironmonger L, Steele RJC, Ormiston–Smith N, Crawford C, Seims A. A review of sex–related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. BMC Cancer 2018; 18(1): 906.

32. Goto R, Hamashima C, Mun S, Lee WC. Why screening rates vary between Korea and Japan––differences between two national healthcare systems. Asian Pac J Cancer Prev 2015; 16(2): 395–400.

33. Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N, Tomatis M, žakelj MP, Dillner J, Fernan M, Elfström KM, Lönnberg S, Soerjomataram I, Sankaranaryanan R, Vale D. Cancer Screening in the European Union. Lyon, France, 2017.

34. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram–Baptiste D, Saslow D, Brawley OW, Wender RC. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2018.

35. Marcus PM, Prorok PC, Miller AB, DeVoto EJ, Kramer BS. Conceptualizing overdiagnosis in cancer screening. J Natl Cancer Inst 2015; 107(4).

36. Matz M, Coleman MP, Carreira H, Salmerón D, Chirlaque López MD, Allemani C, the CONCORD Working Group. World–wide comparison of ovarian cancer survival: morphological group and stage at diagnosis (CONCORD–2). Gynecol Oncol 2017; 144: 396–404.

37. Ministry of Health. Kuwait National Mammography Screening Program. Kuwait: Government of Kuwait, 2015. https://www.moh.gov.kw/knmsp/index–en.html#Mammogram.

38. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. CA Cancer J Clin 2016; 66(4): 337–50.

39. De Angelis R, Minicozzi P, Sant M, Dal Maso L, Brewster DH, Osca–Gelis G, Visser O, Maynadié M, Marcos–Gragera R, Troussard X, Agius D, Roazzi P, Meneghini E, Monnereau A. Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000–2007: Results of EUROCARE–5 population–based study. Eur J Cancer 2015; 51(15): 2254–68.

40. Yadav S, Sharma P, Zakalik D. Comparison of Demographics, Tumor Characteristics, and Survival Between Pancreatic Adenocarcinomas and Pancreatic Neuroendocrine Tumors: A Population–based Study. Am J Clin Oncol 2018; 41(5): 485–91.