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# TRENDS AND INEQUALITIES IN CANCER SURVIVAL IN VICTORIA, AUSTRALIA

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Submitted in total fulfilment of the requirements of the degree of
Doctor of Philosophy

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## Abstract

### Background

Cancer is the second-highest cause of mortality worldwide, accounting for 9.6 million deaths in 2017, and its burden on individuals, economy and health system is a global problem. Although Australia has a universal health-care system, cancer survival varies by socio-economic disadvantage. The magnitude and age-related patterns of these inequalities are not clear in Victoria, Australia and little is known about whether the gap in cancer survival is narrowing or widening over time. Despite strong evidence that sex is associated with the incidence and prognosis of several diseases, few studies have assessed differences in cancer survival by sex, and no Australian study has comprehensively evaluated the magnitude and temporal and age-related patterns of differences in cancer survival by sex.

This thesis aimed to investigate inequalities and trends in cancer patient survival by sex, area-level socio-economic disadvantage and remoteness of residence and identify the underlying causes of socio-economic inequality in colon cancer survival.

### Methods

Six studies were designed and conducted to address the aims of this thesis. The first study was a systematic review of peer-reviewed published articles since 2005 that attempted to identify the underlying reasons for socio-economic inequalities in cancer survival. The second study was a systematic review of peer-reviewed published articles that assessed the association of rural-urban residence with cancer survival in high-income countries and summarised the current evidence in relation to potential contributing factors to the observed differences in survival between rural and urban regions. Studies 3, 4 and 5 used the Victorian Cancer Registry data to assess differences in cancer patient survival by sex, area-level socio-economic disadvantage and remoteness of residence. Study 6 used population-based linked health data to identify factors explaining socio-economic inequalities in colon cancer survival.

Net survival was estimated using the Pohar-Perme method. Inequalities in survival were modelled using Poisson regression to estimate excess mortality rate ratios. Interventional causal mediation analysis was used to assess the underlying reasons for socio-economic inequalities in colon cancer survival.

### Results

Findings from the first systematic review suggest that socio-economic inequalities in cancer survival appear to be partly explained by differences in disease stage, health-related behaviours, co-morbidities and treatment modalities. The second review shows that rural cancer patients generally have worse survival compared with their urban counterparts. The underlying reasons for survival disadvantage for rural patients are not well known, but possible contenders include differences in lifestyle behaviour, stage of cancer at diagnosis, co-morbid conditions, and treatment modalities. Findings from analysing the Victorian Cancer Registry data suggest that cases living in more socio-economically disadvantaged areas or outside major cities generally had lower five-year survival than their counterparts living in less

disadvantaged regions or major cities. In addition, men showed lower survival from most cancers than women. The observed socio-economic inequalities for colon cancer survival were not explained by variations in stage at diagnosis or surgery. Not receiving chemotherapy within 8 weeks after surgery, emergency admission prior to diagnosis and receiving surgery at a public hospital appeared to partly contribute to lower survival for men with stage III colon cancer living in the most disadvantaged areas, although this observation might be due to unmeasured characteristics of disadvantaged men receiving surgery in public hospitals rather than public/private hospitals themselves.

**Conclusions**

This thesis has shown that inequalities in cancer patient survival by sex, area-level socio-economic disadvantage and remoteness of residence exist and have persisted over time, even though Australia has a universal health care system. Monitoring the magnitude of these inequalities and conducting high-quality research to identify the underlying reasons for inequalities in cancer survival is important to prioritise actionable factors to improve cancer outcomes for all patients.

**Declaration**

This is to certify that this thesis comprises only my original work towards the Doctor of Philosophy, except where indicated in the Preface. Due acknowledgement has been made in the text to all other material used. The thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signed

*Nina Afshar*

**Acknowledgements**

Undertaking this PhD has been a life-changing experience for me, and it would not have been possible to achieve without the help, encouragement and guidance that I received from many people.

Words cannot explain my deepest gratitude to my supervisors: Professor Dallas English and Professor Roger Milne. Thank you from the bottom of my heart for sharing your knowledge and experience, and being patient and supportive, especially when I needed it the most. I have been lucky to have had a chance to spend the past four years of my life working on this challenging and rewarding project. What a joyful ride, even in hard times! I will be forever grateful to you both for giving me the opportunity to learn from you, and I hope that you have enjoyed working with me as much as I have enjoyed working with you. I could not have imagined a better experience and supervisors.

Special thanks to Roger for funding my participation at several national and international conferences and workshops, particularly the causal mediation analysis course in Philadelphia in 2018.

My sincere thanks to my advisory committee, Professor Anne Kavanagh, Professor Lyle Gurrin and Dr Louisa Flander, for their ongoing support throughout my PhD journey. Many thanks also to Professor Tony Blakely for his expert advice, constructive feedback and contributions to this thesis. Thank you to Dr Andrew Haydon and Associate Professor Paul Mitchell for their clinical advice.

I acknowledge the contribution of the Victorian Cancer Registry team based at Cancer Council Victoria, the Victorian Department of Health and Human Services and thousands of cancer patients who made this research possible. Thanks also to the Australian Government for funding me during this study.

A very special thank you to Dr Idan Ben-Barak, Dr Rebecca Bergin, Dr Ghazaleh Dashti and Yi Yang, and everyone from the Cancer Epidemiology Division for their help and unwavering support.

Lastly, I would like to thank my parents, sisters and friends for believing in me; your encouraging words and love over the years strengthened and supported my commitment to this work that would not have been possible without you all.

**Preface**

I was supported by a Research Training Scheme Scholarship from May 2016 to December 2016, and a Research Training Program Scholarship (fee offset) from January 2017 to April 2020. I undertook this research while hosted by the Cancer Epidemiology Division (CED), Cancer Council Victoria. Part of this research is a collaborative project between Cancer Council Victoria and the Victorian Department of Health and Human Services (DHHS) using a dataset formed by linking the Victorian Cancer Registry (VCR) with other population-based health-related datasets; the project is supported by the Australian National Health and Medical Research Council (NHMRC grant 1150012).

This thesis uses data from the Victorian Cancer Registry, a population-based cancer registry for the second most populous state in Australia (presented in Chapters 7, 8 and 9), and linked population-based health data (presented in Chapter 10). Approval to conduct the analyses was granted by the data custodians at the Victorian Department of Health and Human Services and the Cancer Council Victoria Human Research Ethics Committee.

Chapters 4, 7, 8 and 9 of this thesis include the author-accepted versions of the following papers:

- Rural-urban residence and cancer survival in high-income countries: a systematic review (Chapter 4, published in *Cancer*)
- Differences in cancer survival by sex: a population-based study using cancer registry data (Chapter 7, published in *Cancer Causes & Control*)
- Differences in cancer survival by area-level socio-economic disadvantage: a population-study using cancer registry data (Chapter 8, published in *PLOS ONE*)
- Differences in cancer survival by remoteness of residence: an analysis of data from a population-based registry (Chapter 9, published in *Cancer Causes & Control*)

Chapters 3 and 10 include the manuscripts submitted for publication, which are in progress at the time of submission of this thesis:

- Factors explaining socio-economic inequalities in cancer survival: a systematic review (Chapter 3, *Cancer Control*, in progress, under revision)
- Factors explaining socio-economic inequalities in survival from colon cancer: a causal mediation analysis (Chapter 10, in progress)

I have been the first author of the studies published or submitted for publication. I led these studies under the supervision of Professor Dallas English and Professor Roger Milne. I analysed and interpreted the results and drafted the manuscripts. All co-authors provided advice in the interpretation of results and reviewed the manuscript. The contributions of the co-authors are detailed at the beginning of the corresponding chapters; they have provided their consent for the publications to be included in the thesis by signing the authorisation forms. The advisory committee approved the inclusion of published and in progress manuscripts.

**Key achievements – PhD candidature**

## 1. Awards

Best presenter award at the 4th Annual Melbourne School of Population and Global Health, Graduate Student Conference, University of Melbourne, Australia | 6 December 2017

Best student oral presentation award at the 2nd Victorian Cancer Survivorship Conference, The Walter and Eliza Hall Institute, Melbourne, Australia | 8-9 February 2018

The Australasian Epidemiological Association (AEA) council prizes awarded to highly ranked abstracts at the AEA annual scientific meeting, Brisbane, Australia | 23-25 October 2019

## 2. Publications

**Afshar N**, English DR, Thursfield V, Mitchell PL, te Marvelde L, Farrugia H, Giles GG, Milne RL. Differences in cancer survival by sex: A population-based study using cancer registry data. *Cancer Causes & Control*. 2018 Nov 1;29(11):1059-69. [Published]

**Afshar N**, English DR, Milne RL. Rural–urban residence and cancer survival in high-income countries: A systematic review. *Cancer*. 2019 Jul 1;125(13):2172-84. [Published]

**Afshar N**, English DR, Blakely T, Thursfield V, Farrugia H, Giles GG, Milne RL. Differences in cancer survival by area-level socio-economic disadvantage: A population-based study using cancer registry data. *PLOS ONE*. 2020 Jan 30;15(1): e0228551. [Published]

**Afshar N**, English DR, Chamberlain JA, Blakely T, Thursfield V, Farrugia H, Giles GG, Milne RL. Differences in cancer survival by remoteness of residence: An analysis of data from a population-based registry. *Cancer Causes & Control*. 2020 Apr 30;31(7):617-629. [Published]

## 3. Media Coverage

Findings related to differences in cancer survival by sex were publicised in electronic and printed media in Australia:

Newspaper interview – Herald Sun (printed media)

Radio interview – 3AW

Online news – Futurity (research news from top universities), higher education morning brief, SBS News, Daily Mail Australia, Daily Telegraph, Medical Xpress.

## 4. Conference/Other presentations

4th Annual MSPGH Graduate Student Conference, Melbourne School of Population and Global Health, Melbourne, Australia | 6 Dec 2017
Differences in cancer survival by remoteness of residence: a population-based study using cancer registry data

2nd Victorian Cancer Survivorship Conference, the Walter and Eliza Hall Institute, Melbourne, Australia | 8-9 Feb 2018
Differences in cancer survival by sex: a population-based study using cancer registry data

Cancer Council Victoria seminars series, Melbourne, Australia | 7 Aug 2018
Differences in cancer survival by sex: a population-based study using cancer registry data

World Cancer Congress, Kuala Lumpur, Malaysia | 1-4 Oct 2018
Do age at diagnosis, tumour thickness and tumour site explain sex differences in melanoma survival? A sequential causal mediation analysis using cancer registry data

Cancer Council Victoria seminars series, Melbourne, Australia | 6 Aug 2019
Inequalities in cancer survival by area-level socio-economic disadvantage: a population-based study using cancer registry data

Australasian Epidemiological Association (AEA) annual scientific meeting, Brisbane, Australia | 23-25 October 2019
Factors explaining socio-economic inequalities in colon cancer survival: a causal mediation analysis

**5. Conference posters**

Poster presentation – 3rd MDHS Early Career Researcher Network Symposium, Brain Centre, Melbourne, Australia | 19 Oct 2017

Differences in cancer survival by sex: a population-based study using cancer registry data

**6. Training workshops attended**

VicBiostat Winter School: 4-day workshop, Melbourne, Australia
Introduction to Causal Inference – Prof Lyle Gurrin, Dr Jessica Kasza & Dr Margarita Moreno Betancur, 5-6 June 2017
Advanced Survival Analysis – Dr Margarita Moreno-Betancur, Prof Rory Wolfe, 8-9 Jun 2017

VicBiostat Summer School: 3-day workshop, Melbourne, Australia
Beyond the Cox Model – flexible parametric models and extensions, 21 February 2018
Statistical methods for population-based studies of cancer patients, 22 February 2018
Hands-on methods – Prof Paul Dickman & Prof Paul Lambert, 23 February 2018

VicBiostat Workshop: 1-day Seminar, Melbourne, Australia
Sources of bias in randomised trials and non-randomised studies of interventions: a causal inference perspective – Prof Jonathan Sterne, 16 March 2018

Statistical Horizons: 2-day Seminar, Philadelphia, USA
Causal Mediation Analysis – Prof Tyler VanderWeele, 12-13 April 2018

The Causal Inference in Epidemiology Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Australia
Contemporary Epidemiology – Prof Tony Blakely, 3-day Short Course, 11-13 September 2019

**7. Course material preparation for Master of Cancer Science degree (Disparities in cancer survival lesson)**

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| Figure of the model of socio-economic indicators at different life-stages, by Galobardes B, Shaw M, Lawlor DA, Lynch JW, Smith GD. Indicators of socioeconomic position (part 1). Journal of Epidemiology & Community Health. 2006 Jan 1;60(1):7-12, with permission from Journal of Epidemiology & Community Health (License number 4757301216134). | Page 5 | Y |

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# Chapter 1. Introduction

## 1.1. Overview

This chapter provides the rationale for assessing inequalities and trends in cancer survival. The studies designed to answer the research questions, their objectives and the contribution of this thesis are also summarised.

## 1.2. Background

Cancer is the second-highest cause of mortality worldwide, accounting for 9.6 million deaths in 2017, [1] and its burden on individuals, economies and health systems is a global problem. [2] The latest analysis by the Australian Institute of Health and Welfare (AIHW) of the impact and causes of disease and death showed cancer to be one of the major disease groups responsible for the greatest burden in Australia. [3] The total cancer cost to the Australian health system during 2009–2013 was reported to be approximately $6.3 billion, with the highest expenditure for cancers of the colorectum ($1.1 billion), breast ($0.8 billion), lung ($0.6 billion) and prostate ($0.5 billion). [4] According to the AIHW, an estimated 49,896 Australians would have died of cancer in 2019, with cancers of the lung, colorectum, prostate, breast and pancreas as the top five leading causes of cancer deaths. [5]

Population-based cancer survival estimates, in addition to cancer incidence, provide valuable information about the performance, effectiveness and equity of a health system, cancer control policies and cancer services. [6] In Australia, five-year relative survival for all cancers combined increased from 50% in the period 1986-1990 to 69% in 2006-2010; prostate cancer, kidney cancer, non-Hodgkin lymphoma and multiple myeloma showed the largest (20% or more) improvements in five-year relative survival. [5] According to the International Cancer Benchmarking Partnership (ICBP), Australia is among the top three high-income countries with the highest cancer survival rates between 1994 and 2014, possibly due to earlier diagnosis and more effective treatment; [6] however, cancer survival varies by social disadvantage. [7]

Although Australia has a universal health care system, inequalities in cancer survival exist. In the period 2010-2014, five-year relative survival for all cancers combined was lower for people living in the most disadvantaged areas (55%) relative to their counterparts from the least disadvantaged regions (67%); the gap in survival was greatest for cancers of the cervix, head and neck, non-Hodgkin lymphoma, kidney, colorectal and prostate. [5] A recent report by the AIHW showed that residents of rural or remote areas have lower cancer survival compared with those residing in Australian major cities; men are also known to do worse than women for most cancers. [5] Similarly, the Australian Cancer Atlas shows that the excess risk of death for all cancers combined in the period 2006-2014 was higher for people living in the most disadvantaged areas and those residing in outer regional, remote and very remote regions. [8]

The magnitude and age-related patterns of these inequalities are not clear in Victoria, Australia and little is known about whether the gap in cancer survival is narrowing or widening over time. Despite strong evidence that sex is associated with the incidence and prognosis of several diseases, [9] few large-scale studies have assessed differences in cancer survival by sex, [10, 11] and no Australian study comprehensively evaluated the effect of sex on survival following cancer. This thesis aimed to investigate inequalities and trends in cancer patient survival by sex, socio-economic disadvantage and remoteness of residence using population-based Victorian Cancer Registry data. Moreover, this thesis focused on identifying the underlying causes of socio-economic inequality in colon cancer survival applying a novel method of causal mediation analysis to linked data from the Victorian Cancer Registry and other population-based health-related datasets. The Victorian Cancer Registry data was linked to inpatient hospital data to investigate the mediating effects of stage at diagnosis, co-morbid diseases and the treatment received in the observed gap in colon cancer survival by socio-economic disadvantage.

### 1.3. Principal aims of the thesis

This thesis had the primary objective of investigating differences and trends in cancer patient survival by sex, remoteness of residence and area-level socio-economic disadvantage. A secondary objective was to investigate the underlying causes of socio-economic inequalities in colon cancer survival.

To address the thesis aims, six studies were designed and conducted. The main objectives of these studies were:

**Study one**

**Objective:** To systematically review peer-reviewed published articles since 2005 that attempted to identify the underlying reasons for socio-economic inequalities in cancer patient survival.
**Research question:** What factors explain socio-economic inequalities in cancer survival?
**Strategy**: A systematic review was conducted to summarise the current evidence in the literature.

**Study two**

**Objective:** To systematically review peer-reviewed published articles that investigated the association of rural-urban residence with cancer survival in high-income countries and to summarise the current evidence in relation to potential contributing factors to the observed differences in survival between rural and urban areas.
**Research question:** What is the current evidence regarding the association between rural-urban residence and cancer survival in high-income countries?
**Strategy**: A systematic review was conducted to summarise the current evidence in the literature.

**Study three**

**Objective:** To examine differences in cancer patient survival by sex.
**Research question:** Does cancer survival differ between men and women?

**Strategy**: Analysis of Victorian Cancer Registry data from 1982 to 2015 and using net survival and excess mortality rates to assess heterogeneity in the excess risk of death due to cancer by sex according to age at diagnosis, time since diagnosis, and year of diagnosis.

**Study four**

**Objective:** To examine differences in cancer survival by area-level socio-economic disadvantage.
**Research question:** Does cancer survival vary between cancer cases residing in more disadvantaged areas than those residing in less disadvantaged regions?
**Strategy**: Analysis of Victorian Cancer Registry data from 2001 to 2015 using net survival and excess mortality rates to assess socio-economic disadvantage in survival according to sex, age at diagnosis, year of diagnosis and time since cancer diagnosis.

**Study five**

**Objective:** To examine differences in cancer survival by remoteness of residence.
**Research question:** Is there inequality in cancer survival between major cities and outside major cities?
**Strategy**: Analysis of Victorian Cancer Registry data from 2001 to 2015 using net survival and excess mortality rates to assess differences in survival for remoteness of residence according to sex, age at diagnosis, year of diagnosis, time since diagnosis and socio-economic disadvantage.

**Study six**

**Objective:** To identify the underlying reasons for socio-economic inequalities in colon cancer survival.
**Research question:** What factors explain socio-economic inequalities in survival from colon cancer?
**Strategy**: Interventional causal mediation analysis using a population-based, linked dataset to estimate the mediating effects of stage at diagnosis, co-morbidities, surgery and chemotherapy on colon cancer-specific survival.

### 1.4. Thesis outline

This thesis has eleven chapters.
**Chapter 2** provides an overview of core constructs of socio-economic position and rurality/remoteness and how they have been measured for studies investigating inequalities in health outcomes, including the studies conducted as part of my PhD research.

**Chapter 3** presents findings of a systematic review (study 1) identifying factors explaining socio-economic inequalities in cancer survival.

**Chapter 4** presents findings of a systematic review (study 2) investigating the association of rural and urban residence with cancer survival in high-income countries and summarises the current evidence in relation to potential explanatory factors for the observed differences in survival.

**Chapter 5** provides an overview of the data and population life tables used in this thesis to investigate trends and inequalities in cancer patient survival by sex, area-level socio-economic disadvantage and remoteness of residence in Victoria, Australia. It also describes the population-based linked data used to identify the underlying reasons for socio-economic inequalities in colon cancer survival in Victoria, Australia.

**Chapter 6** provides an overview of the statistical methods used for the analyses presented in this thesis.

**Chapter 7** presents results of study 3 assessing differences in cancer patient survival by sex using the Victorian Cancer Registry (VCR) data.

**Chapter 8** presents results of study 4 investigating inequalities in cancer patient survival by area-level socio-economic disadvantage using the VCR data.

**Chapter 9** presents results of study 5 examining differences in cancer patient survival by remoteness of residence using the VCR data.

**Chapter 10** presents results of study 6 identifying factors explaining socio-economic inequalities in survival from colon cancer using population-based linked health data.

**Chapter 11** summarises and interprets the key findings of population-based studies, where differences in cancer patient survival by sex, socio-economic disadvantage and remoteness of residence as well as potential reasons for socio-economic inequalities in colon cancer survival were assessed. The strengths and limitations of this thesis are discussed. This chapter also compares the findings with previous studies and discusses areas for future research. The overall conclusions are stated at the end of this chapter.

## Chapter 2 . Concepts of socio-economic position and remoteness

### 2.1. Introduction

This chapter focuses on core constructs of socio-economic position (SEP) and remoteness and how they have been measured for studies investigating inequalities in health outcomes, including the studies conducted as part of this PhD research.

This chapter is based on the comprehensive report entitled 'indicators of socio-economic position, part 1 and 2' by Galobardes *et al*, 2006, which defines the concept of SEP and its indicators. [12, 13]

### 2.2. Concept and indicators of socio-economic position

Socio-economic position, also widely known as socio-economic status (SES), is a complex and multidimensional construct reflecting the social and economic position of a person in society. [12, 14, 15] Numerous indicators or proxy measures, such as education, income and occupation (at the individual, household and area level), as well as combinations of these, have been used to explore socio-economic inequalities in health outcomes. Figure 2.1 shows measures of SEP over a lifetime. [12]

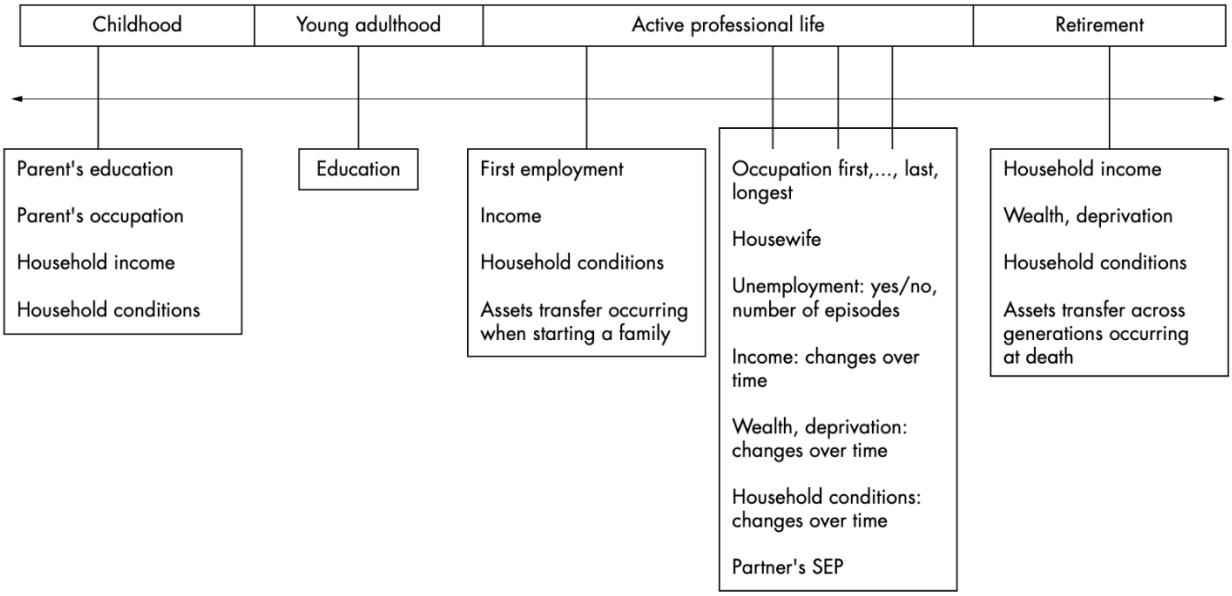


**Figure 2.1.** Socio-economic indicators at different life stages

*Image from: Galobardes B, Shaw M, Lawlor DA, Lynch JW, Smith GD. Indicators of socioeconomic position (part 1). Journal of Epidemiology & Community Health. 2006 Jan 1;60(1):7-12, with permission from Journal of Epidemiology & Community Health (License number 4757301216134)* [12]

Education, income and occupation cover different aspects of SEP providing shared and unique information (Figure 2.2). [15] These indicators are correlated but are not necessarily interchangeable as they are not equally associated with health or mortality, and no single measure is suitable for addressing all epidemiological research questions. [12, 15-17]

Because the choice of SEP indicator can influence research results, it is important to understand the theoretical basis and interpretations of each measure, as well as its strengths and limitations, in order to choose the appropriate indicators for a proposed research question, and to appropriately interpret the findings. [12, 15] The most common individual- and area-level measures of SEP used in health research are discussed below.

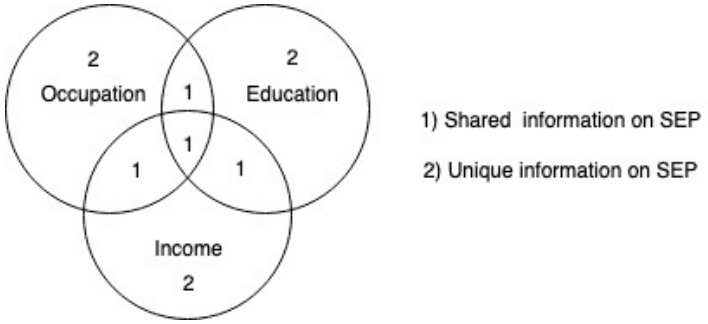


**Figure 2.2.** Shared and unique information on socio-economic position presented by education, occupation and income

*Image redesigned from: Green MJ, Popham F. Interpreting mutual adjustment for multiple indicators of socioeconomic position without committing mutual adjustment fallacies. BMC public health. 2019 Dec;19(1):10. (Permission not required)* [15]

### 2.2.1. Individual-level indicators

Education is commonly used in health inequalities research and can be defined as a continuous variable such as years of education attained, or a categorical variable such as the highest qualification (e.g. never attended school, completed primary or high school, vocational training, and higher education including the type of degree achieved such as diploma, master's or doctorate degree). [12, 14, 15] Education starts early in life and partly measures life-course SEP by reflecting parental or early life circumstances, as well as later-life conditions, by its effect on occupation and income (Figure 2.3). [12, 14, 15]

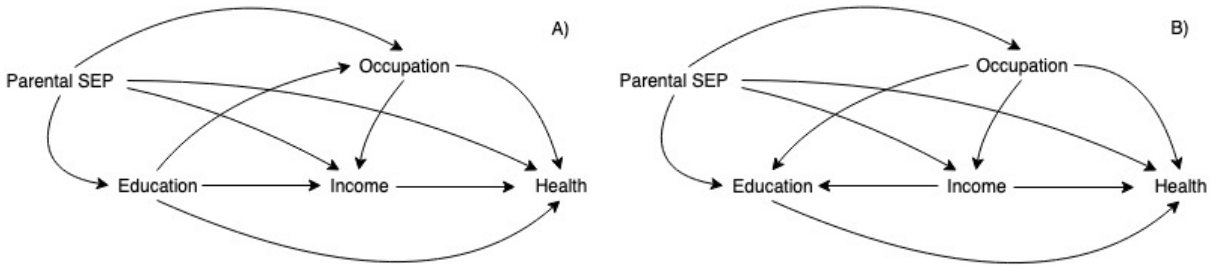


**Figure 2.3.** A) Plausible pathways from education to health; B) Alternative pathways from education to health

*Images redesigned from: Green MJ, Popham F. Interpreting mutual adjustment for multiple indicators of socioeconomic position without committing mutual adjustment fallacies. BMC public health. 2019 Dec;19(1):10.* [15]

The main strength of 'education' as a proxy measure of SEP is that it is relatively stable over time and easy to measure via questionnaire, has high response, and, unlike income and occupation, it is less complicated and sensitive information to disclose, and applicable to most adults regardless of their age

and employment status. [12, 14] However, using similar categories of education for different birth cohorts can produce biased results (if not controlling for the effect of birth cohorts) as the education level classified as 'low' or 'middle' for younger generations might be considered as a higher level of education for older generations. [12, 14]

Income is a determinant of material resources, working conditions and living standards; [12, 14] it has a dose-response relationship with health outcomes and affects health through different pathways such as access to shelter, food, leisure activities, health care services as well as education, particularly in countries where higher education is not free. [12, 14] In epidemiological research, income has generally been measured at the household level rather than the individual level, indicating resources available to each household member, regardless of whether a single or multiple wage is the household's source of income. [12, 14] When using household income, it is necessary to account for the number of people, as a housing unit can be occupied by one or more individuals. [12, 14]

Using income alone as an indicator of SEP has some limitations, which are sometimes not considered in health inequalities research. [12, 14] In general, people consider income as sensitive and private information and they are not keen to report it. [12, 14] Income can change over a short period of time and reverse causation, when a health condition affects a person's or household's income, is a major problem. [12, 14] Further, studies generally collect data on gross income rather than disposable income, which does not accurately indicate the financial capacity of an individual or a household. [12, 14] Another limitation is that income may not be comparable across different settings (e.g. across countries or birth cohorts). [12, 14]

Occupation is another commonly used indicator of a person's social standing and could affect health outcomes through better access to material resources, health services and education. [12-14] Occupation may not accurately capture SEP for students and people who are self-employed, unemployed or retired, or working voluntary or illegally. [12-14] Similar to education, occupation is influenced by birth cohort as well as geographical regions; thus, it is important to take these factors into account when investigating inequalities in health outcomes.

Housing characteristics such as housing tenure, conditions and amenities indirectly measure people's wealth or material sides of SEP and are less frequently used in epidemiological research than education, income and occupation. [12, 14] Housing tenure is the most popular marker providing information regarding house ownership i.e. owner-occupied (with or without a mortgage) or rented. [12, 14] Collecting data on housing characteristics is fairly easy, but the validity of these indicators and their relevance might vary across population and geographical areas. [12, 14]

In summary, the main limitation of using single individual-level indicators is that each does not address the multi-dimensionality of SEP; for instance, a person can be classified as advantaged by one indicator, but not another (e.g. not having a high level of education but having a high level of income). [15, 16] Another problem is that in health inequalities research, it is common practice to mutually adjust for

socio-economic indicators other than the one of interest, not accounting for the complexity of the pathways that connect SEP indicators to health. [15] For example, as shown in Figure 2.3A, the association of education with health outcomes is mediated via occupation and income and confounded by parental SEP, whereas in Figure 2.3B, showing alternative plausible pathways, the effect of education on health is confounded by parental SEP, occupation and income. [15] Thus, adjusting or not adjusting for occupation and income could yield biased estimates.

Composite SEP measures defined by weighting and aggregating several socio-economic dimensions to measure material and social deprivation or social and economic standing, can potentially overcome the problem mentioned above, although they might not be suitable to answer particular policy questions, as they mask the effect of individual SEP indicators. [18, 19]

Composite socio-economic indicators are generally defined based on a formative model, in which the composite measure is not independent of each SEP indicator (e.g. education, income and occupation) and the construct is a common effect of single measures (Figure 2.4). For instance, an increase in income or education results in an increase in the composite indicator. [19]

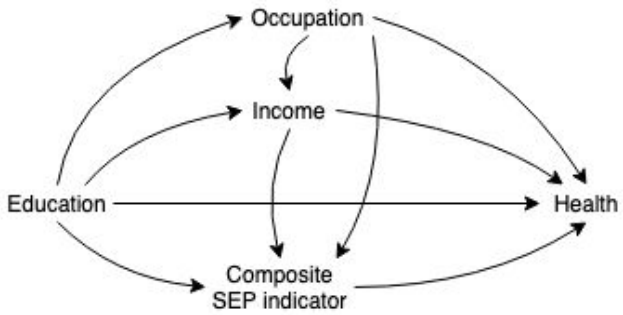


**Figure 2.4.** Formative composite SEP indicator

### 2.2.2. Area-level indicators

The use of area-based aggregated measures is growing as they can be informative in the absence of individual-level socio-economic measures, and they could also be useful for resource allocation and policy-making purposes. [13, 14] Area-based or ecologic socio-economic indicators are measured based on the characteristics of people living in a given area, generally by gathering information from census data. Examples include the proportion of people with high income, education, white- and blue-collar occupations as well as the proportion unemployed or who own or rent their home. [13, 14] The most common area-based SEP measures used in England are the Townsend Deprivation Index and Index for Multiple Deprivation (IMD). [20, 21] Studies in other high-income countries such as Ireland, New Zealand, Canada and the United States use the Small Area Health Research Unit (SAHRU) index of social deprivation, [22] New Zealand Deprivation Index (NZDep), [23] Canadian Index of Multiple Deprivation (CIMD), [24] and Census Tract-level SES, [25] respectively (Table 2.1).

**Table 2.1.** List of socio-economic dimensions used for each census-based index in countries other than Australia

| Census-based socio-economic indexes, countries | Socio-economic dimension |
|---|---|
| **Townsend Deprivation Index, England** | -Households without a car<br>-Overcrowded households<br>-Households not owner-occupied<br>-Persons unemployed |
| **Index for Multiple Deprivation (IMD), England** | -Income Deprivation<br>-Employment Deprivation<br>-Education, Skills and Training Deprivation<br>-Health Deprivation and Disability<br>-Crime<br>-Barriers to Housing and Services<br>-Living Environment Deprivation |
| **Small Area Health Research Unit (SAHRU) index, Ireland** | -Unemployment<br>-Low social class<br>-No car<br>-Rented accommodation<br>-Overcrowding |
| **New Zealand Deprivation Index (NZDep), New Zealand** | -Income<br>-Unemployment<br>-Education<br>-House ownership<br>-Overcrowding<br>-Single parent<br>-No car and no internet connection at home |
| **Canadian Index of Multiple Deprivation (CIMD), Canada** | -Residential instability<br>-Economic dependency<br>-Ethno-cultural composition<br>-Situational vulnerability |
| **Census Tract-level SES, United States** | -Occupation<br>-Income and poverty |

Several studies have examined the reliability of area-based indicators as proxy measures of individual-level SEP and reported discrepancies between the two, [26-29] which leads to misclassification and underestimation of contribution of individual-level SEP to health outcomes, [29] although the characteristics of an area, such as public resources and infrastructure, can also independently affect people's health, thereby over-estimating the association of individual-level SEP with the outcome of interest. [13] Nevertheless, researchers argued that socio-economically disadvantaged people are more likely to live in more disadvantaged areas, and the validity of area-level socio-economic measures depends on the size of the geographical areas considered i.e. the smaller the area is, the smaller the misclassification will be. [13, 30]

### 2.2.3. Area-based measure of socio-economic position in Australia

The Australian Bureau of Statistics (ABS) developed the Socio-Economic Indexes for Areas (SEIFA), the most widely used area-based composite measure of SEP in Australia, using five-yearly census data. [31] Household income, employment status, occupation, education level, housing (e.g. owning or renting and Internet connection), and disability are the main variables that have been used to define SEIFA. [31] SEIFA consists of four indexes (see below) that are constructed using census-based data. Each index is a weighted sum of particular census variables and focuses on a different dimension of SEP in an area (Table 2.2). [31]

- The Index of Relative Socio-economic Disadvantage (IRSD)
- The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD)
- The Index of Education and Occupation (IEO)
- The Index of Economic Resources (IER)

**Table 2.2.** List of candidate variables for each index, by socio-economic dimension, Australian population census 2011

| *Dimension* | *Index of Relative Disadvantage* | *Index of Relative Advantage and Disadvantage* | *Index of Economic Resources* | *Index of Education and Occupation* |
|---|---|---|---|---|
| Income | INC_LOW | INC_HIGH<br>INC_LOW | INC_HIGH<br>INC_LOW | |
| Education | NOYR12ORHIGHER<br>NOEDU<br>CERTIFICATE | NOYR12ORHIGHER<br>NOEDU<br>CERTIFICATE<br>ATUNI<br>DIPLOMA<br>DEGREE | | NOYR12ORHIGHER<br>NOEDU<br>CERTIFICATE<br>ATUNI<br>DIPLOMA<br>DEGREE<br>ATSCHOOL |
| Employment | UNEMPLOYED | UNEMPLOYED | UNEMP_RATIO | UNEMPLOYED |
| Occupation | OCC_LABOUR<br>OCC DRIVERS<br>OCC SERVICE L<br>OCC_SALES_L | OCC_LABOUR<br>OCC DRIVERS<br>OCC SERVICE L<br>OCC_SALES_L<br>OCC_PROF<br>OCC_MANAGER | | OCC_SKILL1<br>OCC SKILL2<br>OCC SKILL4<br>OCC_SKILL5 |
| Housing | LOWRENT<br>OVERCROWD<br>FEWBED | LOWRENT<br>OVERCROWD<br>FEWBED<br>HIGHBED<br>HIGHRENT<br>HIGHMORTGAGE<br>OWNING<br>SPAREBED | LOWRENT<br>OVERCROWD<br>MORTGAGE<br>HIGHBED<br>HIGHRENT<br>HIGHMORTGAGE<br>OWNING | |
| Other | CHILDJOBLESS<br>ONEPARENT<br>NOCAR<br>DISABILITYU70<br>ENGLISHPOOR<br>SEP DIVORCED<br>NONET<br>DIALUP | CHILDJOBLESS<br>ONEPARENT<br>NOCAR<br>DISABILITYU70<br>ENGLISHPOOR<br>SEP DIVORCED<br>NONET<br>DIALUP<br>HIGHCAR | UNINCORP<br>ONEPARENT<br>NOCAR<br>GROUP<br>LONE | |

Note: the definitions of each variable listed in this table is provided in Appendix A
Note: the variables listed in this table are not the final list of variables included in the indexes
*Image from: Technical paper, socio-economic indexes for areas (SEIFA), 2011, page 25* [31]

Most Australian epidemiological studies and reports by Australian health organisations have used SEIFA, particularly the Index of Relative Socio-Economic Disadvantage (IRSD) and the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD), to investigate inequalities in health outcomes by SEP. [32-36] As for any composite measure, a limitation of using the SEIFA measure is that the researchers and policy makers are unable to identify the individual socio-economic components producing health inequalities, to intervene on. [36]

For the aims of this thesis, the Index of Relative Socio-Economic Disadvantage (IRSD) recorded in the Victorian Cancer Registry was used. It was calculated based on Statistical Area Level 1 (with a mean population size of about 400 persons) in 2011 [37] and Collection District (with a mean of 225 dwellings) in 2006. [38] An area with a low IRSD score has a higher proportion of individuals that are more socio-economically disadvantaged (e.g. many people in low-skill jobs or with no qualifications and many households with low income), whereas an area with a high score has low proportion of disadvantaged people (Table 2.3). [31] Geographical areas were ranked according to their calculated scores in terms of relative socio-economic disadvantage (Figure 2.5 and Figure 2.6). [31]

**Table 2.3.** Final list of indicators for the index of relative socio-economic disadvantage (IRSD), Australian population census, 2011

| **Candidate indicators** | **Index of Relative Socio-Economic Disadvantage (IRSD)** |
|---|---|
| Income | % People with stated annual household equivalised income between $1 and $20,799 |
| Education | % People aged 15 years and over whose highest level of education is year 11 or lower, including certificate I and II<br>% People aged 15 years and over who have no educational attainment |
| Employment | % People (in the labour force) unemployed |
| Occupation | % Employed people classified as labourers<br>% Employed people classified as Low Skill Community and Personal Service Workers<br>% Employed people classified as Machinery Operators and Drivers |
| Housing | % Households renting from Government or Community organisation<br>% Occupied private dwellings paying rent less than $166 per week (excluding $0 per week)<br>% Occupied private dwellings requiring one or more extra bedrooms (based on Canadian National Occupancy Standard) |
| Other | % Families with children under 15 years of age who live with jobless parents<br>% Occupied private dwellings with no internet connection<br>% One-parent families with dependent offspring only<br>% Occupied private dwellings with no car<br>% People aged 15 years and over who are separated or divorced<br>% People aged under 70 who have a long-term health condition or disability and need assistance with core activities<br>% People who do not speak English well |

*Table reproduced from: Technical paper, socio-economic indexes for areas (SEIFA), 2011, page 32* [31]

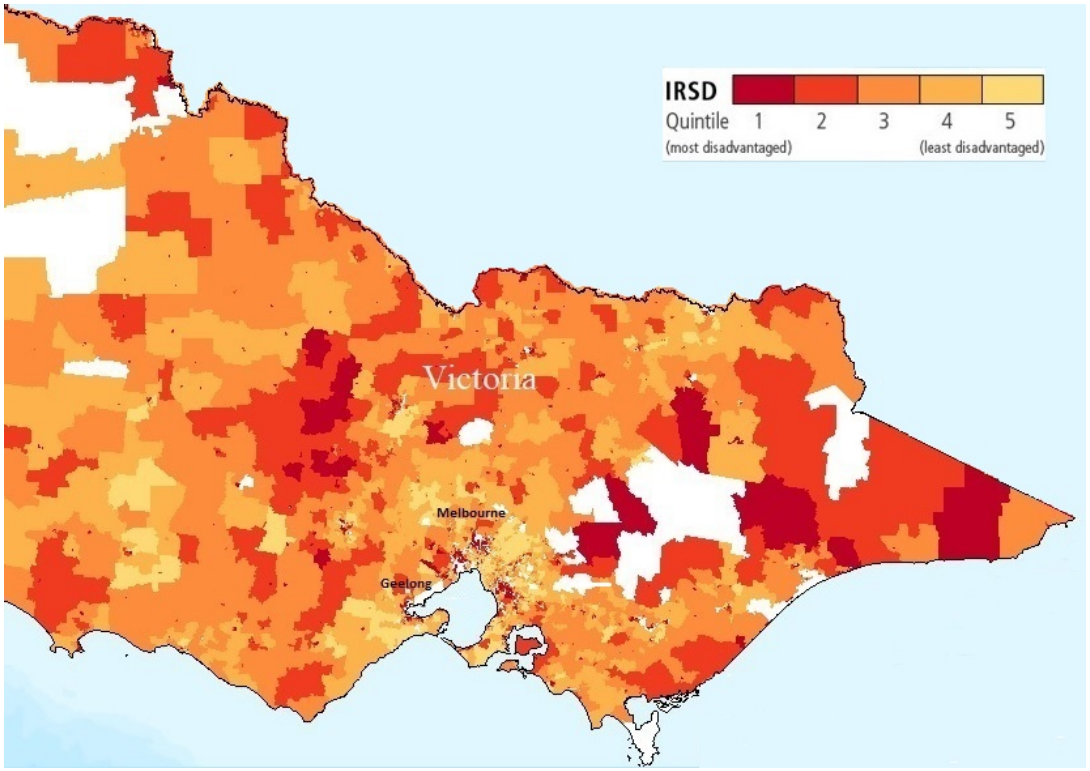


**Figure 2.5.** Distribution of the Index of Relative Socio-economic Disadvantage (IRSD) by SA1 across Victoria, Australian Bureau of Statistics [39]
White areas on the map have no index score due to low population or poor-quality data

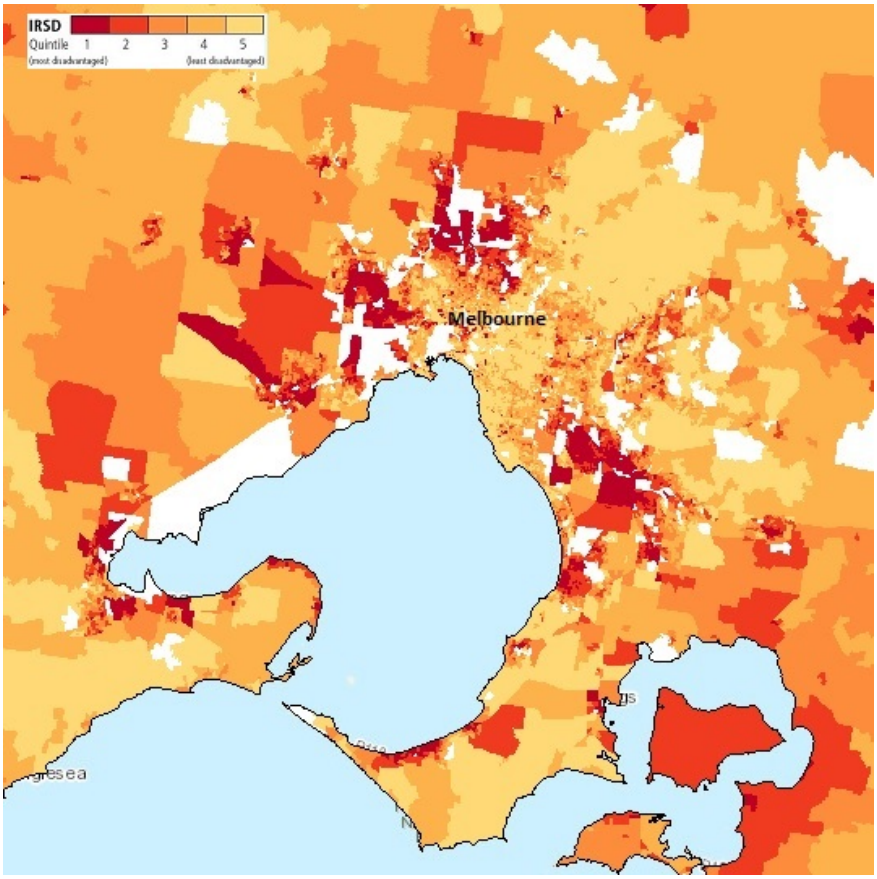


**Figure 2.6.** Distribution of the Index of Relative Socio-economic Disadvantage (IRSD) by SA1 across Melbourne, Australian Bureau of Statistics [39]
White areas on the map have no index score due to low population or poor-quality data

## 2.3. Concept of remoteness

The terms ‘remoteness' and ‘rurality’ are complex concepts defined based on a variety of geographical units and criteria, and they are conceptually different, although used interchangeably. [40] ‘Rurality’ generally refers to regions that have lower population density than urban areas, while ‘remoteness’ is defined based on road distance and accessibility to the nearest service centres. [40] Some countries showed that rural and remote areas tend to have higher rates of unemployment, poverty, co-morbidities, and limited availability of health care facilities. [40-43] There is considerable variation in the measurement of these constructs within and between high-income countries, which makes comparison of findings across studies challenging. In cancer research, several studies have defined rural or remote areas based on population density or size and travel time or distance to services, while others used standard measures of geographical classifications. For example, US studies have applied the Rural-Urban Continuum Codes (RUCC), [44] and Rural-Urban Commuting Area (RUCA) [45] to define rural-urban residence, and Australian research used the Accessibility/Remoteness Index of Australia (ARIA/ARIA+), [46] the Australian Standard Geographical Classification-Remoteness Areas (ASGC-RA) [47] or the Australian Statistical Geography Standard (ASGS) Remoteness Structure. [48]

The ABS remoteness structure (i.e. the Australian Statistical Geography Standard (ASGS)) is used by the VCR to define remoteness of cases’ residence at the time of cancer diagnosis on the basis of 2011 SA1 boundaries. [48] The ASGS used the Accessibility and Remoteness Index of Australia (ARIA+) to measure area remoteness according to relative ease of access to services, by calculating road distance in kilometres to the nearest centres (e.g. education, health and retail). [46] For example, the lowest ARIA scores (0-2 values) indicates that the area has the highest accessibility to service centres (Table 2.4). [46] Each remoteness classification has its advantages and disadvantages based on how it is measured. A disadvantage of ARIA methodology is that it can occasionally give the same remoteness scores to dissimilar areas in terms of accessibility to health services. [49]

**Table 2.4.** Australian bureau of statistics (ABS) remoteness area classification by SA1 average ARIA+ value

| ABS Remoteness Area | SA1 average ARIA+ score range |
|---|---|
| Major Cities of Australia (Highly accessible) | 0 – 0.2 |
| Inner Regional Australia (Accessible) | > 0.2 – 2.4 |
| Outer Regional Australia (Moderately Accessible) | >2.4 – 5.92 |
| Remote Australia | > 5.92 – 10.53 |
| Very Remote Australia | > 10.53 |

*Table reproduced from: Australian Statistical Geography Standard (ASGS): Volume 5 - Remoteness Structure, 2011, page 5* [48]

The Australian states and territories were divided into five categories: major cities, inner regional, outer regional, remote and very remote areas. [48] A map of the 2011 ASGS Remoteness Structure across Australia is shown in Figure 2.7 and a detailed map of Victoria is provided in Figure 2.8. Victoria does not have ‘very remote’ areas and few regions classified as ‘remote’.

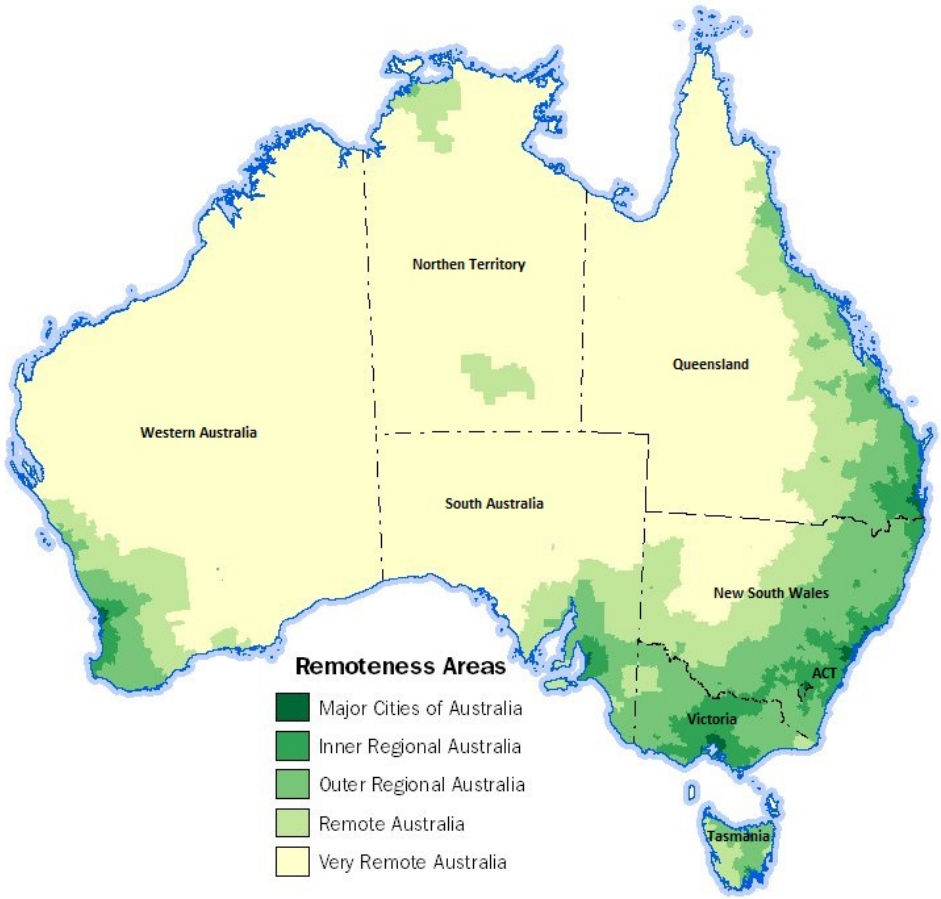


**Figure 2.7.** 2011 Australian Statistical Geography Standard: Remoteness Structure [50]

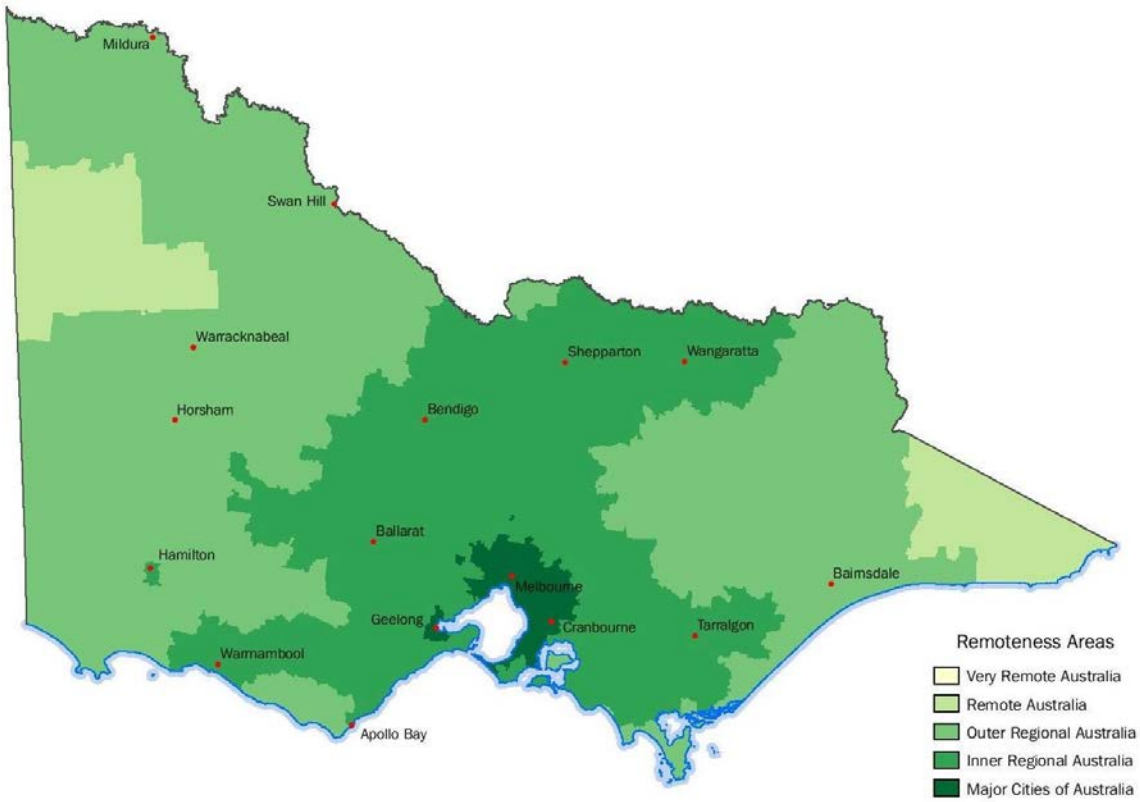


**Figure 2.8.** 2011 Australian Statistical Geography Standard: Remoteness Structure, Victoria [50]

Regardless of how remoteness or rurality is measured, there is no ideal single definition that is suitable for all health inequalities research questions. Moreover, it is difficult to disentangle the effect of rurality or remoteness on health outcomes because rural residence is correlated with socio-economic position and ethnicity. [51] Table 2.5 shows the proportion of Australian residents that are indigenous or living in the most disadvantaged areas, by remoteness area in 2011, which are both notably greater in rural and remote regions than in major cities. [51]

**Table 2.5.** Indigeneity and socio-economic disadvantage by remoteness areas in Australia, 2011.

| Category | Major cities | Inner Regional | Outer Regional | Remote | Very Remote |
|---|---|---|---|---|---|
| Total number (and proportion of the total Australian population) | 15,684,540 (70.2%) | 4,111,029 (18.4%) | 2,026,429 (9.1%) | 314,676 (1.4%) | 203,350 (0.9%) |
| **Proportion of Australians who are** | | | | | |
| Indigenous | 1.5% | 3.6% | 7.2% | 16.3% | 45.1% |
| Living in the most socio-economically disadvantaged areas | 7.9% | 11.7% | 14.7% | 12.6% | 44.1% |

Notes: 'Most disadvantaged areas' refers to SEIFA IRSD decile 1. The SEIFA IRSD data is derived from 2011 Census and has not been adjusted. All other data are derived from the estimated resident population as at 30 June 2011. Victoria does not have 'very remote' areas and few regions classified as 'remote'

*Table reproduced from: Healthcare in Australia 2012–13: Comparing outcomes by remoteness report by the Council of Australian Government Reform Council, 2014, page 37*

## Chapter 3 . Systematic review of factors explaining socio-economic inequalities in cancer survival

This systematic review was conducted during the first year of my PhD candidature and was submitted to *Cancer Control* for publication. The reviewers suggested updating the review to include relevant studies published more recently. An extension was requested because updating the search, screening, data extraction, and assessment of the risk of bias by two independent reviewers would take at least 6 months.

I conceptualised and led the study, conducted the search, extracted the data and drafted the manuscript. Professor Roger Milne was the second independent reviewer and was involved in the selection of eligible studies and assessment of the risk of bias of included articles. Any disagreements were resolved after consulting the third independent reviewer, Professor Dallas English. R.M and D.E provided advice in the interpretation of results and reviewed and edited the manuscript.

This chapter includes the submitted version of the systematic review.

The list of references is formatted according to the journal requirements, with separate numbering to the thesis reference list. Supplementary material related to this study is presented in Appendix B.

Cancer Control: CCX-19-0269 [In progress, under revision]

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**Factors explaining socio-economic inequalities in cancer survival: a systematic review**

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**Keywords:** Cancer survival; socio-economic position; deprivation; disadvantage, inequality, disparity

**Abbreviations:** EMRR: excess mortality rate ratio, HR: hazard ratio, OR: odds ratio, CI: confidence interval

**Abstract**

There is strong and well-documented evidence that socio-economic inequality in cancer survival exists within and between countries, but the underlying causes of these differences are not well understood. We systematically searched the Ovid Medline, EMBASE, and CINAHL databases up to 31 May 2016. Observational studies exploring pathways by which socio-economic position might causally influence cancer survival were included. We found fifty-two eligible articles published between 2005 and 2016. Cancer stage, other tumour characteristics, health behaviours, co-morbidity and treatment were reported as key contributing factors, although the potential mediating effect of these factors varied across cancer sites. For common cancers such as breast and prostate cancer, stage of disease was generally cited as the primary explanatory factor, while co-morbid diseases and treatment were also reported to contribute to worse survival for more disadvantaged cases. In contrast, for colorectal cancer, most studies found that stage did not explain the observed differences in survival by SEP. For lung cancer, inequalities in survival appear to be partly explained by receipt of treatment and co-morbidities. Most studies compare regression models with and without adjusting for potential mediators; this method has several limitations that could result in biased estimates of mediating effects and invalid conclusions. It is therefore essential that future studies apply modern methods of causal mediation analysis to accurately estimate the contribution of potential explanatory factors for these inequalities, which may translate into effective interventions to improve survival for disadvantaged cancer patients.

### 3.1. Introduction

Socio-economic position (SEP) is a complex construct of several aspects of a person's social, financial and occupation position.[1] Cancer patients with lower SEP consistently show worse survival than those with higher SEP, regardless of whether individual-level SEP or area-based measures are used. [2,3] Comprehensive reviews conducted by the International Agency for Research on Cancer (IARC) in 1997 [2] and Woods *et al*., in 2005 [3] found solid evidence for socio-economic inequalities in cancer survival for most malignancies and in many countries. The extent of the survival differences by SEP is moderate for most cancer sites, but substantial for cancers of the breast, colon, bladder and corpus uteri, which all have relatively good prognosis. [2] Stage at diagnosis has been reported to be the primary explanatory factor, but its estimated mediating effect has differed by cancer site and between countries and studies. [3,4] Few studies have assessed the contribution of treatment to cancer survival differences among socio-economic groups. [3,4] It also remains unclear to what degree patient characteristics such as the presence of co-morbidities and health-related behaviours explain socio-economic differences in cancer survival. In this systematic review, we assessed studies exploring underlying reasons for socio-economic inequalities in cancer patient survival, with the aim of identifying potential contributing factors and determining the validity of published estimates of their mediating effects.

### 3.2. Methods

This systematic review was planned, conducted and reported in adherence to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). [5] The review protocol was registered with the International Prospective Register of Systematic Reviews – PROSPERO (registration number CRD42016039227).

#### *Search strategy*

A systematic search of studies published in English from 1 January 2005 to 31 May 2016 was conducted in Ovid Medline, EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases to identify those that investigated the underlying reasons for socio-economic inequalities in cancer survival (Supplementary Table 3.1). The bibliographies of selected studies were reviewed to locate eligible articles that may not have been detected through the above process. Finally, we carried out a further manual search using Google Scholar and reviewed the first three pages to ensure that potentially relevant studies were not missed.

#### *Eligibility criteria*

Eligible studies met all of the following criteria: 1) observational study of adults (men or women diagnosed with cancer at age ≥15 years); 2) written in English and published in a peer-reviewed journal; 3) investigated the underlying causes of socio-economic inequalities in cancer survival; 4) assessed death from any cause or death from a specific type of cancer; and 6) reported an estimate of excess

mortality rate ratio (EMRR), hazard ratio (HR) or odds ratio (OR) with a corresponding 95% confidence interval (CI) or standard error. We excluded eligible abstracts if full text was not available.

***Study screening and data extraction***

N.A. performed the literature search and excluded studies based on the titles and abstracts. Full reports of selected articles were imported to *Covidence*, a web-based program for conducting systematic reviews, for independent screening by N.A. and R.L.M. Any disagreements were resolved after consulting D.R.E. Data from the selected studies were extracted by N.A. with assistance from R.L.M. For each study, we extracted the following information: the first author's last name, year of publication, country where the study was conducted, sources of data, diagnosis years, range of age at cancer diagnosis, cancer types studied, measures and categories of socio-economic position, factors considered as potentially contributing to socio-economic inequalities in cancer survival, statistical methods and covariates included in the analyses.

***Assessment of risk of bias***

N.A. and R.L.M independently assessed the risk of bias of eligible studies using the domains of bias from the ROBINS-E (Risk of Bias In Non-Randomized Studies - of Exposures) tool [https://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/]. The following domains were reviewed: confounding, selection of participants into the study, classification of the exposure, adjustment for mediators, level of missing data, measurement of the outcome, and reporting of results.

**3.3. Results**

***Study selection***

The electronic database search identified 4,682 articles; 1,387 duplicate citations were removed, and an additional 3,190 articles were excluded based on their title and abstract, leaving 105 articles for further assessment. We excluded 53 studies after full-text screening; therefore, 52 articles met the eligibility criteria for inclusion in the review (Figure 3.1).

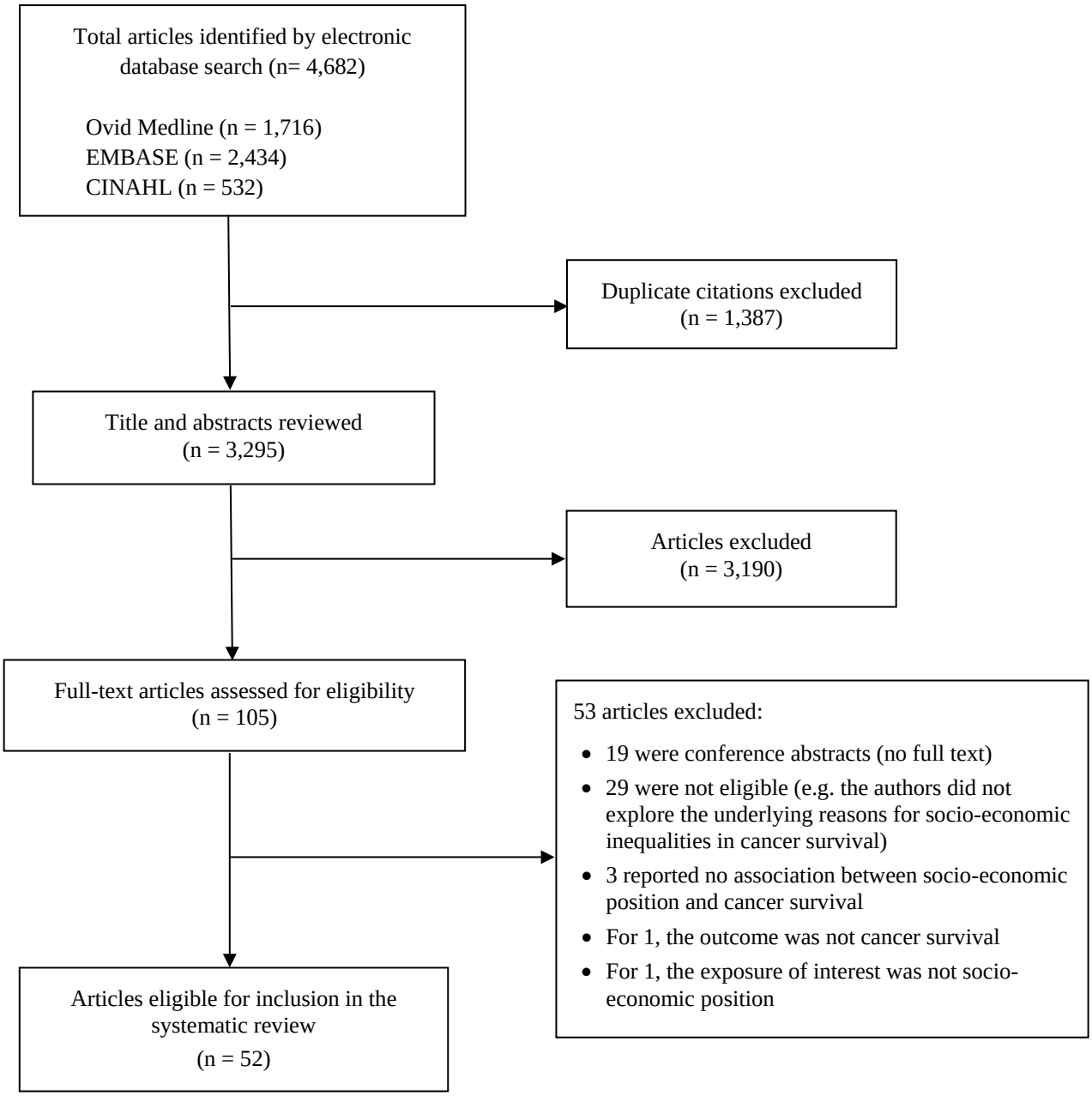


**Figure 3.1.** Flow diagram describing selection of studies for inclusion in the systematic review of factors explaining socio-economic inequality in cancer survival
CINAHL, Cumulative Index to Nursing and Allied Health Literature

***Study characteristics***

Table 3.1 summarises the characteristics of the included studies and factors considered as potentially contributing to socio-economic inequalities in cancer-specific and overall survival. Thirty-two studies were conducted in Europe [6-36] (one study used data from England and Australia),[37] eleven in the United States of America (US), [38-48] four in Canada, [49-52] two in New Zealand, [53,54] two in Australia [55,56] and one in Asia.[57] These studies assessed the following cancers: female breast, [8,9,13,17,18,26,29,30,32,36,37,41,47,48,54] male breast, [46] cervix, [24,38] ovary, [23] endometrium, [33] prostate, [7,34] colorectum, [12,15,22,28,43,45,55] lung, [10,11,16,20,25,44] head and neck, [31,42,50,51] oesophagus, [27] liver, [52] kidney, [40] melanoma [19,35] and non-Hodgkin lymphoma, [21] as well as selected groups of malignancies. [6,14,39,49,53,56,57] The majority of the studies used population-based cancer registry data, [7-11,13,16-20,25,27-30,34-38,40,42-44,46,48,49,51-57], some linking these with healthcare administration, public and private hospital, screening and treatment datasets. [8,20,38,42,51,55] The remaining studies used data from a variety of sources including cohort and case-control studies, [6,12,14,26,31,47] hospitals, [50] cancer surveillance programs [45] or other cancer databases. [15,21-24,32,33,39,41] Nineteen studies reported cancer-specific survival, or relative or net survival, where the cancer under study was considered as the cause of death, [10,13,18,19,27,28,30,32,34-37,40,47,48,51,53-56] while twenty-four studies presented overall survival (i.e. death from any cause). [6-8,11,14,16,17,20-26,33,38,39,41,43-46,52,57] Other studies reported both overall and cancer-specific survival. [9,12,15,29,31,42,49,50]

The measurement of SEP of cancer patients at diagnosis varied across studies. Several studies used composite measures or indices of SEP or deprivation such as census tracts socio-economic status, [31,39-44,46,48-50] Townsend index, [27,28] the index of multiple deprivation , [12,17,20,25,29,32] socio-economic indexes for areas, [55,56] the New Zealand deprivation index, [54] the Scottish Index of multiple deprivation, [34] deprivation index, [30] socio-economic index [10,11] or the Small Area Health Research Unit index of social deprivation. [36] Other studies defined SEP using measures such as educational level, income, unemployment rate, poverty level, median household income or median property value across aggregated or geographical areas based on address, postal code or neighbourhood. [7-9,37,38,45,47,51-53,57] The remaining studies used individual measures including education, gross household or disposable income, last occupation and housing status (rental or owner-occupied). [6, 10, 13-16, 18, 19, 21-24, 26, 33, 35, 47]

Different approaches were used across studies to attempt to explain the underlying reasons for socio-economic inequalities in cancer survival. Most studies applied the 'difference method', which compares regression coefficients for exposure on outcome from models with and without adjusting for potential mediators. [6-8,10-15,17-28,30,31,33,35,36,38-41,43-45,47-57] Other studies examined the distribution of cases across socio-economic categories by the mediator(s) of interest or stratified the relative risk or survival rate estimates by potential mediator. [9,16,32,34,37,46] Two studies applied causal mediation analysis. [29,42]

**Table 3.1.** Characteristics of included observational studies on potential explanations for socio-economic inequalities and cancer survival, 2005-2016

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aarts et al, 2013 | Netherlands | GLOBE, prospective cohort study | Eindhoven and Surroundings | 1991-2008 | NA (15-75 at baseline) | All malignancies with focus on colon, non-small cell lung, prostate and female breast | Education level (individual level) | 4 | Kaplan-Meier method (crude survival), Cox proportional hazards regression (overall survival) | For all cancers combined, 5-year crude survival was superior in highly educated patients compared with low educated cancer patients. Educational inequalities in overall survival were observed in prostate cancer comparing low educated patients with highly educated, while no associations were found for breast, colon and non-small cell lung cancer after adjustment for age, year of diagnosis and stage at diagnosis. Co-morbidities and lifestyle behaviours did not explain educational inequalities in overall survival after prostate cancer. | Age, year of diagnosis, stage at diagnosis and sex (colon and non-small cell lung cancer) Additionally, adjusted for co-morbidity, alcohol consumption, physical activity, smoking status |
| Aarts et al, 2013 | Netherlands | Eindhoven Cancer Registry | South-eastern Netherlands | 1998-2008 | All ages | Prostate | Socio-economic status (SES) defined at neighbourhood level based on the postal code of the residence area derived from individual tax data provided at an aggregated level | 3 | Cox proportional hazard regression (overall survival) | 10-year overall survival was superior in high-SES patients compared with low-SES (both localised and advanced stages). Therapy had a larger impact on the risk of death comparing patients living in low and high socio-economic status areas, except for men aged 75 years and older. Presence of co-morbidities partly contributed to inequalities in overall survival after diagnosis. | Stratified by age and stage at diagnosis Additionally, adjusted for year of diagnosis, co-morbidity, treatments |
| Aarts et al, 2011 | Netherlands | BoBZ database (population-based screening program) linked with Eindhoven Cancer Registry | Southern Netherlands | 1998-2005 | All ages | Breast | Socio-economic status (SES) Provided at an aggregated level for each postal | 3 | Life test method (crude survival), Cox proportional hazards regression (overall survival) | Women with low SES had lower overall survival compared with women with high SES, whether screen- | Age Stratified by screening attendance |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | code (covering an average of 17 households) | | | detected, interval carcinoma or not attended screening at all.<br>Among non-attendees and interval cancers, the differences in survival were largely explained by stage distribution (48% and 35%) and to a lesser degree by therapy (16% and 16%), respectively. Presence of co-morbidities explained 23% of survival inequalities among screen-detected patients; it had less impact on interval cancers or non-attendees. | Additionally, adjusted for stage at diagnosis, co-morbidity, therapy |
| Bastiaannet et al, 2011 | Netherlands | Netherlands Cancer Registry | Netherlands | 1995-2005 | All ages | Breast | Socio-economic status (SES)<br>Area-based measure according to place of residence at the time of diagnosis which consists of data concerning income, employment, and education | 5 | Cox proportional hazard regression (10-year overall survival), 10-year relative survival (Hakulinen method), Relative Excess Risk using generalized linear model with Poisson distribution<br>(cause-specific survival) | Patients with a very low SES had lower overall and cancer-specific survival compared to very high SES group.<br>Cancer stage only partly explains observed socio-economic differences in breast cancer survival.<br>Socio-economic status remained a significant independent prognostic factor of survival. | Age, year of diagnosis, histology, grade, T-stage, nodal status, distant metastases, surgery, and adjuvant treatment |
| Beckmann et al, 2016 | Australia | South Australia Cancer Registry linked with public/private hospital separation data, public/private radiotherapy and clinical cancer registries (teaching hospitals) | South Australia | 2003-2008 | 50-79 | Colorectum | Index of relative Socioeconomic Advantage and Disadvantaged (IRSAD) 2006 (area-based) | 5 | Kaplan-Meier method (Crude cancer-specific survival), Competing risk regression (Fine and Gray method) | Patients from the most advantaged areas had better survival compared with patients from disadvantaged areas.<br>Survival inequalities were not explained by differential stage at diagnosis, patient factors, other tumour characteristics, co-morbidity, and treatment modalities. | Age, sex, year of diagnosis, place of residence, cancer site, stage, grade, co-morbidity, primary treatments |
| Berglund et al, 2010 | Sweden | Regional Lung Cancer Registry | Central Sweden | 1996-2004 | 30-94 | Lung<br>(Non-small cell) | Education level (individual level measure, main | 3 | Kaplan-Meier method (Crude cause-specific | Cause-specific survival was higher among patients from high education level. | Cause-specific crude survival (both SES indicators): |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | indicator of socioeconomic position)<br><br>Socioeconomic index (SEI) based on the occupation of the household | 3 | cancer survival), Cox proportional hazards regression | Stage at diagnosis was not different between educational groups.<br>The authors observed social inequalities in 1- and 3-year crude survival for all patients,<br>but, after adjustment for known prognostic factors and treatment,<br>a social gradient in survival remained only among women with early-stage disease.<br>In men with stage III disease, the reverse pattern was observed, with higher risk of death in patients with high education level. | Sex, age, stage at diagnosis<br><br><u>Cause-specific hazard models (Educational level):</u><br>Sex, age at diagnosis, histopathology, performance status, smoking status, treatment<br>(stratified by stage) |
| Berglund et al, 2012 | England | Thames Cancer Registry | South East England | 2006-2008 | ≤59-≥80 | Lung | Socioeconomic Index (SEI) based on the income domain of the 2007 Indices of Deprivation and postcode | 5 | Logistic regression, Cox proportional hazards regression, Mortality rates modelled with flexible parametric survival models using a restricted cubic spline | Overall survival was higher in the most affluent group, especially for early stages.<br>While survival in advanced stage was poor in all socioeconomic quintiles with minimal difference between affluent and deprived patients.<br>Inequalities in survival from lung cancer could not be fully explained by differences in stage at diagnosis, co-morbidity and type of treatment. | Sex, age at diagnosis, comorbidity, treatment |
| Bharathan et al, 2011 | England | Northern Region Colorectal Cancer Audit Group | Northern England | 1998–2002 | ≤60->80 | Colorectum | Indices of Multiple Deprivation (IMD) 2004 (area-based) | 5 | Logistic regression, crude overall survival (Kaplan-Meier method), Cox proportional hazards regression, Relative survival (Hakulinen-Tenkanen method) | Overall and relative 5-year survival was higher among affluent patients.<br>The difference was partly explained by variation in co-morbidity, urgency of surgery and curative resection status.<br>Deprivation remained as a significant independent predictor of overall survival. | Age, sex, grade, tumour site and differentiation, stage, operative urgency and resection |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Booth et al, 2010 | Canada | Ontario Cancer Registry | Ontario | 2003-2007 | NA | Breast, colon, rectum, non-small cell lung, cervix, and larynx | SES (based on community median household income, census 2001) | 5 | Overall and cancer-specific survival (Kaplan-Meier method), Cox proportional hazards regression | Overall survival was different across socio-economic groups for all cancers. Socio-economic disparities were found in cancers of breast, colon, and larynx.<br>Differences in stage at diagnosis partially explained socio-economic inequalities in breast cancer survival (no other cancers). | Age, stage at diagnosis |
| Bouchardy et al, 2006 | Switzerland | Geneva cancer registry | Geneva | 1980-2000 | <70 | Breast | SES (Based on the occupation | 4 | Overall and disease specific survival (actuarial method), Cox proportional hazards regression | Women from low socio-economic status had higher risk of dying due to breast cancer.<br>Socio-economic inequalities are partly explained by stage at diagnosis, tumour characteristics, method of detection (screening, symptom, other), sector of care (public, private) and treatments. | Age, period of diagnosis, country of birth, marital status, method of detection, stage, histology, tumour characteristics, sector of care and treatment |
| Braaten et al, 2009 | Norway | NOWAC (Norwegian Women and Cancer Study) | Norway | 1996-2005 | 34-69 | Colon and rectum, lung, breast, ovary and other malignancies | Years of Education<br>Gross household Income | 4<br>5 | Cox proportional hazards regression | Both years of education and gross household income were inversely associated with all-cause cancer mortality.<br>Higher-educated women with ovarian cancer had lower risk of dying while mortality risk among colorectal cancer patients increased with years of education (not with income).<br>Educational inequality in overall survival from colon and rectum cancer is explained partially by stage at diagnosis and partly, although less so, by smoking and alcohol drinking.<br>For ovary cancer, stage at diagnosis and smoking status prior to diagnosis did not explain the observed | Age, household size, marital status, stage, smoking, BMI, physical activity, parity, hormone replacement therapy, contraceptives, alcohol, diet, region of living |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | differences across education groups. | |
| Brookfield et al, 2009 | United States | Florida Cancer Data System (FCDS) linked to Agency for Healthcare Administration (AHCA) | Florida | 1998-2003 | All ages | Cervix | Community poverty level (based on postal code) | 4 | Kaplan-Meier method (median survival), Cox proportional hazards regression (overall survival) | Survival was significantly lower among disadvantaged patients as compared with affluent patients.<br>Tumour characteristics and treatment explained some of the observed socio-economic disparities in survival. | Age, race, ethnicity, comorbidities, insurance status, tumour stage, grade, histology, and treatments |
| Byers et al, 2008 | Unite States | Patterns of Care (POC) Study of the National Program of Cancer Registries (NPCR) | California, Colorado, Illinois, Louisiana, New York, Rhode Island, and South Carolina | 1997 | ≥25 | Breast, colorectum, prostate | SES (based on the education and income levels of the census tract of residence) | 3 | Cox proportional hazards regression | Survival was lower among individuals with breast cancer living in low-SES areas compared with those in affluent areas.<br>Socioeconomic inequalities in 5-year survival after breast cancer was explained by later stage at diagnosis and co-morbidity, while treatment had no mediating effect. | Age, race/ethnicity, comorbidity, stage, treatment (colorectum and breast), sex and subsite (colorectum) |
| Cavalli-Björkman et al, 2011 | Sweden | Two Swedish Clinical Quality Registers on colon and rectal cancer | Central Sweden (Stockholm–Gotland and Uppsala–Örebro regions) | 1995-2006 (rectal)<br>1997-2006 (colon) | <75 | Colon and rectum | Educational level | 3 | Kaplan-Meier method (overall survival), Cox proportional hazards regression, Relative Survival, Excess mortality rates modelled using Poisson regression | Highly educated patients with colon or rectum cancer had higher survival.<br>Differences in elective or emergency surgery and type of hospital or preoperative radiotherapy for rectum cancer did not contribute to higher excess risk of death due to colon or rectum cancer in patients with low education. | Age, sex<br>Stratified by stage |
| Chu et al, 2016 | Canada | Princess Margaret Hospital/cancer centre | Toronto | 2003-2010 | All ages | head and neck (squamous cell carcinoma) | Neighbourhood-level SES based on postcode derived from 2006 Canada Census | 5 | Cox proportional hazards regression, logistic regression | Overall survival was worse among patients with lower socio-economic status, which may be due to differences in smoking, alcohol consumptions and stage at diagnosis. | Age, sex, stage,<br>Alcohol consumption, smoking status |
| Dalton et al, 2015 | Denmark | Danish Lung Cancer Register | Denmark | 2004-2010 | 30-84 | Lung | Education<br>Income | 3<br>3 | Logistic regression, Cox proportional hazards regression | Lung cancer survival was different by all socioeconomic status indicators. | Age, gender, period, treatment, comorbidity, performance status |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Educational inequality in survival partly explained by differential stage, first-line treatment, comorbidity and performance status. | Income was adjusted for education. |
| Danzing et al, 2014 | United States | SEER (Survival, Epidemiology and End Results) registry | United States | 2004-2010 | ≥18 | Kidney | Socioeconomic Status (County level) | 4 | Kaplan-Meier method, Cox proportional hazards regression, | Low socio-economic status was independently associated with poorer survival from renal cancer. Authors suggested that the observed difference may be explained by late stage at diagnosis. | Age, gender, race, grade, histology, year of surgery, procedure type, place of residence, and marital status |
| Downing et al, 2007 | England | Northern and Yorkshire Cancer Registry | Northern and Yorkshire regions | 1998-2000 | All ages | Breast | Socioeconomic background was defined using the Townsend Index for area of residence | 4 | Logistic regression, Cox proportional hazards regression | Women from more deprived areas had increased risk of death, which could be partly explained by stage at diagnosis | Age, stage |
| Eaker et al, 2009 | Sweden | Regional Breast Cancer Register of the Uppsala/ Orebro Region | Central Sweden | 1993-2003 | 20-79 | Breast | Level of education | 4 | Cox proportional hazards regression, relative survival | Survival was lower among disadvantaged patients. Differences in diagnostic intensity, tumour characteristics and primary treatments did not explain educational inequalities in breast cancer survival. | Age, year of diagnosis, diagnostic intensity, tumour characteristics and treatments. Stratified by stage at diagnosis |
| Eriksson et al, 2013 | Sweden | Swedish Melanoma Register | Sweden | 1990-2007 | All ages | Melanoma | Level of education | 3 | Kaplan-Meier method, Cox proportional hazards regression | Cause-specific survival was lower among low educated patients which is partially explained by advanced-stage presentation. | Age, gender, clinical stage at diagnosis, tumour site, histogenetic type, tumour ulceration, tumour thickness, Clark's level of invasion, living area, period of diagnosis (all models were stratified by healthcare region) |
| Feinglass et al, 2015 | United States | National Cancer Data Base (NCBD) hospital-based cancer registry | United States | 1998-2006 | All ages | Breast | Socioeconomic status (from patients' combined ZIP | 6 | Cox proportional hazards regression, | The highest SES group had better survival compared with the lowest. | Age, hospital characteristics, time period, insurance status, race and |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | code quartiles of census-based median income and educational attainment at the time of diagnosis) | | Kaplan-Meier method | Disparities in disease stage, insurance status and treatment explained some of survival inequalities. Co-morbidity explained only a very small proportion of the survival gap. | ethnicity, stage, type of treatment |
| Forrest et al, 2015 | England | Linked dataset of the Northern and Yorkshire Cancer registry and Hospital Episode Statistics and lung cancer audit data | Northern and Yorkshire regions | 2006-2009 | All ages | Lung | Index of Multiple Deprivation (IMD) | 5 | Logistic regression | Survival was significantly lower in the most deprived patients.<br>Inequalities in survival from lung cancer were partly explained by differences in receipt of the treatment.<br>Stage of disease and performance status did not contribute to the observed differences. | Age, sex, histology, year of diagnosis, comorbidity, timely GP referral, stage, performance status, type of treatment, timely 1st treatment |
| Frederiksen et al, 2012 | Denmark | Danish national lymphoma database (LYFO) | Denmark | 2000-2008 | ≥25 | Non-Hodgkin Lymphoma | Education (used in multivariable analysis)<br>Household income | 3<br>4 | Cox proportional hazards regression, Kaplan-Meier method | Patients with low socioeconomic position had lower survival.<br>Co-morbidity slightly contributed to survival differences. Other clinical prognostic factors such as stage at diagnosis, performance status, extranodal involvement and level of LDH partly explained differences in survival. | Age, sex, year of operation, clustering at the department level, comorbidity, performance status, stage, extranodal involvement, level of LDH, IPI score |
| Frederiksen et al, 2009 | Denmark | National clinical database of the Danish Colorectal Cancer Group (DCCG) | Denmark | 2001-2004 | 61-76 | Colon and rectum | Income<br>Education<br>Housing status | 1<br>3<br>2 | Cox proportional hazards regression | Survival was superior in patients with higher SES compared with those with low SES.<br>The observed association was partly explained by comorbidity and to a lesser extent by lifestyle, while stage at diagnosis, mode of admittance, type of surgery and specialisation of surgeon did not contribute to survival differences. | Age, sex, year of operation, alcohol, tobacco, BMI, comorbidity, stage, mode of admittance, specialist surgeon, type/radicality of operation<br>Income was adjusted for education. |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Housing status was adjusted for income and education |
| Groome et al, 2006 | Canada | Linked cancer research database (Ontario Cancer Registry, hospital discharged data, and radiotherapy data) | Ontario | 1982-1995 | All ages | Larynx | Area-level SES (based on adjusted median household income from the Canadian Census) | 5 | Cause-specific survival (actuarial method), Conditional Cox proportional hazards regression | Socio-economic status was associated with laryngeal cancer outcomes; survival disparity was only observed for glottic cases.<br>The anatomic extent of the tumour explained some of differences in survival from glottic cancer. | T-category (the anatomic extent of the tumour) |
| Guo et al, 2015 | United States | Florida Cancer Data System (FCDS) | Florida | 1996-2010 | ≥20 | Oral and pharynx | SES (using census tract-level poverty information from the 2000 US census data) | 3 | Cox proportional hazards regression, mediation analysis | Low socio-economic status was associated with poorer survival.<br>Higher rate of individual smoking was the major contributor to poorer survival in disadvantaged patients. The mediation effect of individual smoking was larger in the middle SES group than in the low SES group. | Age at diagnosis, gender, race/ethnicity, marital status, health insurance, year of diagnosis, anatomic site, stage, treatment, regional smoking |
| Hines et al, 2014 | United States | Georgia Comprehensive Cancer Registry (GCCR) | Georgia | 2000-2007 | 45-85 | Colorectum | Census Tract Socioeconomic Status | 3 | Kaplan-Meier method, Cox proportional hazards regression | Patients from low socio-economic position had higher risk of death after colorectum cancer. Survival inequality was not explained by tumour grade, stage and treatment. | Age, gender, race, disease stage, tumour grade, geography, treatment (surgery, chemotherapy, or radiation) |
| Ibfelt et al, 2015 | Denmark | Danish Gynaecological Cancer Database (DGCD) | Denmark | 2005-2010 | ≥25 | Ovary | Education<br>Disposable income | 3<br>3 | Logistic regression, Cox proportional hazards regression | There were socio-economic inequalities in survival after ovarian cancer that were not fully explained by disease stage, histology and co-morbidities. | Age, comorbidity, ASA score, cancer stage, tumour histological subtype<br>Income was adjusted for education and cohabitation status |
| Ibfelt et al, 2013 | Denmark | Danish Gynaecological Cancer Database (DGCD) | Denmark | 2005-2010 | ≥25 | Cervix | Education<br>Disposable income | 3<br>3 | Cox proportional hazards regression | Survival was lower among women with minimum education and lower income.<br>Socioeconomic disparities in survival partly explained by | Age, comorbidity, cancer stage, smoking status<br>Cohabitation status was adjusted for |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | stage at diagnosis and less by comorbidity and smoking status. | education. Income was adjusted for education and cohabitation status |
| Jack et al, 2006 | England | Thames Cancer Registry | South-east London | 1998 | All ages | Lung | Index of Multiple Deprivation (IMD) | 5 | Logistic regression | Variation in treatment partly explained differences in overall survival. | Age, sex, histology, stage and basis of diagnosis, treatment |
| Jeffreys et al, 2009 | New Zealand | New Zealand Cancer Registry | New Zealand | 1994-2003 | 15-99 | All malignancies | Socioeconomic position (SEP) using an area-based measure according to place of residence at the time of diagnosis | 4 | Relative survival, weighted linear regression | Socioeconomic inequalities in cancer survival were evident for all major cancers.<br>Extent of disease explained some of the differences in survival from breast (33.8%), colorectal cancer (12.2%) and melanoma (50%) and it explained all socio-economic inequalities in survival of cervix cancer. | Age |
| Jembere et al, 2012 | Canada | Ontario Cancer Registry | Ontario | 1990-2009 | All ages | Liver (Hepatocellular Carcinoma) | Neighbourhood Income | 5 | Kaplan-Meier method, Cox proportional hazards regression | Patients with higher SES had superior survival compared with those with low SES.<br>Survival disparity was mostly explained by receiving curative treatment and less by co-morbidity. | Age, sex, comorbidity, ultrasound screening, and curative treatment |
| Johnson et al, 2014 | United States | Georgia Comprehensive Cancer Registry (GCCR) | Georgia | 2000-2009 | 50-85 | Lung (non-small cell) | Census Tracts Socioeconomic Status | 4 | Cox proportional hazards regression | Patients living in deprived areas with lowest level of education and highest level of deprivation had poorer survival.<br>Cancer stage at diagnosis, tumour grade and treatment partly explained survival differences. | Age, gender, race, stage, tumour grade, and treatment (surgery, chemotherapy, radiation) |
| Kim et al, 2011 | United States | Cancer Surveillance Program (CSP) | Los Angeles | 1988-2006 | All ages | Rectum | Household income | 3 | Kaplan-Meier method, Cox proportional hazards regression | Affluent patients had higher survival after rectum cancer compare to underprivileged patients.<br>Socio-economic inequity in survival was not fully | Age, sex, race/ethnicity, immigration status, tumour grade, extent of disease, time |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | explained by differential access to treatment, tumour grade and extent of disease. | period, chemotherapy, radiotherapy, surgery |
| Larsen et al, 2015 | Denmark | Danish Diet, Cancer and Health Study | Denmark | 1993-2008 | 54-74 | Breast | Educational level<br>Income | 3<br>3 | Cox proportional hazards regression | Lower education was associated with higher risk of death.<br>Educational differences in survival were partly explained by metabolic indicators, smoking status, alcohol intake and less by disease-related prognostic factors and co-morbidity. | Age, tumour size, lymph node status, no. of positive lymph nodes, grade and receptor status, comorbidity, metabolic indicators (BMI, waist circumference, diabetes, smoking and alcohol at baseline and at time of diagnosis) |
| Launay et al, 2012 | France | Calvados digestive cancer registry | Calvados | 1997-2004 | All ages | Oesophagus | Townsend index | 5 | Relative survival, Excess hazard model based on maximum likelihood estimation (Esteve model) | Deprived patients had poorer survival compared with affluent patients.<br>Survival disparities not explained by differences in cancer extension or morphology at diagnosis, surgery, radiotherapy and chemotherapy. | Age, sex, year of diagnosis, morphology, stage, treatments (surgery, radiotherapy, chemotherapy) |
| Lejeune et al, 2010 | England | Thames Cancer Registry<br>Eastern Cancer Registration and information centre<br>Northern and Yorkshire Cancer Registry and information service | England | 1997-2000 | ≥15 | Colorectum | Townsend index (Area-level socio-economic information) | 5 | Relative survival, generalised linear model with Poisson | Affluent patients had better survival compared with disadvantaged patients.<br>Tumour stage partly explained socio-economic inequalities in survival after colorectal cancer. Early treatment (within the first month following diagnosis) greatly reduced socio-economic differences in survival. | Age, receipt of treatment and time-to-treatment, and stage at diagnosis |
| Li et al, 2016 | England | Northern and Yorkshire Cancer Registry | North East England, Yorkshire and Humber regions | 2000-2007 | 15-99 | Breast | Index of Multiple Deprivation (IMD) | 5 | Net survival, mediation analysis | Socioeconomic inequalities in breast cancer survival were partly explained by differences in stage at diagnosis, surgical treatment. | Year and regions at diagnosis, tumour stage, treatment |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| McKenzie et al, 2010 | New Zealand | New Zealand Cancer Registry | New Zealand | 2005-2007 | All ages | Breast | New Zealand deprivation index (NZDep) | 4 | Relative survival, Excess mortality ratios using generalised linear model (Poisson) | Survival was poorer among underprivileged women. Differential access to health care was a major contributor to theses socioeconomic inequities. | Age, ethnicity, tumour factors (extent, size and grade), hormone status (ER, PR, and HER2 status) |
| O'Brien et al, 2015 | United States | Florida Cancer Data System | Florida | 1996-2007 | ≥18 | Male Breast | Neighbourhood-level SES (based on percentage of households in a census tract 2006) | 4 | Kaplan-Meier method, Cox proportional hazards regression | Higher SES groups had lower risk of death compared with the lowest SES group.<br>Late stage at diagnosis due to poor access to diagnostic and health care services may partly explain worse overall survival among men from lower socio-economic areas. | Age at diagnosis, race/ethnicity, marital status, insurance status, tobacco use, geographic residence, clinical and hospital characteristics, tumour characteristics, treatments, and comorbidity |
| Quaglia et al, 2011 | Italy | Liguria Region Cancer Registry | Genoa | 1996-2000 | All ages | Breast | Deprivation index (based on the information drawn from the census of 2001) | 5 | Relative survival (Hakulinen–Tenkanen method), Excess mortality ratios using generalised linear model (Poisson) | Deprived women had poorer survival compared with affluent women.<br>Observed disparities could be partly explained by differences in tumour characteristics and the treatment received. | Age, tumour size, lymph nodes status, oestrogen receptor status, type of surgery, radiotherapy, lymphadenectomy, hormonal therapy |
| Robertson et al, 2010 | Scotland | Scottish Head and Neck Audit (prospective cohort study) | Scotland | 1999-2001 | All ages | Head and Neck | Area-based SES (using the 2001 DEPCAT score) | 3 | Cox proportional hazards regression | Socio-economic differences in survival from head and neck cancers explained by variations in stage at diagnosis, tumour differentiation, smoking, alcohol drinking and patient's performance status. | Age, stage, tumour site, differentiation, WHO performance status, smoking and alcohol drinking status |
| Rutherford et al, 2013 | England | Eastern Cancer Registration and Information Centre (ECRIC) | East of England | 2006-2010 | ≥30 | Breast | Index of Multiple Deprivation (IMD) | 5 | Relative survival, Excess mortality rate ratios (flexible parametric model) | Survival disparities among women with middle SES almost explained by stage at diagnosis while disease stage had no effect on survival among the most deprived women. | Age, stage |
| Seidelin et al, 2016 | Denmark | Danish Gynaecological Cancer Database | Denmark | 2005-2009 | 25-90 | Endometrium | Education level | 3 | Logistic regression, Cox proportional hazards regression | Minimum education was associated with higher risk of death. | Age, cohabitation status, body mass index (BMI), smoking |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Differences in stage at diagnosis partially explained educational inequalities in survival from endometrial cancer. Comorbidity did not alter the results. | status, comorbidity, stage |
| Shafique et al, 2013 | Scotland | Scottish Cancer Registry | West of Scotland | 1991-2007 | All ages | Prostate | Scottish Index of Multiple Deprivation (SIMD) 2004 score<br>(Area-based measure of socioeconomic circumstances) | 5 | Relative Survival (Ederer II), Relative excess risk (full likelihood approach), Cox proportional hazards regression | Socio-economic inequalities exist in survival of prostate cancer and widened over time.<br>Differential stage at diagnosis only partly explained deprivation gap in prostate cancer survival. | Age at diagnosis, Gleason grade, period of diagnosis |
| Sprague et al, 2011 | United States | 2 population-based, case-control studies | Wisconsin | 1995-2003 | 20-69 | Breast | Individual-level<br>-Education<br>-Income-to-poverty ratio<br>community-level<br>% without a high school diploma<br>% in poverty | <br>3<br>3<br><br>3<br>3 | Cox proportional hazards regression | Survival rate was lower among patients with less education, less income, or living in areas with low community-level education.<br>Screening participation, stage at diagnosis explained survival differences by individual-level income and explained some of the survival differences by individual- and community-level education.<br>Lifestyle factors had a minor effect on the observed differences in survival. | Age, year of diagnosis, histologic type, stage at diagnosis, mammography use, smoking history, family history of breast cancer, BMI, postmenopausal hormone use and socio-economic variables (as required) |
| Stromberg et al, 2016 | Sweden | National Cancer Register and the national Swedish Melanoma Quality Register | Southern and the Western Sweden | 2004-2013 | ≥15 | Melanoma | Education level | 3 | Relative survival, Excess five-year mortality (maximum likelihood model) | Stage at diagnosis explained some of educational inequalities in survival from cutaneous malignant melanoma. | Age, sex, residential area, stage at diagnosis |
| Ueda et al, 2006 | Japan | Osaka Cancer Registry | Osaka | 1975-1997 | All ages | Cervix and corpus | Unemployment<br>Education<br>(Municipality-based socioeconomic status) | 3<br>3 | Kaplan-Meier method (crude survival), Cox proportional hazards regression | Differences in survival for cervix and corpus cancer patients were observed among high, middle and low education/ unemployment municipalities. | Age, cancer stage, histology, treatment type |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Cancer stage, histology and treatment only partly explained observed socio-economic differences in survival from cervix cancer. Stage and histology partially explained socio-economic inequality in survival from corpus cancer; treatment did not make any difference. | |
| Walsh et al, 2014 | Ireland | Irish National Cancer Registry | Ireland | 1999-2008 | 15-99 | Breast | SAHRU index of social deprivation (Area-based) | 5 | Modified Poisson regression, Cox proportional hazards regression, Age-standardised 5- and 10-year cause-specific survival | Women from the most deprived areas were 33% more likely to die of breast cancer compared with women from the least disadvantaged areas.<br>Patient and tumour characteristics partially explained deprivation-related inequality; Treatment did not make any significant difference. | Stratified by age, TNM stage and tumour grade<br>Adjusted for method of presentation, smoking status, region of residence, diagnosis year, tumour morphology, hormone receptor status, treatments within 12 months after diagnosis |
| Woods et al, 2016 | England<br>Australia | West Midlands and New South Wales cancer registries | West Midlands<br>New South Wales | 1997-2006 | 50-65 | Breast | SES based on the unemployment rate of the small area of residence | 5 | Net survival (Pohar-Perme method) | Survival was almost similar among affluent and deprived women in New South Wales irrespective of way of diagnosis; in the West Midlands there were significant large differences among affluent and deprived women in both screening groups.<br>Deprivation gap in survival partly explained by screening (early diagnosis). | Adjusted for region, calendar year, age, lead-time bias and over-diagnosis |
| Yu et al, 2009 | United States | 13 population-based cancer registries participated in the SEER program | 13 states in the US | 1998-2002 | ≥15 | Breast | Area-based measure of socio-economic status based on two characteristics in county of residence: "percent of | 4 | Cox proportional hazards regression (cause-specific survival) | Women from the most disadvantaged areas had higher risk of cancer-related death compared with women from affluent areas, which was mostly explained by stage at diagnosis and less by first course treatment. | Age (group) at diagnosis, year of diagnosis, AJCC stage, number of positive lymph nodes, first course treatments, race, rural/urban residence at diagnosis |

| Paper | Country of study | Data sources/ Settings | Population included | Years of diagnosis | Age at diagnosis | Anatomic site of cancer(s) | Measures of socio-economic position (SEP) | No. of groups | Analyses | Description of results | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | adults with < 12-year education" and "percent of families living below the federal poverty line" | | | | |
| Yu et al, 2008 | Australia | NSW Central Cancer Registry | New South Wales | 1992-2000 | 15-89 | All malignancies (13 major types of cancers) | Socio-Economic Indexes for Areas (SEIFA) | 5 | Relative survival (period method), relative excess risk model using Poisson regression | Patients from the most disadvantaged areas had poorer survival for cancers of the stomach, liver, lung, breast, colon, rectum, ovary, and all cancers combined.<br>After controlling for stage at diagnosis, the significant survival differences between socio-economic groups disappeared for ovary cancer; the effect of SES on survival from liver and breast cancer decreased after adjusting for stage.<br>The survival differences for all cancers in the most disadvantaged areas decreased after controlling for remoteness of residence. Additional adjustment for stage did not change the results. | Age group at diagnosis, sex, and year of follow-up, stage at diagnosis, remoteness of residence |

***Factors explaining socio-economic inequalities in survival***

***Cancer-specific survival***

***Breast cancer***

Twelve studies examined the underlying causes of educational and socio-economic inequalities in breast cancer survival: seven from Europe, [9,13,18,30,32,36,37] two from the US, [47,48] two from New Zealand [53,54] and one from Australia. [56] A study from the Netherlands conducted stage-specific analysis and found that higher stage of breast cancer at diagnosis did not explain the worse survival among underprivileged women. [9] A study from Switzerland applying the difference method reported that stage at diagnosis, other tumour characteristics, method of detection (screening, symptom, other), receiving suboptimal treatment and sector of care (private or public) only explained part of the observed inequalities in breast cancer survival, with an unadjusted HR of 2.4 [95%CI 1.6 – 3.5] for the least educated cases compared with highly educated cases, and a corresponding multivariable-adjusted HR of 1.7 [95%CI 1.1 – 2.5]. [13] A study from New Zealand also used the difference method and found that extent of disease explained 33.8% of the deprivation gap in breast cancer survival; [53] other research in New Zealand using similar methods reported consistent findings that tumour factors only partly explained the observed differences in survival. [54] A Swedish study comparing relative risk models with and without adjusting for potential explanatory factors found that inequalities in breast cancer survival by level of education were not mediated by variation in diagnostic intensity (i.e. the number of nodes examined and whether proliferation or hormone receptor status was checked), tumour characteristics or treatment. [18] In contrast, a study from Italy showed that lower survival from breast cancer in socio-economically deprived women (age adjusted HR 2.34; 95%CI 1.23 – 4.46), relative to affluent patients, was partly explained by tumour characteristics and the treatment received (fully adjusted HR 1.82; 95%CI 0.95 – 3.48). [30] A British study conducted stage-specific analysis and found that lower survival from breast cancer among women from middle socio-economic background, relative to the most advantaged, was entirely explained by stage at diagnosis, while stage had no mediating effect on worse survival among the most disadvantaged patients. [32] A US study measuring socio-economic position both at an individual and community level, found that variation in annual screening mammography participation and disease stage explained some of the socio-economic differences in survival following breast cancer diagnosis, while lifestyle factors had a minor effect. [47]Applying the difference method, a study from Ireland found that method of presentation (symptomatic, screening, incidental, unknown), stage of disease, tumour grade, hormone receptor status, histological subtype, smoking status, co-morbid conditions, region of residence and overall treatment accounted for about half of the observed survival inequalities by SEP. [36] Another study that conducted breast-cancer screening-specific analysis using data from England and Australia observed no differences in survival across socio-economic groups in New South Wales, Australia, irrespective of method of diagnosis (screen-detected or non-screen-detected); [37] however, in the West Midlands, England, there were inequalities in survival

between affluent and disadvantaged women with both screen-detected and non-screen-detected breast cancer, which were not explained by extent of disease at diagnosis. [37] Lastly, a US study found that higher risk of death among the most disadvantaged women with breast cancer relative to the least disadvantaged (HR 1.19; 95%CI 1.13 – 1.26; adjusted by age and year of diagnosis) was mostly influenced by stage at diagnosis (HR 1.10; 95% CI 1.04 – 1.16; additional adjustment for stage) and less by first-course treatment (HR 1.08; 95%CI 1.03 – 1.14; after further adjustment). [48] Another study from Australia, applying the difference method to excess mortality rates, concluded that stage at diagnosis partly contributed to socio-economic inequalities in breast cancer survival. [56]

***Colorectal cancer***

Of the five studies that investigated cancer-specific survival after diagnosis with colon or rectal cancer, an Australian study, reporting multivariable-adjusted HRs, found that worse survival in patients from the most disadvantaged areas was not explained by differential stage at diagnosis, patient factors or other tumour characteristics, nor by differences in co-morbidities or treatment modalities. [55] A study from Sweden concluded that differences in elective or emergency surgery, type of hospital or treatment with preoperative radiotherapy for rectal cancer did not contribute to the higher excess risk of death due to colon or rectal cancer observed for patients with low education (relative risk estimates after adjusting for these variables were not given). [15] Another study from New Zealand found that extent of disease explained an estimated 12% of the observed socio-economic differences in colorectal cancer survival. [53] Similarly, a study from England using the difference method reported tumour stage as a contributing factor to worse survival among colorectal cancer patients living in disadvantaged areas with the EMRR 1.20; 95%CI 1.16 – 1.25 for the most deprived group, relative to the most affluent, decreased to EMRR 1.13; 95%CI 1.09 – 1.16; variations in the provision of treatment within the first month after diagnosis also appeared to explain these inequalities (EMRR 1.04; 95% CI 0.95 – 1.15, adjusted for age at first attendance, stage and treatment). [28] In contrast, an Australian study applying a similar method found that disease stage did not have any explanatory role in the observed differences in survival from colorectal cancer. [56]

***Head and neck cancer***

Three studies assessed the association of socio-economic disadvantage with survival from head and neck cancer. A study from Canada found that the anatomic extent of the tumour accounted for 3-23% of differences in survival from glottic cancer; [51] the authors also reported waiting time to receive treatment as an explanatory factor for worse survival among disadvantaged patients. [51] A US study of oral and pharyngeal cancer reported cigarette smoking as a contributing factor to socio-economic inequalities in survival; the authors reported that the indirect effect of smoking was larger for patients in the middle socio-economic group (21%) than for those in the lowest category (13%). [42] A Scottish study comparing HRs with and without adjusting for potential mediators proposed that socio-economic

differences in survival from head and neck cancers (deprived compared with affluent cases, unadjusted HR 1.33; 95%CI 1.06 – 1.68) were explained by variations in stage at diagnosis, tumour differentiation, alcohol drinking, smoking status and patient performance status (fully adjusted HR 0.93; 95%CI 0.64 – 1.35). [31]

***Other cancer types***

Of the remaining studies, two from Sweden [19,35] and one from New Zealand [53] assessed cancer-specific survival from melanoma by education level or an area-based measure of SEP. A Swedish study, comparing models with and without adjusting for mediators of interest, found that stage at diagnosis largely explained worse survival among low educated relative to highly educated individuals (age and sex adjusted HR 1.58; 95%CI 1.40 – 1.77 decreased to HR 1.19; 95%CI 1.06 – 1.34 after adjusting for clinical stage). [19] Another study from Sweden reported consistent findings. [35] A New Zealand study showed that 50% of the observed deprivation gap in survival from melanoma was explained by extent of the disease. [53] A study of oesophageal cancer from France applying the difference method concluded that worse survival among patients living in deprived areas was not explained by differences in stage, morphology, surgery, radiotherapy or chemotherapy. [27] A US study conducted tumour characteristics-specific analysis and suggested that worse survival from renal cancer among individuals from lower socio-economic background may be partly explained by advanced tumour at diagnosis, or tumour size or grade. [40] An Australian study compared excess mortality rates with and without accounting for stage of disease, concluded that stage at diagnosis was the underlying reason for worse survival from ovarian cancer in women living in the most disadvantaged areas. [56] Another study from New Zealand found that the extent of disease fully explained the observed worse survival from cervical cancer among more deprived women, while it only contributed to 5% of the deprivation gap in survival from uterine cancer. [53] A Swedish study of lung cancer showed that better survival from early stage disease in women with high educational level, relative to low educated, persisted after adjusting for treatment (HR 0.33; 95%CI 0.14 – 0.77), while for stage III, the observed worse survival comparing high versus low educated men also remained (fully adjusted HR 1.41; 95%CI 1.04 – 1.90). [10] Lastly, a study from Scotland stratifying the relative risk estimates by Gleason score found that differential stage of prostate cancer contributed to some of the observed deprivation-based gap in survival. [34]

***Overall survival***

***Breast cancer***

We identified eight studies that assessed overall survival following breast cancer diagnosis. A Dutch study observed socio-economic differences in overall survival for women with screen-detected, non-screen-detected and interval breast cancers. [8] Worse survival among more disadvantaged women diagnosed via screening was partly explained by the higher prevalence of co-morbidities. For women with non-screen-detected and interval breast cancers, inequalities in survival appeared to be largely

explained by differences in stage at diagnosis, while treatment explained very little. [8] A Canadian study found that later stage partially contributed to worse overall survival for women from lower socio-economic areas. [49] Similarly, a study from England noted that the higher risk of death for women from more socio-economically disadvantaged areas was largely explained by their generally more advanced stage, possibly due to lower screening uptake in deprived areas. [17] A US study reported that differences in stage at diagnosis and in the prevalence of co-morbid conditions largely contributed to socio-economic inequalities in survival following breast cancer. [39] Another study from the US found that overall survival gap across socio-economic groups was mainly explained by insurance status, disease stage and treatment, and less by co-morbidities. [41] A study conducted in Denmark showed that metabolic indicators, smoking status and alcohol intake accounted for part of the higher risk of death among women with lower educational attainment, while disease-related prognostic factors and co-morbidities played on a minor role. [26] Another study, from England, found that socio-economic inequalities in overall survival after breast cancer were partly mediated by differential stage and surgical treatment. [29] The only study of male breast cancer, conducted in the US, suggested that later stage due to poor access to diagnostic and health care services may partly explain worse overall survival among men from lower socio-economic neighbourhoods. [46]

***Colorectal cancer***

Six studies investigated the association of SEP and education with overall survival following diagnosis with colon or rectal cancer. One study from England reported that variations in co-morbidities, urgency of surgery and curative resection status explained part of lower overall survival among the most deprived patients with colorectal cancer. [12] Another study of colon cancer, conducted in Canada, found no evidence that stage at diagnosis contributed to socio-economic differences in overall survival, [49] while a study from Norway found that educational inequality in overall survival from colon and rectal cancer is explained partly by stage at diagnosis and partially, although less so, by smoking and alcohol drinking. [14] A study from Denmark noted that observed socio-economic differences in overall survival from colorectal cancer were partly mediated by co-morbidities and to a lesser extent by health-related behaviours, while stage at diagnosis, mode of admittance (admitted for surgery electively or acutely), type of surgery and specialisation of surgeon did not contribute to these differences. [22] A US study found that worse overall survival among disadvantaged individuals with colorectal cancer was explained in part by disease stage, tumour grade and the treatment received. [43] Another US study of rectal cancer suggested that the survival disadvantage of underprivileged patients relative to affluent cases was partially explained by tumour grade, extent of disease or differential access to treatment. [45]

***Lung cancer***

Five studies examined socio-economic and educational inequalities in overall survival from lung cancer. Of the three studies conducted in England, one found that the higher overall survival in the most

affluent group, especially those with early-stage disease, was partly explained by variations in co-morbidities and treatment. [11] Two other studies also reported that differences in receipt of treatment explained part of the worse overall survival among patients residing in the most deprived areas. [20,25] A study from the US found differential disease stage, tumour grade and receipt of the treatment explained some of the observed overall survival disadvantage among lung cancer patients from areas with higher concentration of deprivation and lower levels of education. [44] Similarly, a study from Denmark noted that educational inequalities in overall survival were partially explained by differences in stage of lung cancer at diagnosis, delivery of first-line treatment, co-morbidity and performance status. [16]

***Prostate cancer***

Of the three studies that investigated prostate cancer, two were conducted in the Netherlands [6,7] and one in the US. [39] One study found that co-morbid conditions, physical activity level and smoking status did not contribute to worse overall survival in patients with lower levels of education. [6] Another study reported that socio-economic-based inequalities in overall survival were partly mediated by differences in treatment selection and by co-morbidity. [7] The US study found that disease stage explained at least part of worse survival among prostate cancer patients either living in poverty or having low educational level. [39]

***Head and neck cancer***

With respect to head and neck cancers, a study from Canada found that worse overall survival among disadvantaged patients was explained by differences in cigarette smoking, alcohol consumption, and stage at diagnosis. [50] In contrast, a second Canadian study of laryngeal cancer specifically found that survival differences among socio-economic groups were not explained by stage at diagnosis. [51]

***Gynaecological cancers***

We identified six studies that explored educational or socio-economic inequalities in relation to overall survival from cancers of the cervix, ovary, corpus or endometrium. A US study of cervical cancer showed that tumour characteristics and treatment explained some of the inequalities in overall survival. [38] A study from Japan reported similar findings that stage of cervical cancer at diagnosis, histology and treatment contributed in part to socio-economic differences in overall survival. [57] A study from Denmark found that overall survival disadvantage in low educated women with cervical cancer was partially explained by stage at diagnosis and, to a lesser extent, by co-morbidity and smoking status. [24] Both studies, from Japan [57] and Denmark, [33] investigating uterine and endometrial cancer found that the worse survival among disadvantaged or less educated women was partly mediated by disease stage and histology, while co-morbid conditions and treatment had no mediating effect. Of the two studies that assessed ovarian cancer, a Danish study reported differential stage at diagnosis, tumour histological type, co-morbidities and health-related lifestyle behaviours as some of the explanatory factors. [23] In

contrast, a study from Norway found that stage of ovarian cancer or smoking status prior to diagnosis did not contribute to overall survival gap between education groups. [14]

***Other cancer types***

Of the remaining studies, a study from Denmark noted that stage at diagnosis contributed in part to educational inequalities in overall survival form non-Hodgkin lymphoma. [21] Lastly, a Canadian study reported variations in the provision of curative treatment and co-morbidity prevalence as major contributing factors to worse overall survival in disadvantaged patients with hepatocellular carcinoma. [52]

***Risk of bias***

Results from the assessment of the risk of bias of the eligible studies are summarised in Supplementary Table 3.2. All included studies had low risk of bias with respect to measurement and classification of the exposure and the outcome. Age at cancer diagnosis, sex (for non-sex-specific cancers) and ethnicity/race (where applicable) were considered to be important confounding domains that should be adjusted for in the analyses. Studies that applied a relative survival framework to estimate EMRRs should have used socio-economic or deprivation-specific population life tables. With respect to confounding, several studies had moderate risk of bias. [1,9,12,15,18,27,37,49] Bias in the selection of participants into the study was low for all studies except one. [31] All studies had a low risk for the domain of bias due to selective reporting of results. With respect to missing data and inappropriate adjustment for potential mediators, most studies were classified as having moderate to high risk of bias. We considered health-related lifestyle factors, screening participation, stage of cancer at diagnosis, co-morbidities and treatment modalities as potential mediators on the causal pathway that should not be adjusted for (Figure 3.2). We assumed rural-urban residence as a potential mediator as SEP generally determines where a person lives, while acknowledging that it might be also a confounder (i.e. rural-urban residence affects SEP as well).

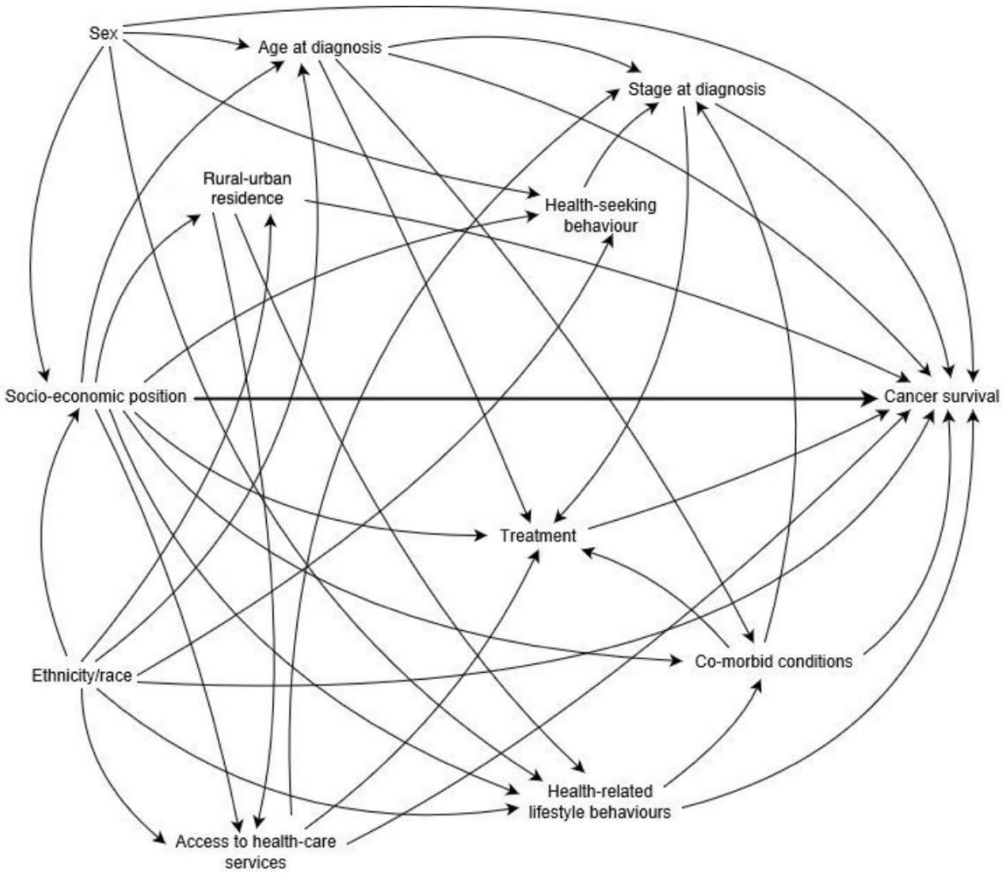


**Figure 3.2.** Directed acyclic graph (DAG) showing assumed causal associations between socio-economic position and cancer survival

### 3.4. Discussion

In this systematic review, studies relatively consistently reported differences in disease stage, other tumour characteristics such as size, grade or morphology, lifestyle behaviours including smoking and excessive alcohol intake, co-morbid conditions and the treatment received as contributing causes of socio-economic inequalities in cancer-specific survival, but the estimated mediating effects of these factors varied across countries and cancer sites. Of the studies investigating survival from breast cancer, the majority reported stage at diagnosis as a contributing factor to worse survival among disadvantaged women, while a few acknowledged the potential role of co-morbidities and treatment. Most research on survival following colon or rectal cancer showed that stage of disease did not explain inequalities in survival, whereas treatment and co-morbid conditions partly contributed to the observed differences. Research on survival from head and neck cancer, found stage at diagnosis, smoking and alcohol intake as the primary reasons for these inequalities. Similarly, for melanoma and cancers of the ovary, cervix, kidney and prostate, disease stage was reported as a contributing factor to the observed survival gap across socio-economic groups.

Findings of studies investigating underlying reasons for socio-economic inequalities in overall survival following a cancer diagnosis were generally in line with studies that assessed cancer-specific survival, although the estimated effects of potential mediators varied relative to studies considering death from a particular cancer as the outcome.

The most recent review published by IARC highlighted several factors, which may contribute to observed inequalities in cancer outcomes. There is compelling evidence from existing literature that individuals with lower levels of income and education have limited awareness about adverse effect of health-related behaviours; therefore, unhealthy diet, physical inactivity, smoking, heavy alcohol intake and co-morbid conditions are more prevalent among disadvantaged people. [58] Stage at diagnosis is cited as the primary reason for inequalities in cancer survival by SEP, possibly due to higher rates of screening participation and better access to diagnostic services among advantaged people. [58] Differential access to treatment facilities and the quality of care received have also been reported as potential contributing factors to worse cancer survival. [58] We should also consider the fact that the mediating effect of these factors may be country-specific, generally due to variation in healthcare systems.

The contribution of the above factors and social or psychological stresses to socio-economic inequalities in cancer survival is not clear due to methodological issues and data limitations. In the absence of more in-depth knowledge, it is challenging to identify and prioritise actionable factors to address survival inequalities and improve cancer outcomes for disadvantaged patients.

#### *Limitations*

The findings of this review should be interpreted with caution mainly due to various measures of SEP (measured at individual or neighbourhood level) and the methods used across included studies to

identify the underlying causes of socio-economic inequalities in cancer survival. The majority of the studies applied the difference method, by which regression models were compared with and without adjusting for potential mediators. This standard approach has some major limitations. The first problem arises when there are unmeasured mediator-outcome confounders. Adjusting for the mediator in the presence of mediator-outcome confounding is inappropriate as it creates a non-causal association between the exposure and the mediator-outcome confounder, which can induce substantial bias, known as collider bias. [59] Another limitation is the assumption of no interaction between the effects of the exposure and the mediator on the outcome (for example, interactions between age at diagnosis and treatment, stage and treatment or co-morbidity and treatment), which may result in invalid inferences. [59,60] Moreover, this approach fails when multiple mediators are of interest and the mediators affect or interact with each other. In this case, adding mediators one-by-one to the model could give biased estimates. [59,60]

About half of the included studies assessed overall survival, which is problematic when exploring the reasons for socio-economic inequalities in cancer survival as there is solid evidence that socio-economic position is associated with death due to causes other than cancer. [61] In addition, for screen-detectable cancers such as breast, colorectal and prostate cancer, the effect of overdiagnosis, lead-time and length-time bias should not be neglected as screen-detected cancers show higher survival, even in the presence of co-morbidities and ineffective treatment.

***Conclusion***

Socio-economic inequalities in cancer survival appear to be partly explained by differences in disease stage, health-related behaviours, chronic conditions and treatment modalities. Discrepancies in findings across studies could be due to variations in the covariates included in the analyses. It is essential that future studies apply novel methods of mediation analysis to generate more reliable evidence about the medical and psychological mechanisms underlying these inequalities, which may lead to better resource allocation and change in cancer control policies to improve cancer survival for all patients.

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## Chapter 4 . Systematic review of rural-urban residence and cancer survival in high-income countries

This systematic review was conducted during the first year of my PhD candidature and submitted to *Cancer* for publication. I conceptualised and led the study, conducted the search, extracted the data and drafted the manuscript. Professor Roger Milne was the second independent reviewer and was involved in the selection of eligible studies and assessment of the risk of bias of included articles. Any disagreements were resolved after consulting the third independent reviewer, Professor Dallas English. R.M and D.E provided advice in the interpretation of results and reviewed and edited the manuscript.

This chapter includes the author-accepted version of the systematic review.
The list of references is formatted according to the journal requirements, with separate numbering to the thesis reference list. Supplementary materials related to this publication are presented in Appendix C.

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**Rural-urban residence and cancer survival in high-income countries: a systematic review**

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**Keywords:** Neoplasms, Cancer survival, Remoteness, Urban, Rural, Systematic review

**Abstract**

There is some evidence that place of residence is associated with cancer survival, but the findings are inconsistent, and the underlying mechanisms by which residential location might affect survival are not well understood. We conducted a systematic review of observational studies investigating the association of rural versus urban residence with cancer survival in high-income countries. We searched the Ovid Medline, EMBASE, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases up to May 31, 2016. Forty-five studies published between 1984 and 2016 were included. We extracted unadjusted and adjusted relative risk estimates with the corresponding 95% confidence intervals. Most studies reported worse survival for cancer patients living in rural areas than those in urban regions. The most consistent evidence, observed across several studies, was for colorectal, lung, and prostate cancer. Of the included studies, 18 did not account for socio-economic position. Lower survival for more disadvantaged patients is well documented; therefore, it could be beneficial for future research to take socio-economic factors into consideration when assessing rural/urban differences in cancer survival. Some studies cited differential stage at diagnosis and treatment modalities as major contributing factors to regional inequalities in cancer survival. Further research is needed to disentangle the mediating effects of these factors, which may help to establish effective interventions to improve survival for patients living outside major cities.

## 4.1. Introduction

The potential influence of patients' place of residence on survival from cancer has come to the attention of many researchers, as it may highlight where health care resources need to be allocated to reduce the burden of cancer and improve cancer outcomes.[1,2]

The majority of studies that have investigated the association between area of residence and cancer survival were conducted in high-income countries, but the findings have been inconsistent.[3-8] Furthermore, the potential roles of stage at cancer diagnosis, comorbidity, treatment, and health-related lifestyle factors in rural/urban differences in cancer outcomes have not been fully explored. A review conducted in 1992 of patterns of cancer mortality and survival in rural and urban regions suggested that residents of rural areas were more likely to be diagnosed at advanced stage compared with those living in urban communities.[1] Some studies have proposed that people in rural areas have limited access to diagnostic and treatment services.[9-11] A more recent systematic review found that rural patients had worse prognosis and quality of life; travel distance was reported as a significant barrier to early diagnosis, receiving optimal cancer treatment and compliance to prescribed treatment.[12]

The purpose of this review was to systematically summarize the published literature on the association between rural/urban residence and cancer survival. We focused on high-income countries only, because residents of low- and middle-income countries have less access to adequate health care services. In addition, we evaluated the current evidence in relation to the underlying reasons for rural/urban inequalities in cancer survival.

## 4.2. Methods

### *Search Strategy*

We systematically searched the Ovid Medline, EMBASE, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases to identify observational studies published in English up to May 31, 2016, that investigated the association between place of residence defined as rural or urban and cancer survival in high-income countries (the search strategy is provided in Supporting Table 4.1). The World Bank Data 2014 was used to identify high-income nations.[13] We expanded our search by reviewing the bibliographies of all eligible studies and related reviews.[1,12,14,15] We also conducted a search using Google Scholar to identify potentially eligible studies that might not have been detected through the above process. This systematic review was planned and performed in adherence to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines.[16] The review protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews), reference number CRD42016039228, which is available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016039228.

### *Eligibility Criteria*

Studies were eligible if they met the following criteria: (1) observational study; (2) written in English and published in a peer-reviewed journal; (3) included people diagnosed with cancer at age ≥15 years in a high-income country; (4) compared rural with urban areas; (5) outcome of interest was death from any cause or death from a specific type of cancer; (6) reported estimates of a hazard ratio (HR), odds ratio, or excess mortality rate ratio (EMRR) derived from relative survival analysis with a corresponding 95% confidence interval (CI) or standard error. Eligible abstracts that did not have full text available were excluded. We included the most comprehensive version of a report if multiple publications from a study were available.

### *Screening and Data Extraction*

N.A. performed the literature search and excluded studies based on the titles and abstracts. Full reports of selected articles were imported to Covidence, a web-based program for conducting systematic reviews, for detailed, independent screening according to the eligibility criteria by N.A. and R.L.M. Discrepancies were discussed and resolved by consulting with D.R.E. Information from the identified studies was extracted by N.A. with assistance from R.L.M. The following data were extracted from each study: the first author's last name, publication year, country where the study was conducted, data sources, sample size, years of cancer diagnosis, range of age at diagnosis, cancer types, measure and categories of area of residence, statistical methods, measures of association and their 95% CI, and covariates used for adjustment. All information regarding factors that might explain rural and urban differences in cancer survival were also extracted.

### *Assessment of Risk of Bias*

The risk of bias of individual studies was appraised by N.A. and checked by R.L.M. using the domains of bias from the ROBINS-E (Risk of Bias in Non-randomized Studies–of Exposures) tool, available at https://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/.
The following areas were assessed for risk of bias: confounding, selection of participants into the study, classification of the exposure, inappropriate adjustment for potential mediators, extent of missing data, measurement of the outcome, and reporting of results.

### *Evidence Synthesis*

Meta-analyses across studies were not performed because of the diversity of definitions of urban versus rural residence and outcome (overall versus cancer-specific survival). We used fixed-effects meta-analysis to combine results from the same study for remote and very remote areas as well as by disease stage. Forest plots of study-specific results are presented. We considered the strength of association weak if the relative risk (RR) was <1.05, moderate if it was 1.05-1.20, and strong if it was >1.20. Caution should be used when interpreting the various measures of RR. The EMRR based on relative

survival analysis and HRs from an analysis of cause-specific survival or overall survival are not equivalent. An HR of 1.15 comparing the overall survival of rural versus urban patients indicates that rural patients had a death rate from any cause that was 1.15 times that of urban patients; this HR is usually derived from a Cox regression analysis with death from any cause as the outcome. An HR of 1.15 for cause-specific survival (derived from a Cox regression analysis with death from the cancer as the outcome) indicates that rural patients had a death rate from the cancer under study that was 1.15 times higher than that of urban patients. The EMRR is derived from a model in which the total hazard of death is composed of the sum of the expected hazard based on population mortality rates (usually accounting for age, sex, and calendar period) and an additional component (excess mortality) due to the cancer. An EMRR of 1.15 indicates that the excess mortality due to the cancer for rural patients is 1.15 times higher than that for urban patients.

### 4.3. Results

#### *Study Selection*

We identified 1771 articles on the Ovid Medline, EMBASE, and CINAHL databases. Of these articles, 599 duplicate citations were removed, and an additional 1090 articles were excluded based on their title and abstract, leaving 82 articles for further evaluation. After full-text screening, we excluded a further 37 studies. Therefore, 45 articles were eligible for inclusion in the systematic review. The criteria for exclusion are provided in Figure 4.1; 65% of the excluded studies did not assess rural/urban differences in cancer survival, and 24% were conference abstracts without full text.

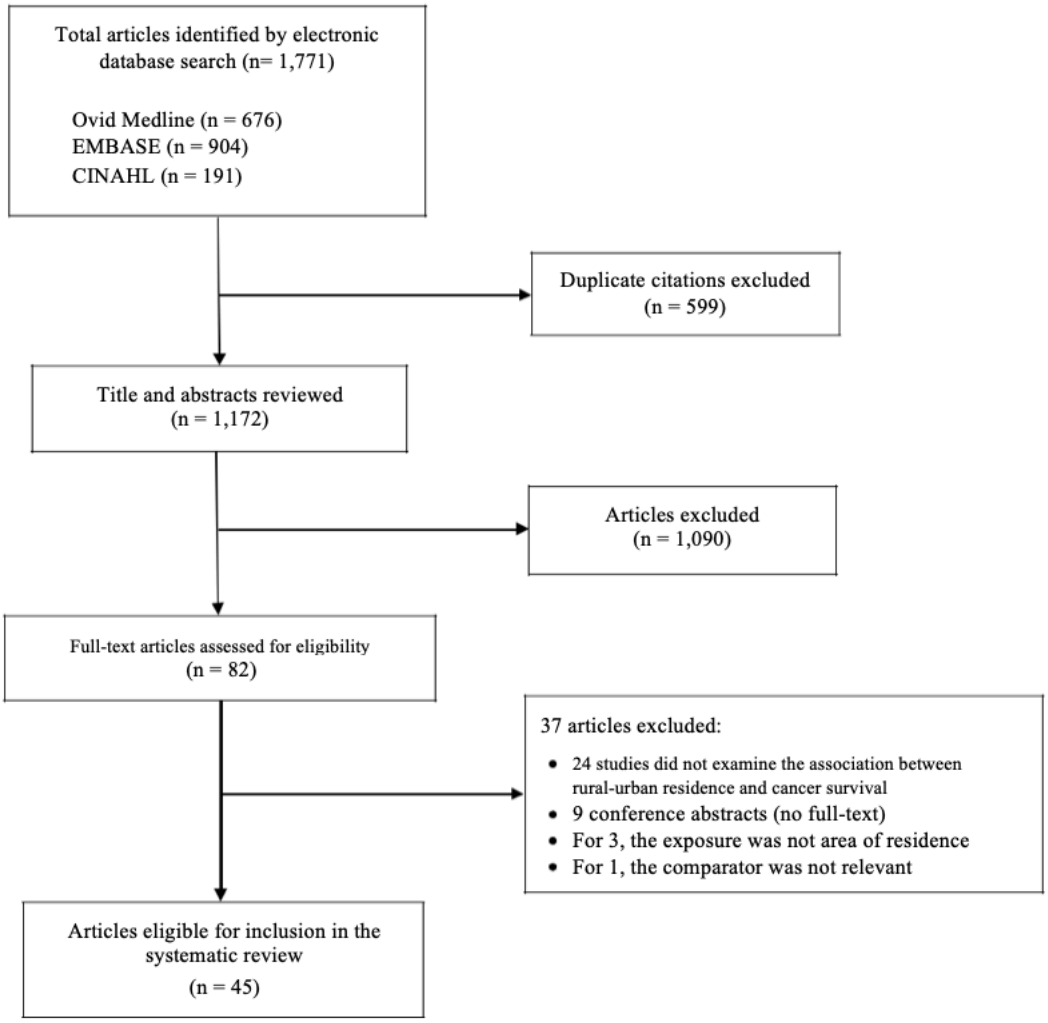


**Figure 4.1.** Flow diagram of inclusion criteria for a systematic review of rural-urban residence and cancer survival in high-income countries. CINAHL, Cumulative Index to Nursing and Allied Health Literature

### *Study Characteristics*

Supporting Table 4.2 summarizes the characteristics of the eligible studies and the estimates with corresponding 95% CIs for the association between place of residence and overall or cancer-specific survival. We considered the following categorizations, hereafter referred to as "urban," as reference: "metropolitan," "major or capital city," "inner, main or large urban," "city core," "large or big metro" and "very or highly accessible." We treated "inner regional," "outer regional," "remote/very remote," "large, small or isolated rural," "country area," "outer urban," "suburban," "small cities or towns," "densely populated outer," "rural outer," "non-metropolitan counties," "non-urban," "less urban," "small urban," and "moderately accessible' as the other category, "rural."

Seventeen studies were conducted in Australia,[8,11,17-31] 16 in the United States,[7,32-46] 6 in Europe,[10,47-51] 4 in Canada,[52-55] and 2 in New Zealand.[56,57] These studies investigated several neoplasms including

female breast,[24,27,31,40,42,47,49,52,56] male breast,[38] cervix,[34,57] colorectum,[8,19,20,25,32,35,36,45,46] endometrium,[43] esophagus and stomach,[7] liver (intrahepatic cholangiocarcinoma),[39] lung,[33,37,48,51] melanoma,[23] neuroendocrine tumours,[53] non-Hodgkin lymphoma,[50,54] ovary,[17,44] pancreas,[41,55] prostate,[18,28,30] and selected groups of cancers.[10,11,21,22,26,29] Most studies used only population-based cancer registry data, while others used data from a range of sources including hospitals,[26,51] academic medical centers,[41] or treatment services or registries[28,29,44,45]; others used population-based cancer registries linked with public and private hospitals and treatment datasets.[20,25,49,53,55] Twenty-one studies reported overall survival (i.e., death from any cause).[8,17,18,25,26,29,33,35-39,41,42,46,48,51-53,55,56] The remaining studies presented cancer-specific or relative survival, which estimate effects on death due to the cancer under study only.[7,10,11,19-24,27,28,30-32,34,40,43-45,47,49,50,54,57]

There were differences in the definition of rural and urban residence across studies. Several used standard measures of geographical classification. Most Australian studies used the Accessibility/Remoteness Index of Australia (ARIA/ARIA+),[11,17,19,20,22,24,25] or the Australian Standard Geographic Classification – Remoteness Areas (ASGC-RA) to define place of residence,[8,18,28-31] whereas most studies in the United States applied the Rural/Urban Continuum Codes (RUCC),[7,33,40,42,43,45] the Rural/Urban Commuting Area (RUCA),[36,37,41] or Census Tracts classifications.[34,48] Others defined rural/urban residence based on population size or density, local government area, or distance from treatment centers.[10,23,35,38,39,46,52-54,56,57] Some studies defined location based on the patients' medical service study area, address, residential postal code, or main income sources for the municipality.[26,27,32,44,47,49,51,55] One Australian study simply compared metropolitan and other residence,[21] and one study did not provide detailed information on how "rural" and "urban" were defined.[50]

***Evidence of Differences in Cancer Survival by Rural and Urban Residence***

Thirteen studies examined the association between place of residence and colorectal cancer survival: 7 from Australia,[8,11,19-22,25] 5 from the United States,[32,35,36,45,46] and 1 from Germany.[10] Three Australian studies[19,21,25] and 1 United States study[35] found that living in outer regional, remote, rural, and country areas was associated with an 8% to 15% higher risk of death. In contrast, another study in the United States[46] reported a moderate, inverse association between rural residence and overall survival (Figure 4.2). With respect to cancer-specific survival, a consistent pattern of worse survival outside major cities was noted in several studies from Australia[11,19,22] and the United States,[32,36] although 2 Australian studies[8,20] and 1 United States study[45] observed no significant rural or urban differences in survival from colon or rectal cancer (Figure 4.2). In contrast, a German study found weak evidence of survival advantage among rural female patients with colorectal cancer relative to women living in the city.[10]

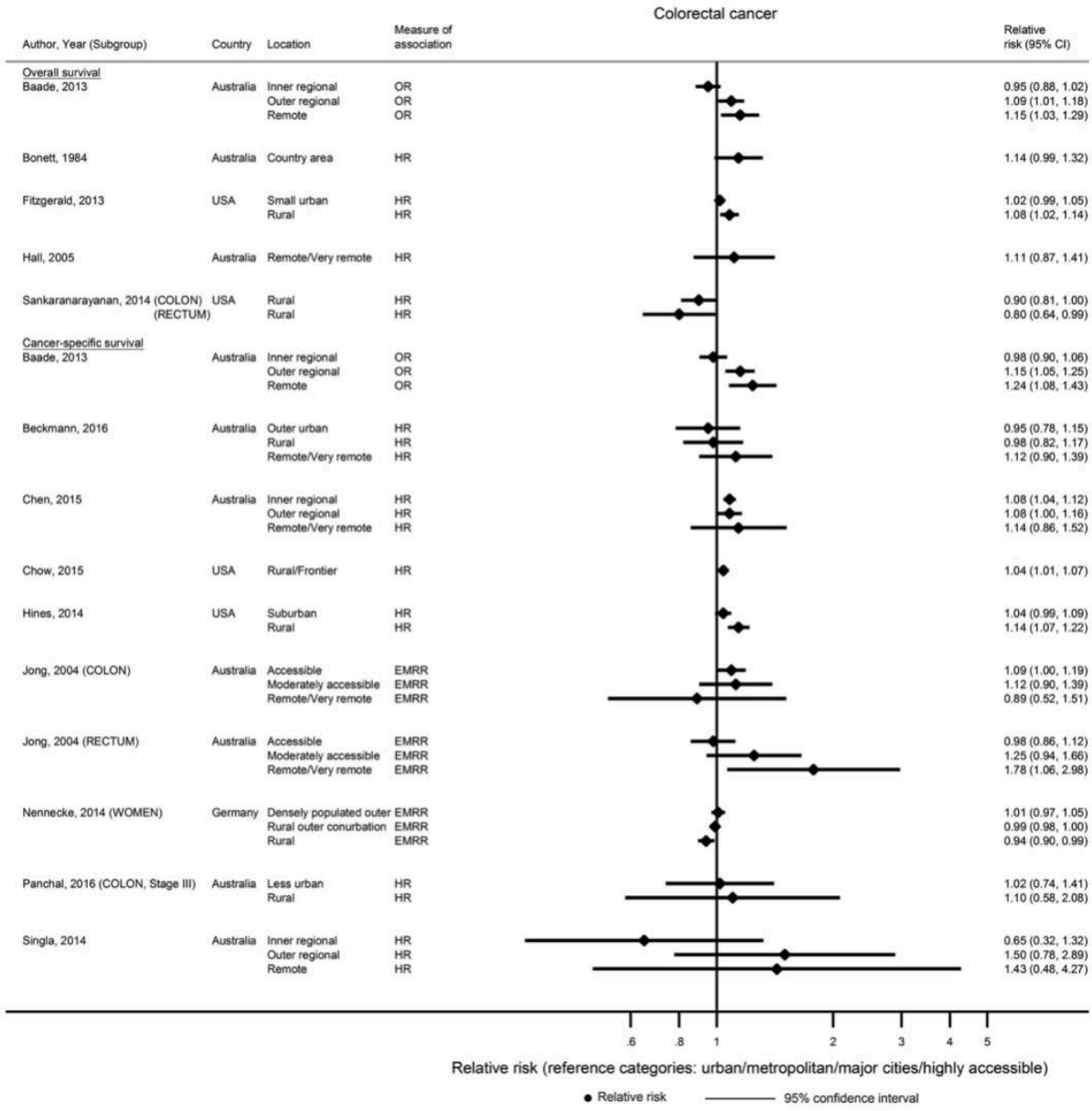


**Figure 4.2.** Relative risk estimates for overall and cancer-specific survival of colorectal cancer comparing rural categories with urban areas. CI, confidence interval; EMRR, excess mortality rate ratio; HR, hazard ratio; OR, odds ratio

Of the 13 studies that investigated female breast cancer, 3 studies from the United States,[42] Australia,[21] and New Zealand[56] observed no differences in overall survival between rural and urban areas (Figure 4.3). Another Australian study[27] found strong evidence of worse survival for women living in rural areas (RR, 1.84; 95% CI, 1.28-2.64). In contrast, a Canadian study [52] reported higher overall survival for women residing in towns, villages, and rural areas relative to their counterparts in urban areas; but this was not the case for women living in more remote areas. Regarding cancer-specific survival, studies from the United States[40,42] reported no association between place of residence and survival from breast cancer, whereas studies from Australia[11,24] showed moderate association. Other studies conducted in Poland[47] and Australia[22,31] observed worse survival for patients residing in rural and outer regional

regions (Figure 4.3). A German study[10] found an 8% (95% CI, 2%-15%) higher risk of death due to breast cancer among women living in densely populated outer areas. Conversely, a study from Norway[49] that included 5042 patients observed higher breast cancer survival in rural areas than in urban areas. The only study of male breast cancer, a United States study that included 4222 patients, reported lower overall survival in non-metropolitan areas (RR, 1.19; 95% CI, 1.01-1.40).[38]

We identified only 4 studies[11,18,28,30] that compared rural and urban residence in relation to prostate cancer survival, all conducted in Australia. One study[18] showed lower overall survival for residents of regional and rural areas, and the RR estimates increased from 1.01 (95% CI, 0.97-1.05) to 1.24 (95% CI, 1.17-1.31) over time. Another study[28] found no significant evidence of survival inequalities between patients in major cities and those in regional or rural areas. The 3 studies that examined prostate-specific survival[11,28,30] all reported worse survival for men living outside urban areas, with RR estimates in the larger study ranging from 1.31 (95% CI, 1.22-1.41) to 1.61 (95% CI, 1.46-1.77) (Figure 4.4).

Seven studies[11,21,22,33,37,48,51] assessed the association of area of residence with lung cancer survival (Figure 4.5). Of the 5 studies that investigated overall survival, 3 studies from the United States[33,37] and France[48] observed moderate to strong association between place of residence and survival, whereas the other 2 studies from Australia[21] and Poland[51] found no rural or urban differences in overall survival. Of the 2 Australian studies[11,22] that presented results for lung-specific survival, both found some evidence of worse survival among patients living in rural areas (Figure 4.5).

Figure 4.6 summarizes the results from studies of female reproductive cancers. Of the 7 studies [11,17,21,22,34,44,57] that investigated ovarian or cervical cancer, 2 Australian studies[17,21] reported worse overall survival in rural compared with urban areas, with RR estimates of 1.20 (95% CI, 1.01-1.42) and 1.53 (95% CI, 1.05-2.23), respectively. With respect to cancer-specific survival, other studies from New Zealand,[57] Australia,[11] and the United States [34] found that rural residence was associated with lower survival from cervical and ovarian cancer. A fourth Australian study[22] reported worse survival from ovarian cancer among women living in inner or outer regional areas, whereas another study from the United States[44] found that residents of rural Northern California and Sacramento had a more than 2-fold higher risk of death compared with patients living in the San Francisco Bay (i.e., urban) area (Figure 4.6). A study conducted in Australia reported a strong association between rural residence and worse survival from uterine cancer.[11] The only relevant study of endometrial cancer found no differences in overall survival (RR, 0.98; 95% CI, 0.86-1.12), but higher cancer-specific survival among rural patients than their urban counterparts (RR, 0.77; 95% CI, 0.63-0.94).[43]

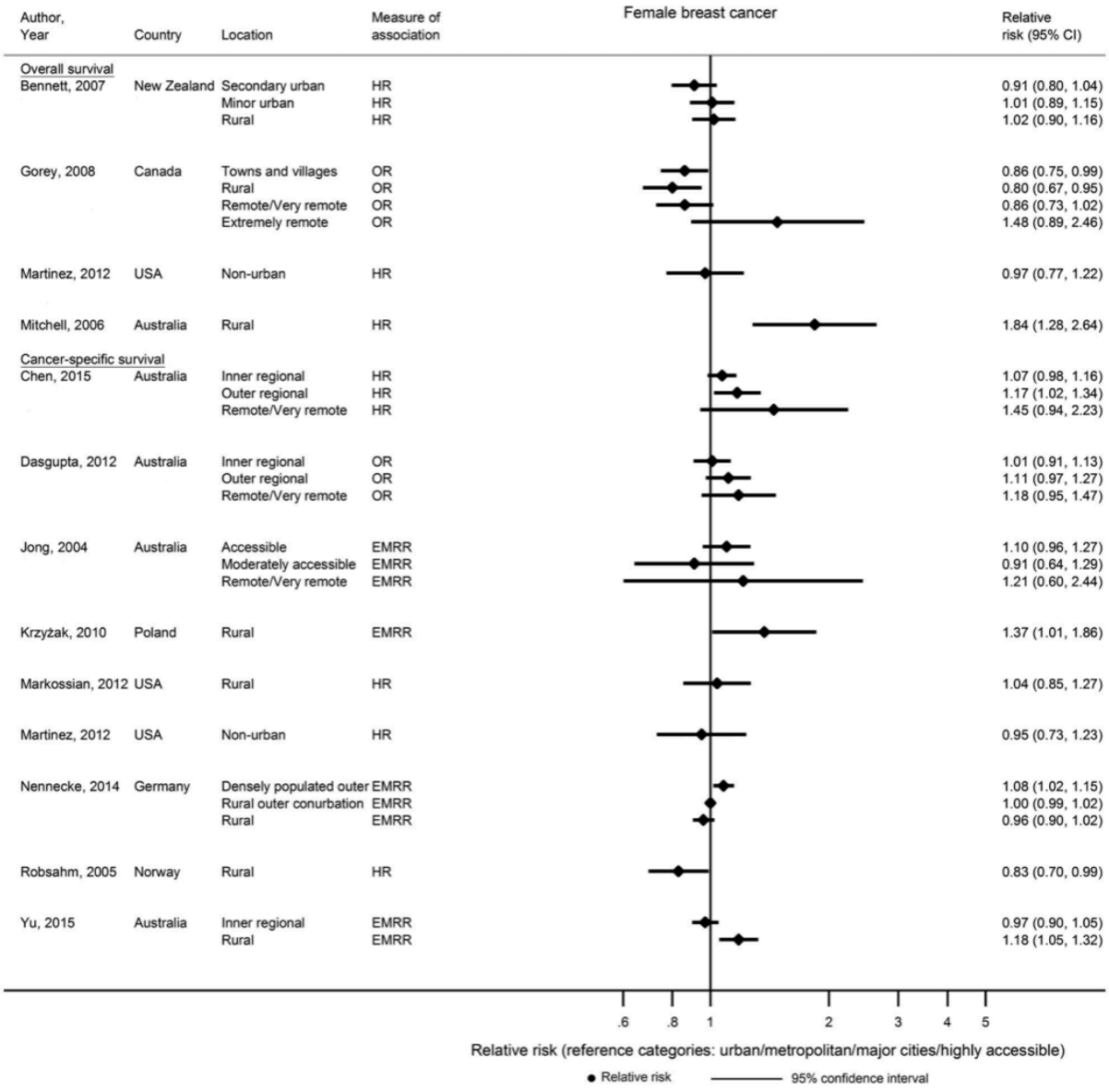


**Figure 4.3.** Relative risk estimates for overall and cancer-specific survival of female breast cancer comparing rural categories with urban areas. The results of an Australian study (Bonett et al, 1984) are not shown as the authors did not report hazard ratios for breast cancer. CI, confidence interval; EMRR, excess mortality rate ratio; HR, hazard ratio; OR, odds ratio

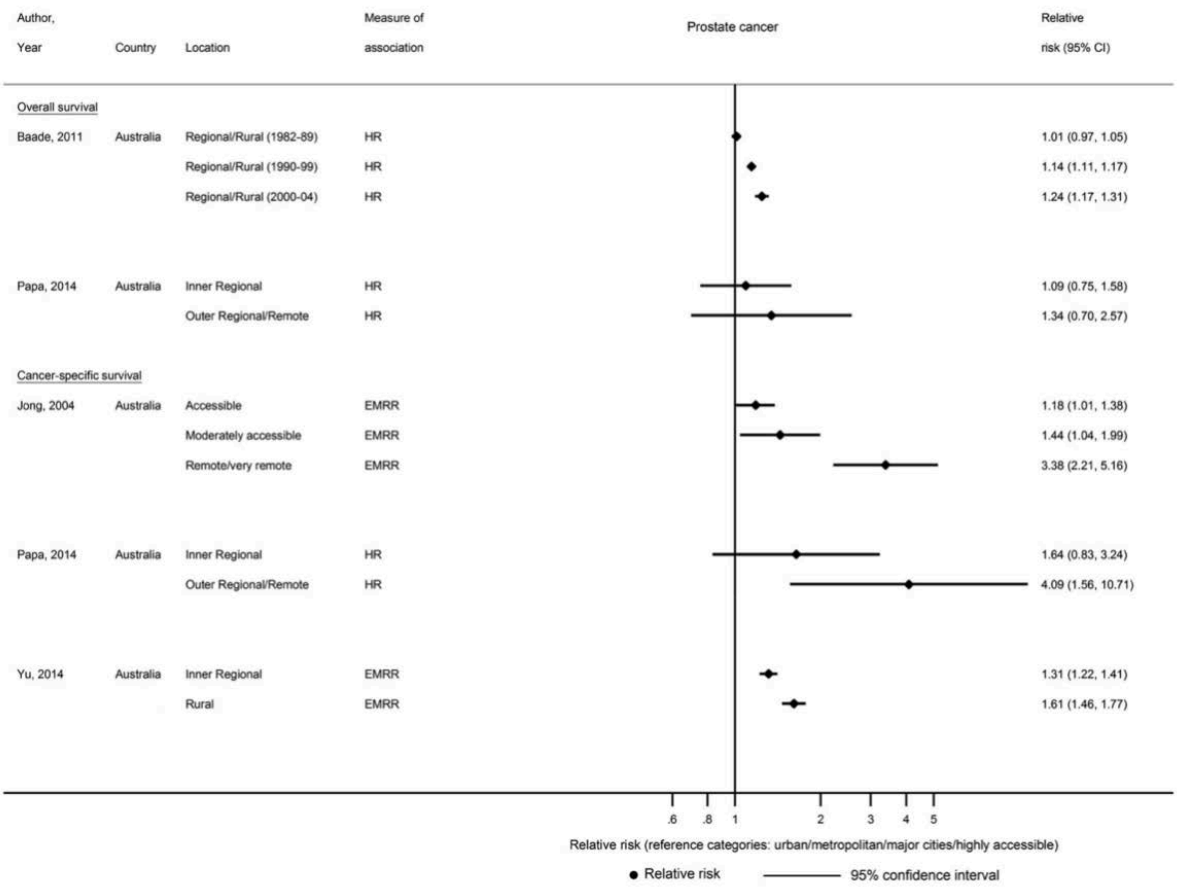


**Figure 4.4.** Relative risk estimates for overall and cancer-specific survival of prostate cancer comparing rural categories with urban areas. CI, confidence interval; EMRR, excess mortality rate ratio; HR, hazard ratio

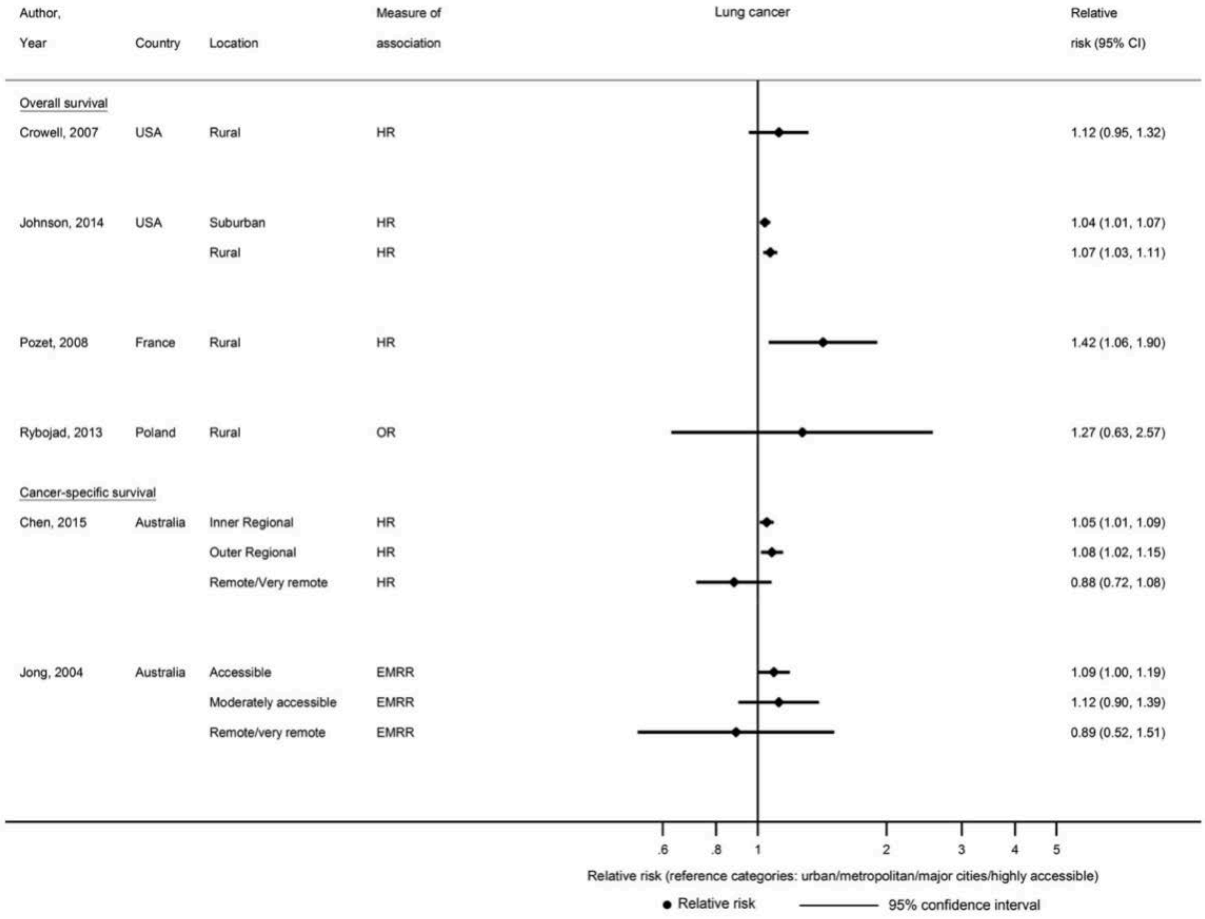


**Figure 4.5.** Relative risk estimates for overall and cancer-specific survival of lung cancer comparing rural categories with urban areas. The results of an Australian study (Bonett et al, 1984) are not shown as the authors did not report hazard ratios for lung cancer. CI, confidence interval; EMRR, excess mortality rate ratio; HR, hazard ratio; OR, odds ratio

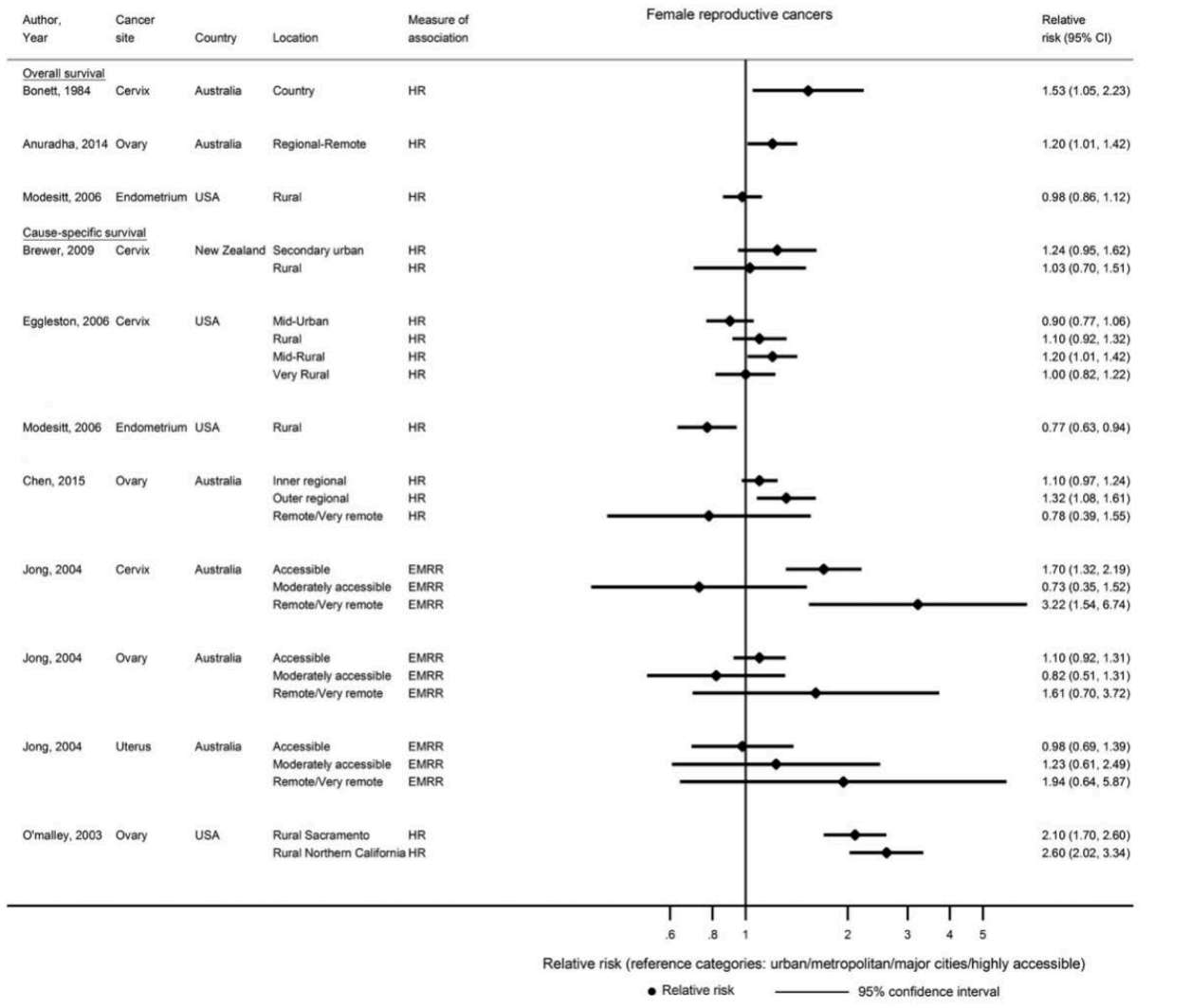


**Figure 4.6.** Relative risk estimates for overall and cancer-specific survival of female reproductive cancers comparing rural categories with urban areas. Rural Northern California and Sacramento were compared with the San Francisco Bay (i.e., urban) area. CI, confidence interval; EMRR, excess mortality rate ratio; HR, hazard ratio; OR, odds ratio

Of the remaining studies, 3 from the United States or Australia assessing overall and cancer-specific survival from liver,[11,39] stomach, and esophagus[7] observed similar survival for rural and urban regions (Supporting Table 4.2). An Australian study of 12,827 melanoma patients found survival disadvantage for rural (RR, 1.20; 95% CI, 1.02-1.43) but not regional areas.[23] Another Australian study reported higher survival for individuals with melanoma living in accessible areas, whereas no differences were observed in moderately accessible and remote areas, relative to highly accessible regions.[11] A study from Canada found lower overall survival for rural residents diagnosed with neuroendocrine cancers (RR, 1.16; 95% CI, 1.04-1.30).[53] Of the 3 studies examining rural and urban differences in survival from non-Hodgkin lymphoma, a Canadian study[54] and an Australian study[11] observed no significant differences in survival between rural and urban regions, whereas a study from France[50] reported that

rural patients had a 2-fold higher risk of death compared with urban cases. Lastly, an Australian study[11] reported similar survival experience from pancreatic cancer among patients living in rural and urban regions, whereas 2 studies from the United States[41] and Canada[55] found that rural residents with pancreatic cancer have worse overall survival than those living in urban areas, although the sample size in the United States study was small (245 cases).

***Risk of Bias***

The results from the assessment of the risk of bias of the included studies are shown in Supporting Table 4.3. Almost all studies had low risk of bias with respect to classification and measurement of the exposure and the outcome, respectively. We considered age at diagnosis, sex (for non-sex-specific cancers), ethnicity/race (where applicable), and an individual-level measure of socio-economic position as important confounding domains that should be accounted for in the analyses (Supporting Figure 4.1). In addition, studies that applied a relative survival framework to estimate EMRRs should have used a region-specific population life table; of the 6 studies that reported EMRRs, 3 did not use an appropriate population life table.[30,31,50] With respect to confounding, about half of the included studies were at moderate risk of bias, mainly due to not accounting for socio-economic factors. Bias in the selection of participants into the study was determined to be low for most studies, except for 7 studies that were considered to be at high risk for this bias.[26,28,29,41,44,45,51] For the domain of bias due to selective reporting of results, all had a low risk of bias except for 2 studies.[10,22] With respect to missing data and inappropriate adjustment for potential mediators, most studies were classified as having a moderate to high risk of bias (Supporting Table 4.3). We considered health-related lifestyle factors, screening participation, stage of cancer at diagnosis, comorbidities, and treatment modalities including surgery, chemotherapy, and radiotherapy as potential mediators that should not have been adjusted for in the analyses.

Of the 45 studies included in the review, 18 did not adjust for measures of socio-economic position (SEP) or deprivation.[7,10,11,17,18,22,23,26,27,33,39,42,47,48,50-52,54] Most studies that adjusted for individual- or area-level measures of SEP or deprivation observed weak to moderate association between rural and urban residence and cancer survival. Of the 6 studies [24,25,30,36,49,57] that presented the results with and without adjustment for socio-economic deprivation, 3 found no significant differences in survival between rural and urban areas,[24,25,57] although adjustment for SEP decreased the RR estimates. Of the remaining studies, 1 study[36] found that an apparent worse survival observed in rural than urban areas disappeared after adjusting for SEP, whereas the survival gap persisted in the other 2 studies.[30,49]

We identified 35 studies that included covariates in multivariable analyses that are on the potential causal pathway between rural and urban residence and cancer survival (Supporting Fig. 4.1).[7,8,10,11,17,19,20, 23-25,27,28,30,32-34,36-38,40-50,53-57] Of these, 15 studies that adjusted for at least one mediator did not report any significant differences in survival by area of residence,[7,8,20,24,25,27,33,34,37,40,42,45,54,56,57]

whereas the remaining studies found evidence of association between rural and urban residence and cancer survival.[10,11,17,19,23,28,30,32,36,38,41,43,44,46-50,53,55] Of 5 studies that observed inequalities in survival and reported the results with and without including the mediators in the models, 3 suggested that treatment partially explained rural/urban differences in survival from colorectal, lung, and breast cancer.[27,36,37] The fourth study found that stage of prostate and cervical cancer at diagnosis contributed in part to the observed worse survival in rural areas,[11] whereas the fifth study showed that stage at diagnosis and the treatment received did not explain better survival from colon cancer for rural regions.[46]

### 4.4. Discussion

In this systematic review, the majority of studies reported worse survival for cancer patients living in rural and remote areas relative to those living in urban regions. The most consistent evidence, observed across several studies, was for colorectal, lung, and prostate cancer.

These findings are broadly in line with previous related reviews. A review examining the influence of travel burden on cancer outcomes found that cancer patients living in rural areas have poorer survival and a worse quality of life than their urban counterparts.[12] Furthermore, a long travel distance to a specialist hospital and treatment facilities appeared to have a negative effect on stage of cancer at diagnosis and receipt of optimal treatment.[12] Another review of rural/urban differences in prostate cancer incidence and mortality reported a higher risk of death among rural men in half of the studies, whereas the remaining studies did not show any differences; the authors suggested that variations in rural/urban definitions and in accounting for ethnicity, sociodemographic characteristics, comorbidities, and stage at diagnosis may have contributed to inconsistent findings.[15] Some other studies have shown that rural men are more likely to be diagnosed at advanced stage of prostate cancer due to lower rates of PSA testing in rural areas.[11,18]

A systematic review of differences by place of residence in clinical management and outcomes for colorectal cancer patients in Australia found worse survival for patients who lived outside major cities.[14] Some of the reviewed factors appeared to explain part of the observed differences in survival. For example, patients living in rural areas had more unhealthy behaviors and were less likely to participate in colorectal cancer screening; differences in stage at diagnosis, the prevalence of comorbidities, and the treatment received, as well as access to oncology services and options for treatment, could also have contributed to lower survival from colorectal cancer in rural areas.[14] A United States study showed that rural patients are less likely to receive information regarding participation in cancer treatment trials than urban residents, which may contribute to worse survival in rural and remote regions.[58]

There are discrepancies between populations in the association of residential location with cancer stage at diagnosis. Several studies that have assessed rural/urban differences have found that rural patients present with more advanced disease stage.[9,59-62] In contrast, other studies have shown that rurality or travel distance have an inverse or no association with late diagnosis.[6,14,63,64]

In several countries, rural regions tend to have more socio-economic disadvantage than urban regions.[65-67] Moreover, other studies have found that rural regions have higher prevalence of physical inactivity, obesity, smoking, alcohol consumption, and chronic diseases, often related to socio-economic deprivation.[68-72] We therefore assumed that SEP would confound associations between place of residence and cancer outcome, but we acknowledge that this assumption might not be correct, and that place of residence might also influence SEP. A review addressing the health disadvantage of rural and remote populations argued that worse cancer survival among rural patients is partially due to higher rates of poverty and lower levels of education and health literacy than for urban residents, which in turn affect health behaviours and the use of health care services in rural regions.[73] Another review of the association between comorbidity and cancer survival found that individuals with psychiatric disorders or severe comorbidities are more likely to be diagnosed at advanced stages, whereas those with chronic conditions tend to have early diagnosis due to regular medical check-ups.[72] In addition, patients with comorbid conditions are less likely to receive standard cancer treatment or adhere to prescribed treatment. It is not well understood whether undertreatment or noncompliance is associated with patient preferences or treatment adverse effects and toxicity.[72]

***Limitations***

This review has several limitations that should be considered when interpreting the findings. A significant limitation was the considerable variation in the criteria and methods used to define rural and urban regions. It is possible that screening participation for cancers such as breast, prostate, and colorectal cancer differs by place of residence. If so, this would affect comparisons of survival by place of residence because, even in the absence of effective treatment, screen-detected cancers will appear to have better survival due to lead time and length time bias and overdiagnosis. Therefore, it was challenging to make comparisons across included studies and draw conclusions. Moreover, many of the studies had an overall high risk of bias due to several factors such as confounding, missing data, and inappropriate adjustment for mediators.

To investigate the underlying reasons for differences in cancer survival by place of residence, we extracted RR estimates adjusted for variables in the putative causal pathway. Unfortunately, most studies only reported fully adjusted estimates, which may have masked survival differences between rural and urban areas. Comparing results with and without accounting for mediators in the analyses, known as the difference method, is a common approach in epidemiological research, but it has some limitations. It fails when there are unmeasured mediator-outcome confounders or when multiple mediators of interest interact with each other.[74] Adjusting for mediators in these situations could yield misleading or biased results.[74,75] Thus, we could not draw definitive conclusions about whether stage at diagnosis and the treatment received explain part of the observed rural/urban differences in cancer outcomes.

Finally, aggregated or composite indicators of socio-economic deprivation do not necessarily match with the individual measures[76]; therefore, it is not clear to what extent the observed inequalities in cancer survival between rural and urban area is influenced by patients' socio-economic position.

***Conclusions***

Rural cancer patients generally have worse survival relative to their urban counterparts. The lack of consistent findings across studies may arise from discrepancies in measurement and classifications of rural and urban regions and the covariates accounted for in multivariable analyses. This review highlights the importance of appropriate adjustment for prognostic factors when exploring differences in cancer survival by area of residence. The underlying reasons for survival disadvantage for rural patients are not well known, but possible contenders include differences in health-related lifestyle behaviour, stage of cancer at diagnosis, comorbid conditions, and treatment modalities. Further research is required to unravel the potential mediating role of these factors, which may help to establish effective interventions to address inequalities and improve survival for all cancer patients.

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## Chapter 5 . Data sources and life tables

### 5.1. Introduction

This chapter provides an overview of the data and population life tables used in this thesis to investigate trends and inequalities in cancer patient survival by sex, remoteness of residence and area-level socio-economic disadvantage in Victoria, Australia. It also describes the population-based, linked dataset used to identify the underlying reasons for socio-economic inequalities in survival from stage III colon cancer in Victoria, Australia.

### 5.2. The Victorian Cancer Registry

The Victorian Cancer Registry (VCR) is a population-based cancer registry for the state of Victoria, the second most populous state in Australia. [52] All Victorian public and private hospitals, cancer screening registries and pathology laboratories are required to report new cases of primary and invasive neoplasms to the VCR. [53] More than 75% of notifications are collected electronically, and the VCR applies International Agency for Research on Cancer (IARC) case definitions and coding recommendations using the international statistical classification of disease and related health problems, tenth revision (ICD-10) and the international classification of diseases for oncology (ICD-O-3). [54, 55] To maximise the quality and accuracy of the data, pathology reports are matched with hospital registrations once diagnosis is confirmed by histology. The VCR routinely collects demographic details (patient name, residential address, sex, date of birth, country of birth, indigenous status) and tumour characteristics (date of diagnosis, site, morphology, grade, histology, behaviour code) for each case of incident cancer. VCR records are linked monthly to the Victorian Registry of Births, Deaths and Marriages and annually to the National Death Index at the Australian Institute of Health and Welfare (AIHW) to update vital status and, if applicable, record cause of death. [53, 56]

### 5.3. The Victorian Registry of Births, Deaths and Marriages and the National Death Index

The Registry of Births, Deaths and Marriages (BDM) was established in 1986 and keeps records of all births, deaths and marriages occurring in Victoria since 1853. [57] The National Death Index (NDI), stored at AIHW, obtains the data from the registrars of births, deaths and marriages in each state and territory, the National Coronial Information System, and the Australian Bureau of Statistics (ABS). The AIHW maintains all records of deaths registered in Australia since 1980 to facilitate medical and epidemiological research. [58]

### 5.4. The Victorian Admitted Episodes Dataset and the Victorian Emergency Minimum Dataset

The Victorian Admitted Episodes Dataset (VAED) includes comprehensive data (demographic, administrative and clinical) for every admitted episode of care occurring in Victorian public and private hospitals, including rehabilitation centres, extended care facilities and day procedure centres. [59]

### 5.5. Description of population-based linked dataset

The Victorian Department of Health and Human Services, in collaboration with Cancer Council Victoria, linked the VCR data with in-patient hospital data from the VAED, and with vital status data from the BDM and NDI (Figure 5.1). The linkage was undertaken at the Centre for Victorian Data Linkage (CVDL) and was based on personal identifiers including full name, date of birth, sex, and Medicare number, as well as, when required, address, postcode and state of residence at last contact date.

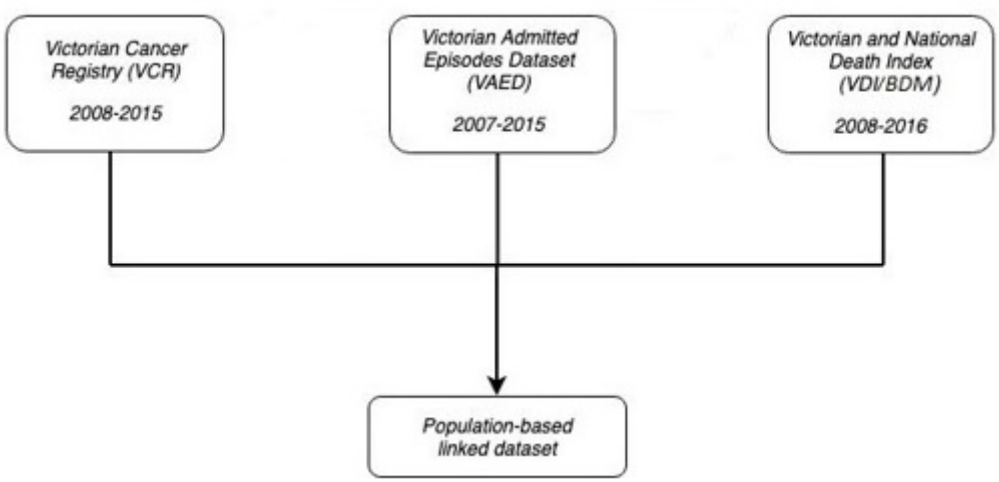



**Figure 5.1.** Data sources used by the Department of Health and Human Services in Victoria to assemble the linked dataset

### 5.6. Victorian population life tables

Life tables were produced from age- and sex-specific mortality rates, by calendar year. The standard Victorian life tables by sex and single year of age *x* for each year from 1982-2015 were generated by the Australian Bureau of Statistics (ABS) based on mortality rates ($q_x$, the probability of dying at age *x*) at statistical area level 4 [SA4] geography. The probability in a given year of a person of a given sex surviving between from age *x* to age *x*+1 ($p_x$) was calculated as $p_x$=1- $q_x$. To avoid fluctuations in data and to attain reasonable mortality curves, crude death rates were smoothed by using the Hodrick-Prescott filter (Hodrick and Prescott, 1977). [60] Specific life tables for Victorian residents of major cities (Melbourne, Geelong) and for those residing outside major cities (combining inner regional, outer regional and remote areas) were produced by the ABS for each year from 2001-2015 by sex and single years of age. These life tables were constructed by aggregating Victorian population death rates at Statistical Area Level 2 [SA2] geography into the two defined residential areas (in and outside major cities). The mortality rates for each area were smoothed to reduce the variability of $q_x$. Applying a similar method, the ABS also constructed SA2-based socio-economic disadvantage-specific life tables by year, sex and single years of age for the period of 2001-2015 using socio-economic indexes for area (SEIFA). To generate SEIFA-quintile specific life tables, smoothed mortality rates at SA2 geography were aggregated into five socio-economic disadvantage quintiles.

## Chapter 6 . Statistical methods

### 6.1. Introduction

This chapter provides an overview of the statistical methods used for the analyses presented in this thesis. The results of these analyses have been published or submitted for publication, but the methods and their limitations were not discussed in detail in those papers. The methods used for the two systematic reviews are described in Chapters 3 and 4.

### 6.2. Causal concepts in epidemiology

A fundamental task of much epidemiological research is to find the cause(s) of an outcome to inform interventions to improve population health. [61, 62] The modern approach to causal inference is defined according to the framework of potential or counterfactual outcomes. To understand this concept, let X be an exposure of interest where X=0 indicates 'unexposed' and X=1 'exposed', and let Y denote an outcome where Y=1 indicates the occurrence of an event (e.g. death) and Y=0 indicates the absence of the event (e.g. alive). Each individual has two potential outcomes, one corresponding to when she is exposed ($Y_{X=1}$), and the other to when she is not exposed ($Y_{X=0}$). In reality, it is impossible to allocate a person to the exposure of interest and measure the outcome and go back in time to allocate the same person to no exposure and observe the outcome, assuming everything else remains the same. [62-64] Therefore, we are only able to observe one potential outcome corresponding to whether an individual is exposed or unexposed (Table 6.1).

**Table 6.1.** Counterfactual outcomes of individuals with binary exposure (X) and outcome (Y)

| *Individuals* | *Exposure* | *Observed outcome* | *Counterfactual outcome* |
|---|---|---|---|
| ***1*** | 0 | 1 | ? |
| ***2*** | 1 | 1 | ? |
| ***3*** | 1 | 0 | ? |
| ***4*** | 0 | 0 | ? |
| ***5*** | 0 | 1 | ? |
| ***6*** | 1 | 0 | ? |
| ***7*** | 0 | 1 | ? |

Individual causal effects of an exposure on an outcome cannot be estimated as the counterfactual outcome for each individual under the other condition is unobserved and missing (Table 6.1). [62-64]

$$\textbf{Individual causal effect} = Y_{X=1} - Y_{X=0} = ?$$

Although it is not feasible to make inferences about causation at the individual level, it is possible to estimate average causal effects in a population of interest, assuming exchangeability of exposed and non-exposed groups. [62-64] Other conditions such as strength of a cause, positivity, consistency and temporality are required to identify the average causal effects; [61-64] I focus on exchangeability criteria as it is a common issue in observational studies. The exchangeability concept implies that the average

risk of the disease or death would have been identical if the unexposed people had been exposed and vice versa, i.e. the counterfactual outcomes are not dependent on the actual exposure. [64, 65] Randomised controlled trials are known as a gold standard approach to assess causality, based on the counterfactual framework, as the trial groups are exchangeable if a trial is designed and conducted properly, i.e. the characteristics of individuals in both arms are identical.

$$\textbf{Average causal effect} = \text{Average } [Y_{X=1}] - \text{Average } [Y_{X=0}]$$

In observational studies, the measures of association (e.g. risk ratio or risk difference) are not unbiased because the exposure groups are not exchangeable due to confounding. Accordingly, the observed association between an exposure and an outcome in a given population is not necessarily due to a causal relationship. [64, 65]

### 6.3. Causal diagrams

Causal diagrams, also known as directed acyclic graphs (DAGs), have been used throughout this thesis to show the causal assumptions underlying each analysis. A DAG is a useful structural approach to identify exchangeability and the variables or conditions that can create bias in the analyses. [64, 66] A DAG comprises measured and unmeasured confounding and mediating variables; arrows represent causal associations and putting a variable in a box indicates conditioning on it. [64, 66] Figure 6.1 shows a DAG including an exposure 'X' (socio-economic position) and an outcome 'Y' (cancer survival), a confounding variable 'C' (ethnicity) i.e. a common cause of an exposure and an outcome, an intermediate or mediating variable 'M' (smoking) on the causal pathway, a collider 'L' i.e. a common effect of any pair of variables, and an unmeasured confounding variable 'U'.

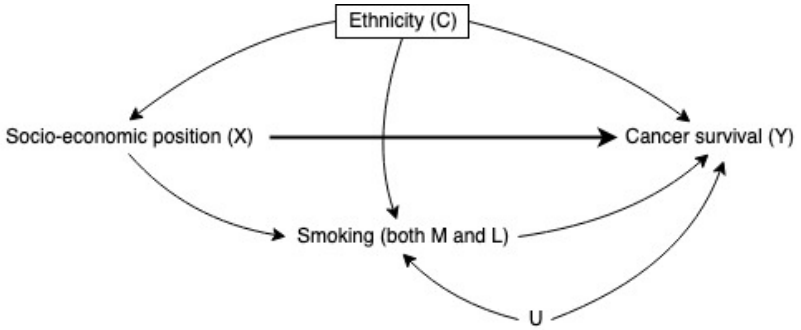



**Figure 6.1.** Directed acyclic graph (DAG) representing a causal association between socio-economic position and cancer survival. Smoking is included as a mediator and a collider; ethnicity is a confounder and U is an unmeasured variable

If the assumptions encapsulated in the above figure are correct, conditioning on ethnicity is necessary to control for confounding, but controlling for 'smoking' should be avoided as smoking is on the causal pathway and adjusting for a mediator will bias the observed association between socio-economic position (SEP) and cancer survival. Further, smoking is a collider, i.e. it is a common effect of SEP and U, SEP and ethnicity as well as ethnicity and U. Thus, conditioning on smoking creates 'collider bias'

by inducing an artefactual association between the unmeasured variable (U) and SEP (represented by dashed line in Figure 6.2).

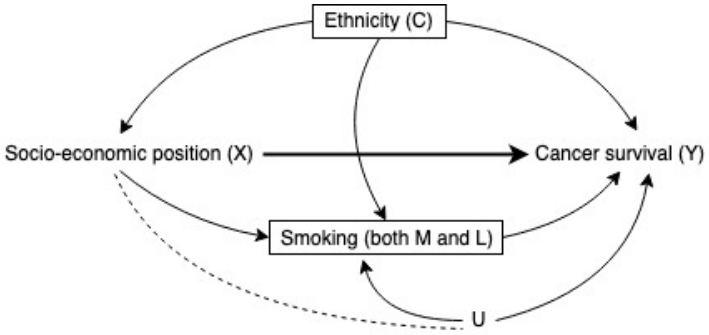



**Figure 6.2.** The effect of adjusting for smoking on the effect of socio-economic position on cancer survival conditional on ethnicity in the presence of a mediator-outcome confounding (U)
The dashed line shows an artefactual non-causal association between socio-economic position and U after adjusting for smoking

Similarly, selection bias, for example due to selection of participants/cases in health inequalities research, can be shown in a DAG as a collider or common effect of two variables (Figure 6.3). It is essential to use population-based cancer registry and other population-based health-related datasets to avoid selection bias when assessing differences in cancer survival by SEP and identifying the underlying reasons for these inequalities.

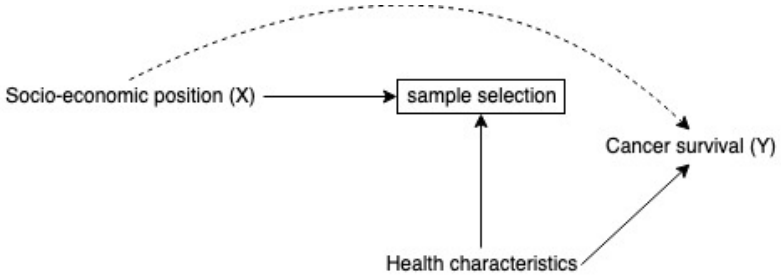



**Figure 6.3.** Directed acyclic graph (DAG) representing selection bias

### 6.4. Estimation of cancer survival

There are two methods for estimating cancer patient survival: overall survival and net survival i.e. cancer-specific and relative survival, the latter defined as the observed survival if the cancer under study were the only cause of death, directly or indirectly. [67] Assessing cancer-specific survival is a common analytical approach within a competing risk setting, where patients who died from any other causes are censored at death. Many have argued that this approach is not suitable for analysing cancer registry data due to absence, misclassification or unreliability of information on cause of death. [67, 68] Therefore, relative survival, where information on cause of death is not needed, has been widely used. [67, 68] Relative survival is the ratio of the observed all-cause survival of a cohort of cancer patients over a given period (t) after diagnosis to the expected survival of comparable people from the general population without cancer over the same period. [67, 68]

$$\textbf{Relative survival (t)} = \frac{\text{Observed all–cause survival of cancer patients (t)}}{\text{Expected survival of comparable population (t)}}$$

In a relative survival framework, the excess mortality rate, i.e. the excess risk of death due to a cancer diagnosis, can be estimated as:

**Excess Mortality Rate** = observed all-cause mortality rate – expected mortality rate of comparable group

To estimate expected survival or mortality, life tables from general population with similar demographic characteristics to those of the study cohort based on factors such as sex, age, year and, where applicable, socio-economic position, rural-urban residence, and ethnicity or race are used. [67, 68] It is assumed that these life tables provide precise estimates of an individual's expected survival or mortality if he or she did not have the cancer of interest. [67]

The most widely used method to quantify relative or net survival using population life tables is known as the Ederer II estimator. [69] However, Pohar-Perme *et al* showed that the Ederer II estimator is prone to bias due to 'informative censoring', where the assumption of independence between censoring and the risk of death is violated. [68, 70] This leads to errors in the estimation of relative survival, particularly for elderly cancer patients as they are more likely to die from other causes. The Pohar-Perme method was developed in 2012 to overcome this problem. [70] Under this approach, net survival estimates the average relative survival across individuals (Equation 1), whereas the Ederer II estimates relative survival by using the ratio of the average observed survival over the average expected survival (Equation 2). [68]

$$\textbf{1) Net survival} = \frac{1}{n}\sum_{i=1}^{n}\frac{all{-}cause\ survival\ (t)}{expected\ survival\ (t)}$$

$$\textbf{2) Relative survival} = \frac{\frac{1}{n}=\sum_{i=1}^{n} all{-}cause\ survival\ (t)}{\frac{1}{n}=\sum_{i=1}^{n} expected\ survival\ (t)}$$

*Equations from: Dickman PW, Covell E. Estimating and modelling relative survival. The Stata Journal. 2015 Apr;15(1):186-215* [68]

There is some debate about the most appropriate, least biased method for estimating net survival. A simulation study by Lambert *et al* showed that the bias of the age-standardised Ederer II estimates of five-year cancer survival was negligible in practice. [71] Another simulation study by Roche *et al* found that, relative to the Pohar-Perme method, the errors in age-standardised net survival estimates using Ederer II were small at five years, but more substantial over longer follow-up. [72]

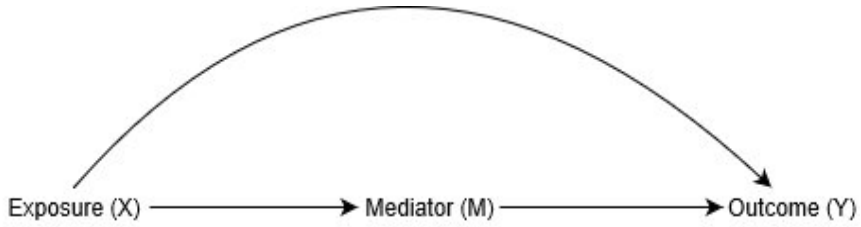
Although Ederer II and Pohar-Perme estimate five-year net survival equally well, there is a possibility of 'non-comparability' bias using these methods. This bias occurs when the expected mortality of cancer cases in the absence of the disease is not comparable to that of the general population. [67, 73] For example, lung cancer patients are more likely to smoke relative to the general population; therefore,

their expected mortality is underestimated as their probability of dying from other causes is higher than that of the general population. [67, 73] This bias not only occurs for smoking-related cancers, but also for estimating cancer survival across sub-populations such as ethnic or socio-economic groups, as indigenous and disadvantaged people have higher prevalence of adverse health-related behaviours than the general population; [67, 73] therefore, they have higher expected mortality rates.

In this thesis, for all cancer types, net survival by sex, remoteness of residence and area-level socio-economic disadvantage was first estimated by the Pohar-Perme method using Victorian population life tables stratified by calendar year, age, sex, and either remoteness of residence or socio-economic disadvantage (SEIFA). Because the life tables were not stratified by SEIFA quintile, derived life tables were formed by combinations of two separate lifetables by remoteness of residence and SEIFA (S9.4). Because the Pohar-Perme method does not explicitly estimate relative survival, we used the Ederer II method to estimate five-year relative survival and collapsed the data by covariates of interest to be able to estimate the excess mortality rates due to a cancer diagnosis. [68] The excess mortality rate ratio (EMRR) is the ratio of the observed all-cause mortality rate of all cases and their expected mortality rate if they did not have cancer (expected mortality was calculated from Victorian population life tables). [67, 68] The grouped data and a generalised linear model with a Poisson error structure have been used to estimate the EMRR for each cancer type. [68]

### 6.5. Mediation analysis

One of the objectives of this thesis is to identify factors explaining the well-established effect of SEP on colon cancer survival. Mediation analysis allows researchers to estimate the separate effects of an exposure on an outcome through a potential variable on the causal pathway, known as a mediator or an intermediate variable, and not through the mediator (Figure 6.4). The effect through the mediator is known as the indirect effect (IE) and the effect not through the mediator is known as the direct effect (DE). [74, 75]




Direct effect = X→Y
Indirect effect = X→M→Y
Total effect = DE + IE

**Figure 6.4.** Causal diagram showing pathways from an exposure to an outcome

A method commonly used by epidemiologists for mediation analysis is known as the ‘difference method’, which compares regression coefficients for an exposure (x) on an outcome (Y) with and

without adjusting for potential mediator(s) (m). [74, 75] The first model, which estimates the total effect, is the regression of the outcome on the exposure and confounding variables (c)

$$E[Y|x, c] = \alpha_0 + \alpha_1 x + \alpha_2' c$$

The second model also includes the mediator of interest

$$E[Y|x, m, c] = \beta_0 + \beta_1 x + \beta_2 m + \beta_4' c$$

The direct and indirect effects are calculated as DE= $\beta_1$ and IE= $\alpha_1 - \beta_1$.

*Equations reproduced from: VanderWeele TJ. Mediation analysis: a practitioner's guide. Annual review of public health. 2016 Mar 18; 37:17-32.* [75]

To appropriately estimate and interpret the direct and direct effects from the difference method, the following assumptions must be satisfied:

1. There is no unmeasured confounding between the exposure and the outcome, given C1
2. There is no unmeasured confounding between the exposure and the mediator, given C2
3. There is no unmeasured confounding between the mediator and the outcome, given C3 and X
4. There is no confounding between the mediator and the outcome affected by the exposure, i.e. there is no arrow from the exposure (X) to mediator-outcome confounder C3 (Figure 6.5). [74,75]

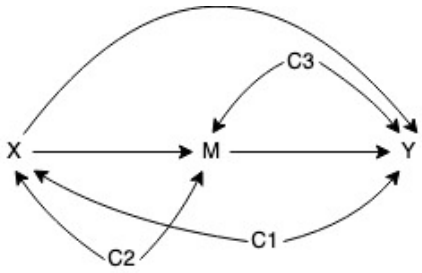



**Figure 6.5.** Directed acyclic graph (DAG) showing causal pathways from an exposure (X) to an outcome (Y)

It is essential to control for all confounding variables mentioned above as violation of those assumptions can produce biased results. [74-76] Further, the assumption of no interaction between the exposure and the mediator is essential using the difference method. If the assumption is violated, the results of mediation analysis might be invalid. [74-77] Fitting an interaction between the exposure and the mediator(s) does not accurately estimate the direct and indirect effects as handling the interaction coefficients and multiple direct effects is challenging. [74-77] In a later section on multiple mediators, I discuss the issue of exposure-induced mediator-outcome confounding (violation of assumption 4) in mediation analysis.

### 6.5.1. Causal mediation analysis

Causal mediation analysis based on the counterfactual framework is the modern way to estimate to what extent the effect of an exposure on an outcome is mediated by a particular variable(s) and to providing insight into the mechanisms underlying the effect of socio-economic disadvantage on cancer survival

by decomposing the total effect (TE) into the product of DE and IE. These novel methods not only quantify the contributions of potential mediators, but have also led to new definitions of direct and indirect effects, which improves the validity and interpretation of the mediation analysis results. [74, 75]

The counterfactual definitions of DE and IE rely on the construct of what happens if we intervene on either one or both the exposure and the intermediate variable. [74, 75] For illustration, Y indicates the outcome, X refers to the exposure of interest, M denotes the post-exposure intermediate variable, and C represents common cause(s) of any two variables. $Y_0$ is the counterfactual outcome when setting the exposure level of X=1 to X=0, $M_0$ is the counterfactual outcome when setting the exposure level of X=1 to X=0, and $Y_{00}$ is the counterfactual outcome when setting the exposure and the mediator level from X=1 and M=1 to X=0 and M=0. [74, 75]

The counterfactual-based concept and definition of controlled direct effect (CDE), natural direct effect (NDE) and indirect effect (NIE) was introduced by Robins and Greenland (1992) and Pearl (2001). [78, 79] Robins and Greenland argued that NDE and NIE are not identifiable or separable using data from randomised trials or observational studies. [79] In contrast, Pearl proved that the decomposition of the TE into NDE and NIE is possible in the presence of interactions and nonlinearities if the above four strong assumptions (shown in the box) hold. [78]

The controlled direct effect compares the exposure effect at level X=1 with X=0, fixing the mediator to a particular value M=m. [74, 75]

$$CDE = Y_{1m} - Y_{0m}$$

The natural direct effect compares the exposure effect at level X=1 with X=0, fixing the mediator to the value that naturally arises when individuals are unexposed ($M=M_0$). [74, 75]

$$NDE = Y_{1M0} - Y_{0M0}$$

The natural indirect effect comparing the mediator effect $M=M_1$ with $M=M_0$, fixing the exposure value to X=1 is: [74, 75]

$$NIE = Y_{1M1} - Y_{1M0}$$

The total effect is estimated as

$$TE = Y_1 - Y_0 = Y_{1M1} - Y_{0M0}$$

$$NIE + NDE = (Y_{1M1} - Y_{1M0}) + (Y_{1M0} - Y_{0M0})$$

### 6.5.2. Multiple mediators

In mediation analysis, we frequently face the violation of the fourth assumption when the exposure affects the mediator-outcome confounder. The traditional method of adjusting for mediators fails to identify NDE and NIE in the presence of multiple mediators that are interrelated and interacting with each other (Figure 6.6). In this more complex setting, adding mediators one at a time to the regression model gives rise to biased estimates, and sometimes the sum of the estimated indirect effects can be more than the total effect. [74, 75] Moreover, the difference method for binary common outcomes

underestimates the mediated effect as the odds ratios are not collapsible; [74, 75] therefore, the exposure coefficient may slightly decrease or increase after adding the mediator as the marginal and conditional odds ratios are incomparable. [74, 75]

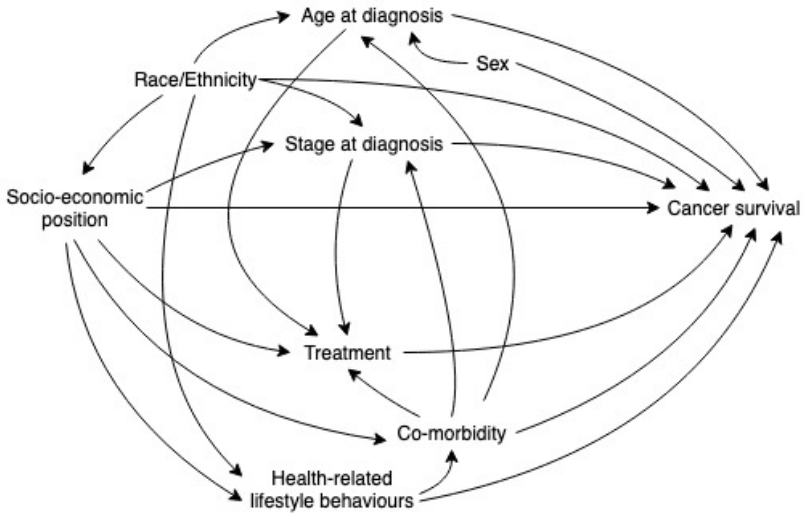



**Figure 6.6.** A directed acyclic graph (DAG) showing assumed causal associations between socio-economic position and cancer survival

VanderWeele, Vansteelandt and Robins (2014) developed regression-based methods to deal with the presence of exposure-induced mediator-outcome confounding. [77] These approaches are useful for decomposing the total effect where the first three assumptions hold, although natural (in)direct effects may not be identifiable. [77] One approach is to consider the exposure-induced confounder and the mediator jointly as one mediator; another method is to identify path-specific effects using sequential causal mediation analysis; and a third is to consider interventional analogues of natural direct and indirect effects. [77] To explain these three alternative approaches, a causal diagram is presented below (Figure 6.7).

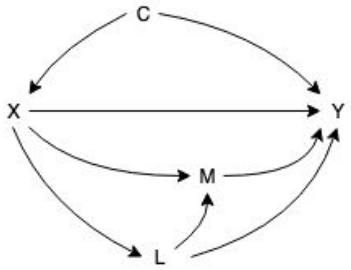



**Figure 6.7.** A directed acyclic graph (DAG) with mediator (M)-outcome (Y) confounder (L) affected by the exposure (X), (C) is an exposure-outcome confounder

In the joint mediator approach, variables L and M are considered together as a single mediator. This approach is inadequate if we are interested in estimating the separate IEs through M and L. [77] Sequential methods allow us to identify indirect effects through each of the pathways X→M→Y, X→L→M→Y and X→L→Y, although the direct and indirect effects with M as primary mediator are not identified. [77]

The validity of this approach depends on whether the sequence and the direction of arrows between the mediators are correct.

The third approach, also known as interventional, randomly assigns M a value chosen from the distribution of a particular level of exposure (X). Under this scenario, the controlled direct effect of the exposure (X) on the outcome (Y) is estimated by randomly allocating the mediator to a value (M=m) from the distribution of the mediator among exposed (X=1) versus non-exposed (X=0) individuals. [77] Then, the direct effect is estimated by comparing the exposed (X=1) versus non-exposed (X=0) group, with the mediator randomly set to a value from the distribution of those unexposed ($M=M_0$) i.e. set the mediator to a value that could naturally arise in the absence of the exposure. [77] Lastly, the anticipated outcome is compared when individuals are exposed (X=1), with the mediator randomly assigned to a value from the distribution of those exposed ($M=M_1$) to a value from the distribution of the individuals unexposed ($M=M_0$). [77]

The feasibility of identifying natural direct and indirect effects has been questioned due to untestable and generally unsatisfied strong assumptions of no unmeasured confounding as well as dependence on unobservable "cross-world" counterfactuals, in which the potential outcome is assumed to be independent of interventions on the exposure or the mediator. [80] Vansteelandt and Daniel (2017) reviewed interventional direct and indirect effects proposed by VanderWeele *et al* in 2014 and introduced a revised version which is not based on a cross-world counterfactual independencies framework and is applicable under weaker assumptions. [80] In contrast to natural effects, the direct and indirect effects are defined based on population-level interventions applying a regression approach. [80] The interventional approach, without changing the causal structure, allows decomposition of the total effect into different pathways through multiple mediators, in situations where (i) we cannot intervene on the exposure (e.g. socio-economic position), (ii) the causal sequence is uncertain or unknown, and (iii) there are unmeasured confounders between the mediators. [80] Thus, the mediated effects through single mediators or via the mediators' dependence are identifiable. [80]

In this thesis, for all of the reasons discussed above, the interventional causal mediation analysis method proposed by Vansteelandt and Daniel (2017) is used to assess the underlying causes of socio-economic inequalities in survival from colon cancer.

## Chapter 7 . Differences in cancer survival by sex: a population-based study using cancer registry data

In this chapter, an analysis of the Victorian Cancer Registry data was carried out to investigate differences in cancer patient survival by sex.

This study was conceptualised and designed in consultation with Professor Dallas English and Professor Roger Milne. I led this study, conducted the analyses and drafted the manuscript. Associate Professor Paul Mitchell provided clinical advice. Helen Farrugia and Vicky Thursfield curated the data. All co-authors reviewed the manuscript.

This chapter includes the author-accepted version of the paper.

The list of references is formatted according to the journal requirements with separate numbering to the thesis reference list. Supplementary materials related to this publication are presented in Appendix D.

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**Differences in cancer survival by sex: a population-based study using cancer registry data**

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**Keywords:** Sex differences; Inequalities; Cancer registries; Survival analysis; Cancer survival; Excess mortality

**Abstract**

**Purpose** Few large-scale studies have investigated sex differences in cancer survival, and little is known about their temporal and age-related patterns.

**Methods** We used cancer registry data for first primary cancers diagnosed between 1982 and 2015 in Victoria, Australia. Cases were followed until the end of 2015 through linkage to death registries. Differences in survival were assessed for 25 cancers using the Pohar-Perme estimator of net survival and the excess mortality rate ratio (EMRR) adjusting for age and year of diagnosis.

**Results** Five-year net survival for all cancers combined was lower for men (47.1%; 95% CI 46.9–47.4) than women (52.0%; 95% CI 51.7–52.3); EMRR 1.13 (95% CI 1.12–1.14; $p < 0.001$). A survival disadvantage for men was observed for 11 cancers: head and neck, esophagus, colorectum, pancreas, lung, bone, melanoma, mesothelioma, kidney, thyroid, and non-Hodgkin lymphoma. In contrast, women had lower survival from cancers of the bladder, renal pelvis, and ureter. For the majority of cancers with survival differences, the EMRR decreased with increasing age at diagnosis; for colorectal, esophageal, and kidney cancer, the EMRR increased with time since diagnosis.

**Conclusion** Identifying the underlying reasons behind sex differences in cancer survival is necessary to address inequalities, which may improve outcomes for men and women.

## 7.1. Introduction

Despite well-established evidence that sex is an important determinant of the incidence of and survival from several diseases, the potential role of patients' sex is often left unexplored, and is even under-reported, in cancer research [1–3]. Some studies have shown higher survival for women, relative to men, for cancers such as lung [4–8], colorectal [9–11], and melanoma [12–14]. In contrast, it has been consistently reported that women with bladder cancer have lower survival than men [15–18]. To date, few of the studies that have explicitly addressed sex differences in cancer survival have found that men typically have lower survival than women for the majority of cancers, but the reasons remain unknown [19–26]. There is limited knowledge about sex differences in cancer survival, and whether these inequalities are changing over time. This highlights the need to explore the magnitude and temporal and age-related patterns of survival differences between men and women based on robust data, which may provide useful information to improve cancer survival and decrease the global burden of cancer.

In this study, we investigated sex differences in cancer survival using data from the population-based Victorian Cancer Registry. We modeled excess mortality to assess heterogeneity in the excess risk of death due to cancer by sex according to age at diagnosis, time since diagnosis, and year of diagnosis.

## 7.2. Materials and methods

### *Data sources*

All incident cancers were identified from the Victorian Cancer Registry (VCR), a population-based registry to which, since 1982, all new cases of primary, invasive cancer diagnosed in the state of Victoria, Australia are reported under statutory requirements. For each cancer, demographic details (patient name, sex, date of birth, country of birth, ethnicity, residential address) and tumor characteristics (date of diagnosis, anatomical location, morphology, grade, behavior code) are collected from hospitals and pathology laboratories in Victoria. The VCR is linked monthly to the Victorian Registry of Births, Deaths and Marriages and annually to the National Death Index at the Australian Institute of Health and Welfare to update mortality information. Ethical approval to conduct the analyses of these data was granted by the Cancer Council Victoria Human Research Ethics Committee.

### *Study cohort*

The study cohort comprised cases (aged 15–99 years) with a first primary cancer of any type diagnosed between January 1982 and December 2015. We restricted to first primary cancers to ensure that the survival estimates reflected the experience of the vast majority of cancer patients, who do not have multiple primary cancers. We excluded *in situ* neoplasms, keratinocyte carcinoma, sex-specific cancers (vulva, vagina, cervix uteri, corpus uteri, uterus unspecified, ovary, other unspecified female genital organs, placenta, penis, prostate, testis, other and unspecified male genital organs; ICD-10 C51–C58, C60–C63), and breast cancer (C50). Cases notified via autopsy and death certificate only or diagnosed

on 31 December 2015 (the last date of follow-up for vital status) were also excluded. Cases with the same date of diagnosis and death were given 1 day of survival because otherwise they would have been excluded from the statistical analyses, which could have biased the estimates of net survival [27]. We included 412,471 cases and analyzed all 25 individual cancer types with at least 1,000 cases defined according to the International Statistical Classification of Disease and Related Health Problems, tenth revision [28]. In addition, we classified lymphoma and leukemia based on the revised World Health Organization (WHO) classification of neoplastic diseases of the hematopoietic and lymphoid tissue, [29] in accordance with the recommendations of the Australasian Association of Cancer Registries and Australian Blood Cancer Registry [30].

Lung cancer morphology codes were grouped into six categories according to the International Agency for Research on Cancer (IARC) histological classifications: [31] squamous cell carcinoma (International Classification of Diseases for Oncology-Third Edition (ICD-O-3) codes: 8050–8078, 8083–8084), adenocarcinoma (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, 8576), small cell carcinoma (8041–8045, 8246), large cell carcinoma (8010–8012, 8014–8031, 8035, 8310), unspecified malignant neoplasm (8000–8005), and other specified malignant neoplasm [31].

***Statistical analysis***

Net survival probabilities with 95% confidence intervals (CIs) were calculated by the Pohar-Perme method [32] using Victorian population life tables stratified by calendar year, age, and sex [33]. We estimated 5-year cumulative net survival for men and women for all cancers combined and separately by cancer type. To allow comparison between men and women, we generated age-standardized net survival estimates for each cancer type using site-specific weights calculated from the observed proportion of cases across age groups 15–44, 45–64, 65–74, and 75–99 years. In addition, we calculated case-mix-standardized net survival estimates for all cancers combined to account for sex variations in the distribution of cases by cancer site [20]. Follow-up began at date of diagnosis and ended 5 years after diagnosis, on the patient's 100th birthday, date of death, or 31 December 2015, whichever came first.

We modeled the effect of sex on the excess mortality rate, which is the additional hazard of death due to a cancer diagnosis. We first estimated expected survival for each patient using the Ederer II method [34], collapsed the resulting data by time since diagnosis, age, and sex and then modeled excess mortality rates using Poisson regression with a non-standard link function [35]. The covariates included in the main model (Model 1) were time since diagnosis (1st, 2nd, 3rd, 4th, and 5th year of follow-up), sex, age at diagnosis (15–44, 45–64, 65–74, and 75–99 years), and year of diagnosis (1982–1986, 1987–1991, 1992–1996, 1997–2001, 2002–2006, 2007–2011, 2012–2015). For comparative studies of cancer survival, it has been recommended that analyses cannot be restricted to first primary cancers because

completeness of ascertainment of previous cancers is dependent on the length of time that registries have been in existence [36]. Adjustment for year of diagnosis prevented any bias arising from the restriction to first primary of any site. Excess mortality rate ratios (EMRRs) for men relative to women are derived from the models; an EMRR of 1.2 indicates that males have a 1.2 times higher excess mortality than females.

An interaction between time since diagnosis and age group was also fitted, as older cancer patients generally have higher excess risk of death during the first 2 years following diagnosis [37]. To assess trends in the EMRR, we compared models with and without interactions between sex and time since diagnosis (Model 2), sex and age at diagnosis (Model 3), and sex and year of diagnosis (Model 4). Models 2, 3, and 4 were run for each cancer type that showed significant differences by sex in Model 1. Stratified analyses by time since diagnosis, age at diagnosis, and year of diagnosis were also conducted.

Statistical significance was assessed using the likelihood ratio test and a two-sided p value threshold of 0.05. Model goodness of fit was assessed using the deviance Pearson Chi- square ($\chi 2$) statistic and the residual degrees of freedom. All statistical analyses were conducted using Stata/MP version 14.2 (Stata Corporation LLC, College Station, TX, USA).

**7.3. Results**

We analyzed data for 412,471 Victorians (239,517 men and 172,954 women) diagnosed between 1 January 1982 and 30 December 2015 (Figure. 7.1) with one of 25 cancers (listed in Table 7.1). Of those, 3,217 (0.8%) died on the day they were diagnosed, but the cancer was reported independently of the death certificate. For all 25 cancers combined, the mean age at diagnosis of men was slightly lower than for women (65.2 compared with 65.7 years). Most cancers were more common in men, except cancers of the anus and anal canal, gallbladder and biliary tract, and thyroid (Table 7.1).

Five-year net survival for all 25 cancers combined was lower for men (47.1%; 95% CI 46.9–47.4) than for women (52.0%; 95% CI 51.7–52.3). As shown in Table 7.1 and Figure. 7.2, of the 25 cancer types, a survival disadvantage for men was observed for 11. The largest difference was observed for melanoma; men had twofold higher excess mortality compared with women (EMRR 2.02; 95% CI 1.86–2.19). A greater excess risk of death for men than for women was evident for common cancers such as colorectal (EMRR 1.04; 95% CI 1.02–1.07) and lung (EMRR 1.09; 95% CI 1.07–1.11). Similar patterns were also observed for cancers of the head and neck, esophagus, pancreas, bone and cartilages, mesothelioma, kidney, thyroid, and non-Hodgkin lymphoma, with EMRR estimates ranging from 1.07; 95% CI 1.03–1.11 to 1.47; 95% CI 1.1.21–1.79. In contrast, men had a survival advantage for bladder cancer and cancers of the renal pelvis, ureter, or other/unspecified urinary organs ($p< 0.001$). We observed no significant evidence of survival differences between men and women for cancers of the stomach, small intestine, anus and anal canal, liver, gallbladder and biliary tract, connective and soft

tissue, eye, brain and central nervous system or unknown primary, or for Hodgkin lymphoma, multiple myeloma, or leukemia (Figure. 7.2), although men had lower survival than women for chronic lymphoblastic leukemia (Supplementary Fig. 7.1).

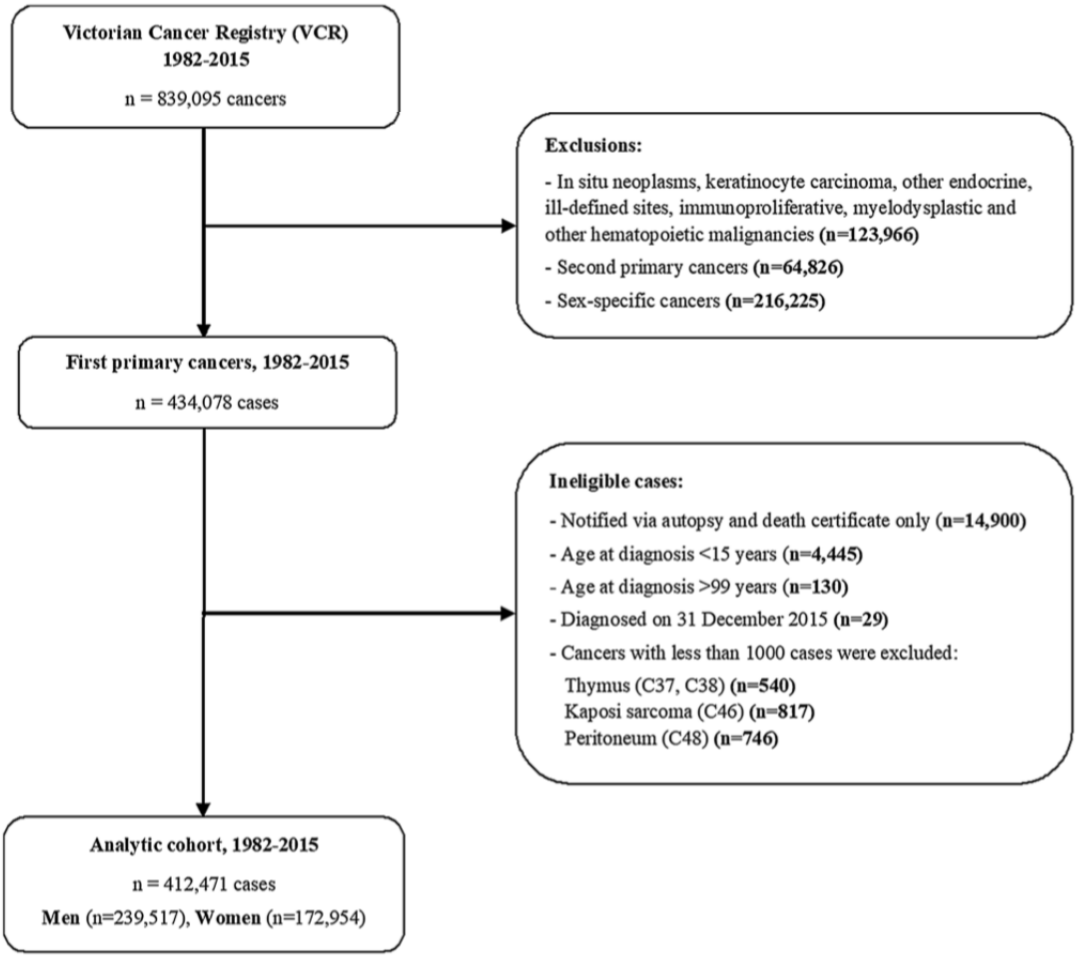


**Figure. 7.1.** Flowchart of case selection from the Victorian Cancer Registry for the analysis in the study

**Table 7.1.** Number of cases and deaths, and 5-year age-standardized net survival in Victoria, Australia for men and women, 1982–2015

| ICD-10 | Cancer site | Men | | Women | | Men | Women | p value (Wald test) |
|---|---|---|---|---|---|---|---|---|
| | | Cases | Deaths | Cases | Deaths | Net survival (%) (95% CI) | Net survival (%) (95% CI) | |
| C00–14, C30–32 | Head and neck | 17,817 | 11,024 | 6,710 | 3,828 | 67.5 (66.6–68.5) | 72.5 (71.1–73.8) | < 0.001 |
| C15 | Esophagus | 5,169 | 4,531 | 2,901 | 2,561 | 15.4 (14.2–16.6) | 20.9 (19.2–22.7) | < 0.001 |
| C16 | Stomach | 10,336 | 8,745 | 5,699 | 4,745 | 23.4 (22.4–24.4) | 26.0 (24.7–27.3) | 0.4 |
| C17 | Small intestine | 972 | 571 | 893 | 507 | 57.1 (52.9–61.0) | 56.6 (52.6–60.4) | 0.5 |
| C18–20 | Colorectum | 47,614 | 31,059 | 41,693 | 26,585 | 59.8 (59.2–60.4) | 61.2 (60.6–61.8) | 0.001 |
| C21 | Anus and anal canal | 691 | 408 | 1,022 | 557 | 61.4 (56.1–66.3) | 64.5 (60.6–68.0) | 0.1 |
| C22 | Liver | 4,929 | 4,096 | 1,785 | 1,502 | 14.3 (13.1–15.5) | 15.0 (13.0–17.1) | 0.2 |
| C23–24 | Gallbladder and biliary tract | 1,988 | 1,722 | 2,743 | 2,403 | 16.7 (14.8–18.7) | 17.3 (15.7–19.0) | 0.2 |
| C25 | Pancreas | 7,473 | 6,919 | 7,038 | 6,504 | 6.6 (6.0–7.4) | 7.3 (6.6–8.0) | < 0.001 |
| C33–34 | Lung, bronchus, and trachea | 39,895 | 36,779 | 21,163 | 18,340 | 11.7 (11.4–12.1) | 15.2 (14.6–15.7) | < 0.001 |
| C40–41 | Bone and cartilages | 741 | 353 | 544 | 243 | 62.7 (58.5–66.6) | 71.5 (67.1–75.5) | 0.001 |
| C43 | Melanoma | 26,817 | 9,801 | 24,347 | 6,864 | 88.0 (87.4–88.7) | 93.4 (92.8–94.0) | < 0.001 |
| C45 | Mesothelioma | 2,413 | 2,275 | 534 | 476 | 5.1 (4.2–6.3) | 8.4 (6.0–11.3) | 0.03 |
| C47–49 | Connective and soft tissue | 2,207 | 1,233 | 1,619 | 881 | 63.4 (60.6–66.0) | 62.7 (59.8–65.5) | 1.0 |
| C64 | Kidney | 8,948 | 4,833 | 5,106 | 2,625 | 63.8 (62.5–65.1) | 68.1 (66.6–69.6) | < 0.001 |
| C67 | Bladder | 11,991 | 8,778 | 4,137 | 3,124 | 63.3 (62.0–64.6) | 57.2 (55.2–59.2) | < 0.001 |
| C65–66, C68 | Renal pelvis, ureter, other/ unspecified | 1,330 | 949 | 993 | 762 | 52.0 (48.2–55.6) | 43.2 (39.6–46.8) | < 0.001 |
| C69 | Eye | 763 | 418 | 638 | 318 | 75.7 (70.8–79.8) | 77.7 (72.7–82.0) | 0.8 |
| C70–72 | Brain and central nervous system | 5,916 | 4,869 | 4,459 | 3,605 | 21.5 (20.5–22.5) | 24.2 (23.0–25.4) | 0.4 |
| C73 | Thyroid | 2,001 | 505 | 5,868 | 801 | 89.3 (87.3–91.0) | 93.7 (92.8–94.5) | < 0.001 |
| C80 | Unknown primary | 9,095 | 8,447 | 8,776 | 8,212 | 11.8 (11.0–12.6) | 10.7 (10.0–11.5) | 0.5 |
| C81 | Hodgkin Lymphoma | 2,099 | 594 | 1,724 | 446 | 83.9 (82.1–85.5) | 84.0 (82.1–85.7) | 0.6 |
| C82–86 | Non-Hodgkin lymphoma | 14,425 | 8,123 | 11,995 | 6,628 | 62.9 (61.8–63.9) | 65.5 (64.5–66.5) | < 0.001 |
| C90 | Multiple myeloma | 4,571 | 3,299 | 3,831 | 2,752 | 39.1 (37.3–40.9) | 41.5 (39.6–43.4) | 0.1 |
| C91–95 | Leukemia | 9,316 | 6,330 | 6,736 | 4,614 | 46.6 (45.3–47.9) | 46.2 (44.8–47.6) | 0.5 |
| **C00–95** | **All cancers combined*** | **239,517** | **166,661** | **172,954** | **109,883** | **47.1 (46.9–47.4)** | **52.0 (51.7–52.3)** | < **0.001** |
| **C00–95** | **Case-mix-standardized*** | | | | | **48.2 (48.0–48.4)** | **50.4 (50.2–50.7)** | < **0.001** |

*Excluding sex-specific cancers and breast cancer

*CI* confidence interval, *LR* likelihood ratio

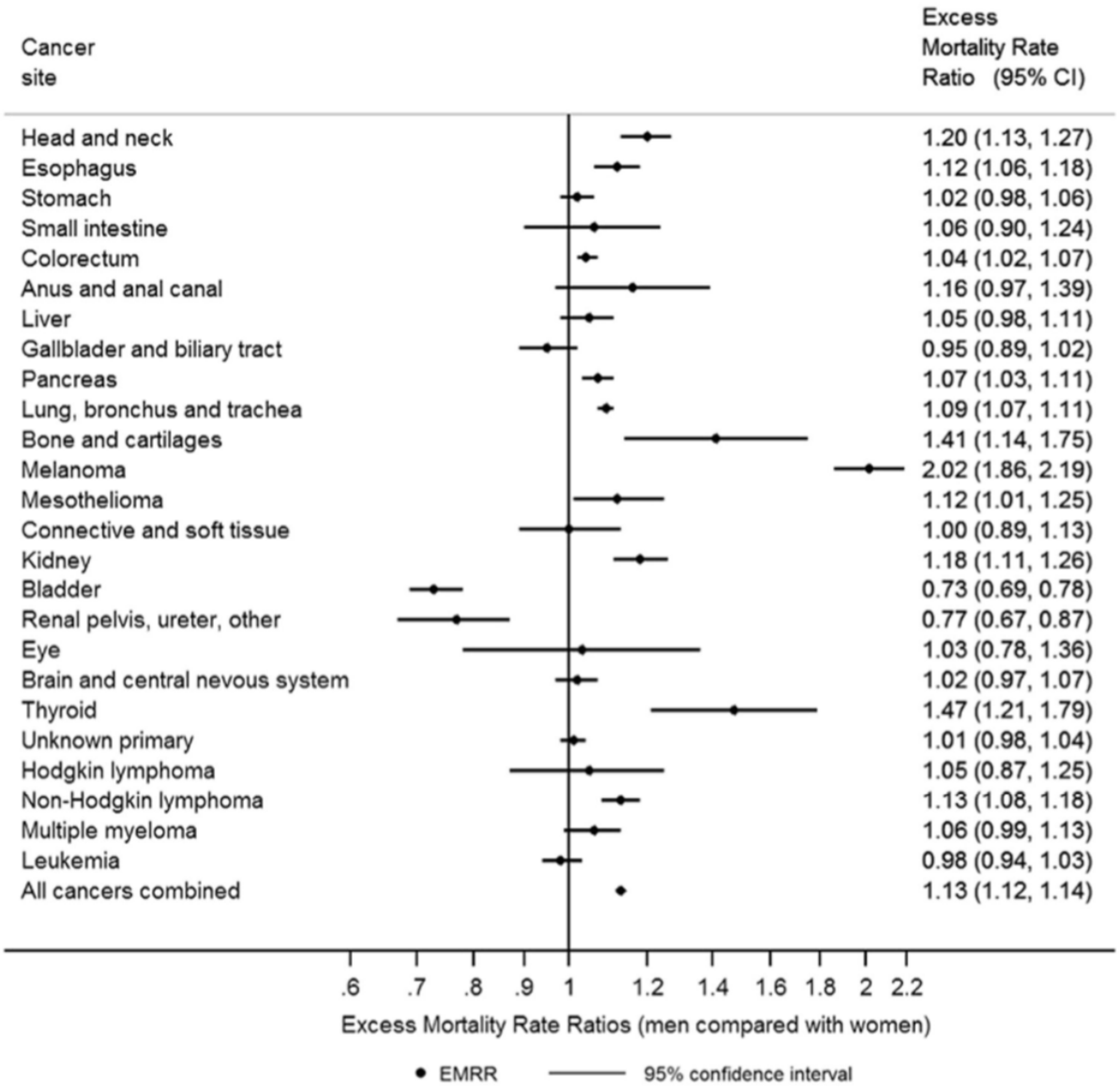


**Figure. 7.2.** Excess Mortality Rate Ratios (EMRRs) within 5-years post diagnosis for men compared with women, 1982–2015

For seven of the 11 cancers with a male excess risk of death, the excess decreased with increasing age at diagnosis (Figure. 7.3; Supplementary Table 7.1). For all of these, except melanoma, there was no difference in survival between men and women diagnosed at age 75 years or older; for head and neck and colorectal cancer, this trend was observed for cases aged ≥ 45 years, but no difference was observed for early-onset disease (age < 45 years) (p departure from linearity ≤ 0.02).

For esophageal and colorectal cancer, the EMRRs increased from approximately one with time since diagnosis (Figure. 7.4; Supplementary Table 7.2); weaker evidence was observed of a similar trend for kidney cancer. The survival advantage of men over women for bladder cancer was only present in the first 2 years following diagnosis (Figure. 7.4, Supplementary Table 7.2; p-departure from linearity = 0.03).

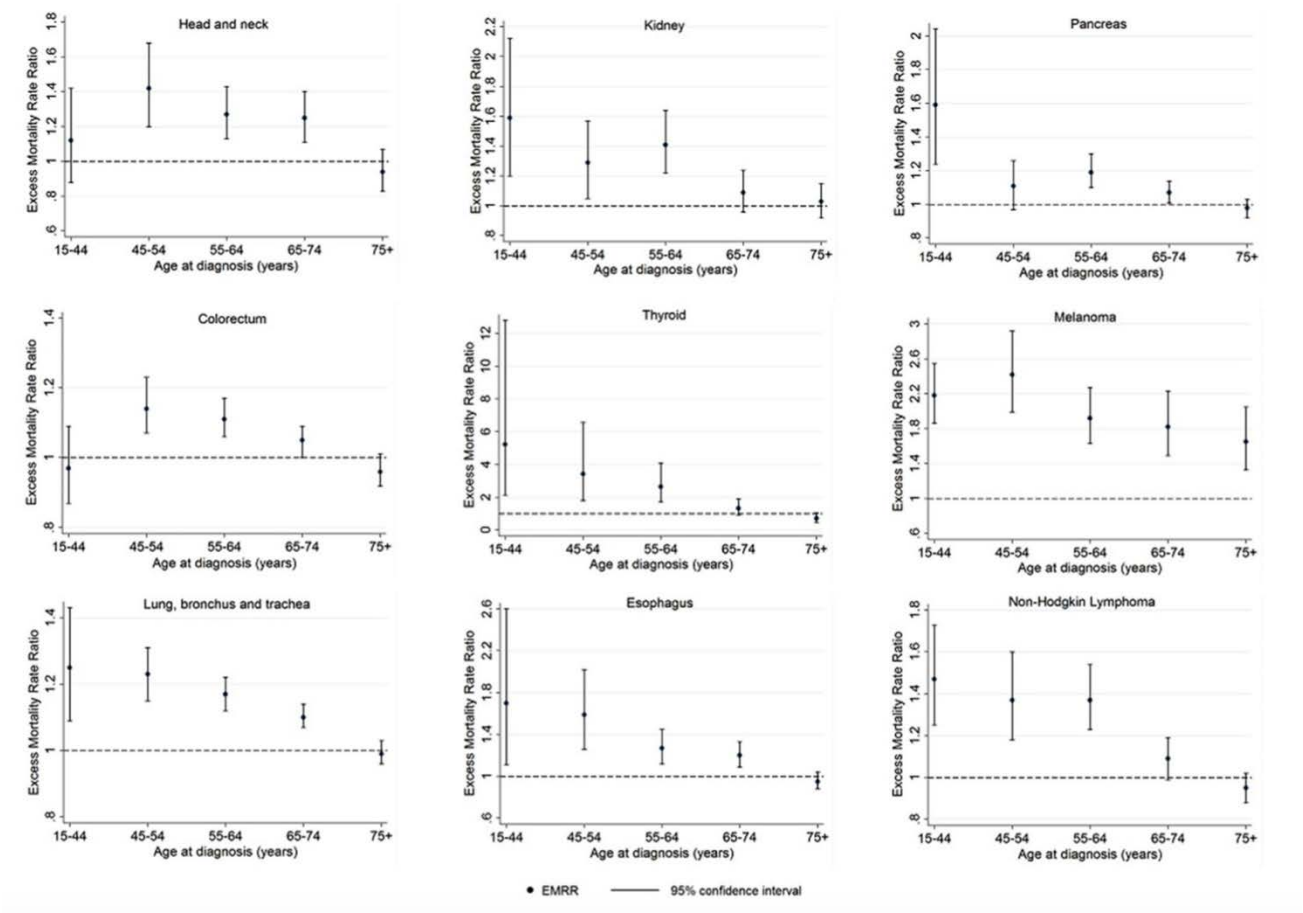


**Figure. 7.3.** Excess Mortality Rate Ratios (EMRRs) for men compared with women, by age at diagnosis. The dashed line shows the reference value for the EMRR, representing no difference between men and women

With respect to year of diagnosis, sex differences for lung cancer increased over time, although no difference was observed for the first three periods (Figure. 7.5; Supplementary Table 7.3); weaker evidence of this pattern was also noted for bladder and thyroid cancer. In contrast, sex differences in colorectal and pancreatic cancer diminished over time and were not observed in the most recent 9 years.

Given the widening sex differences in lung cancer survival over calendar time, we investigated whether this phenomenon could be explained by changing patterns of histological type over time. We therefore examined trends of lung cancer incidence and excess mortality rates by histological type. Age-adjusted incidence rates for men declined over the 33-year period for all histological types except adenocarcinoma (Supplementary Fig. 7.2). For women, the incidence of squamous and small cell carcinoma did not change markedly over time, while it decreased for large cell carcinoma. The incidence of adenocarcinoma has increased for both men and women since 1982, and it is now the most common type of lung cancer diagnosed in both sexes.

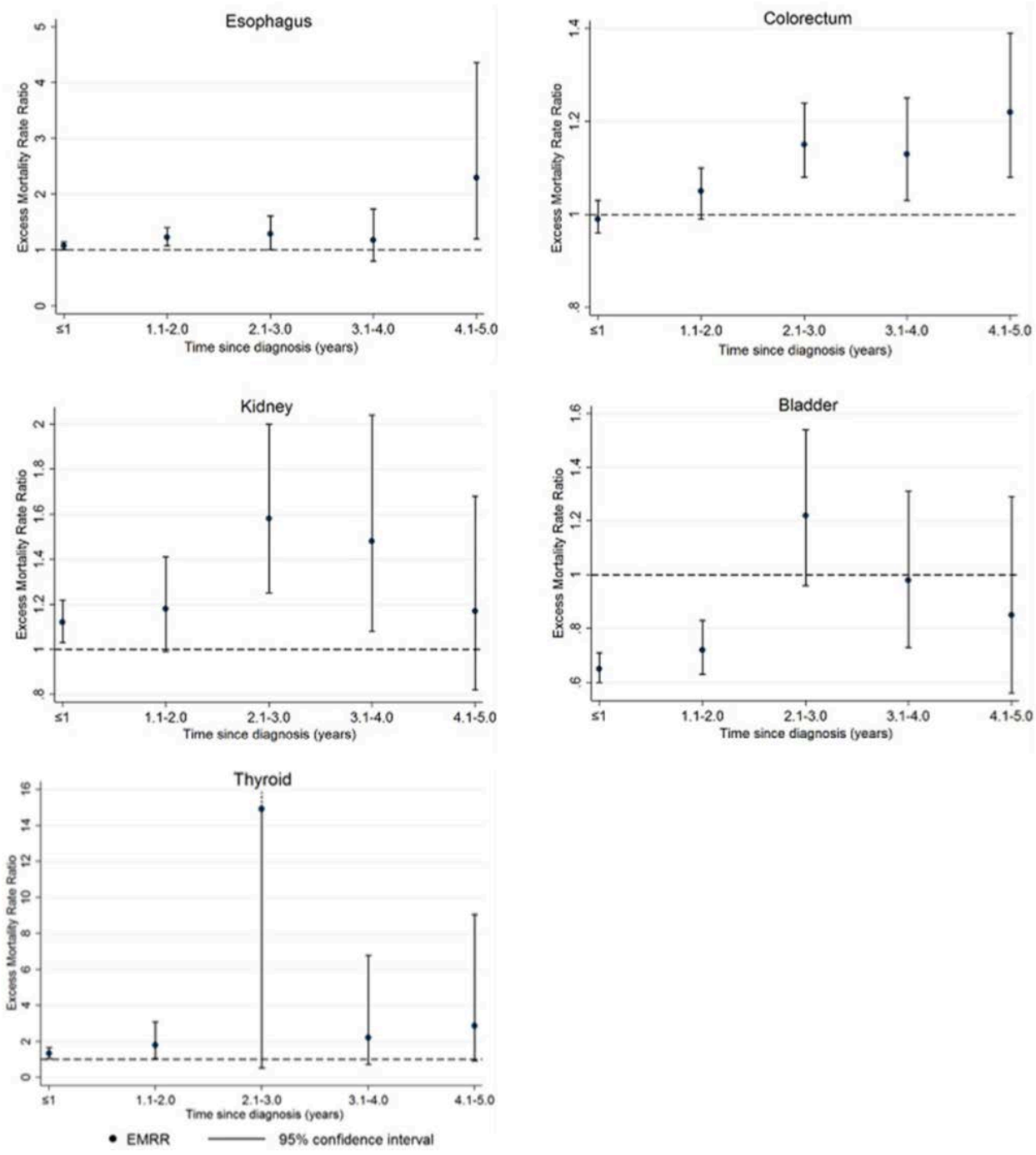


**Figure. 7.4.** Excess mortality rate ratios (EMRRs) for men compared with women, by time since diagnosis. The dashed line shows the reference value for the EMRR, representing no difference between men and women

Relative to women, men had a higher excess risk of death within five years following diagnosis with adenocarcinoma (EMRR 1.23; 95% CI 1.18–1.27) and small cell carcinoma (EMRR 1.12; 95% CI 1.07–1.18), but men did not have lower survival than women for squamous and large cell carcinoma

(Supplementary Table 7.4). There were no significant trends in the EMRR over calendar time for any histological type. (Supplementary Table 7.5).

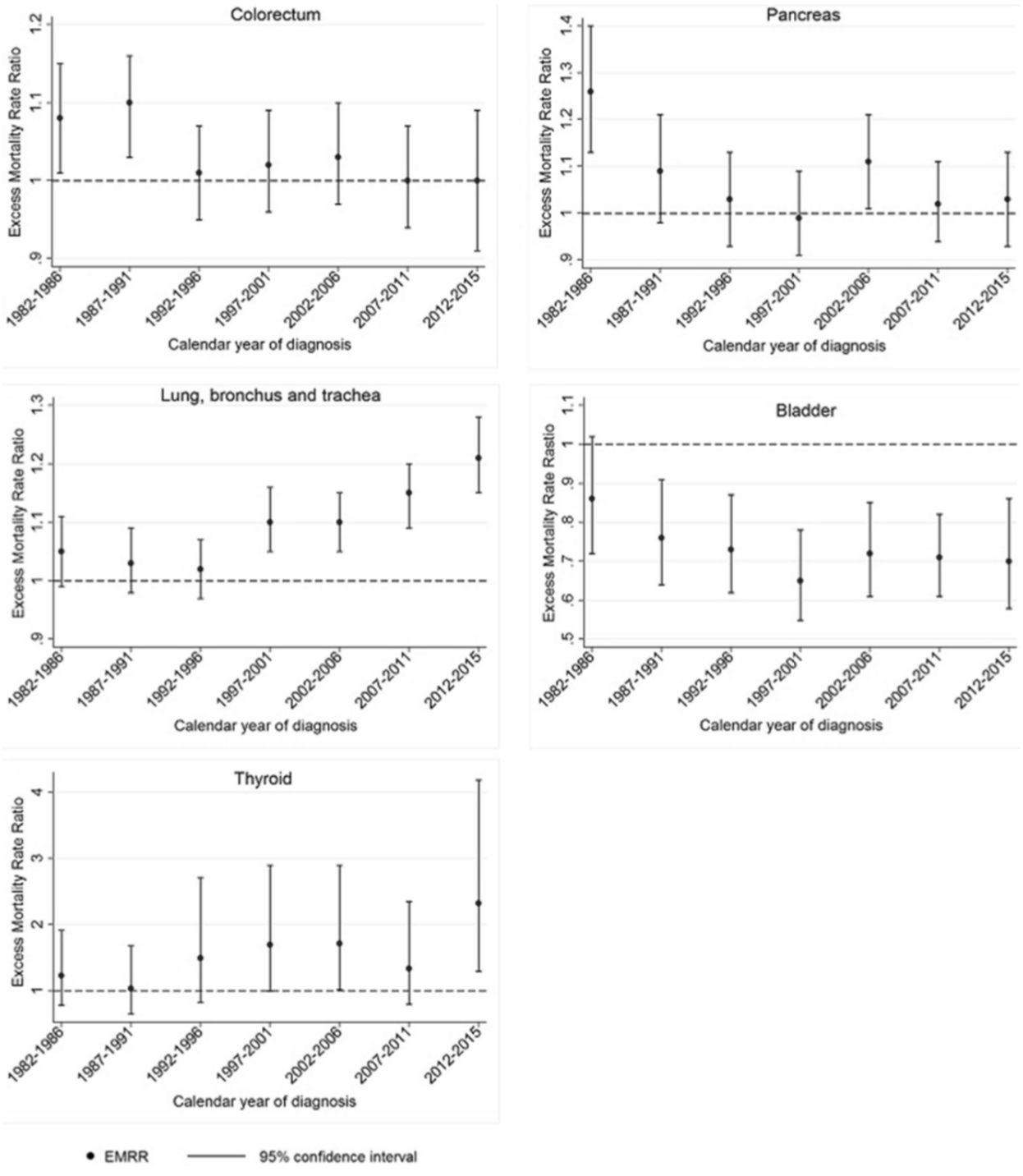


**Figure. 7.5.** Excess mortality rate ratios (EMRRs) for men compared with women, by year of diagnosis. The dashed line shows the reference value for the EMRR, representing no difference between men and women

### 7.4. Discussion

In this population-based study, men had a survival disadvantage relative to women for 11 of 25 cancer types. In contrast, women had lower survival than men for bladder cancer and cancers of renal pelvis or ureter and for 12 cancer types there were no differences in net survival. The sex differences were generally greatest for people diagnosed at younger ages. For esophagus and colorectal cancer, survival differences increased with time since diagnosis. Sex differences in cancer survival have decreased since 1982 for colorectal and pancreatic cancer to the point where they are no longer apparent. In contrast, for lung cancer, the male survival disadvantage is worse today than previously. An increase in the proportion of adenocarcinoma in women and decrease in squamous cell carcinoma in men may at least partly contribute to the increasing sex differences in lung cancer survival over time, as women have the greatest survival advantage for adenocarcinoma but no advantage for squamous cell carcinoma.

The main strengths of our study include the population-based design, complete follow-up through record linkage and the large sample size, permitting analyses by cancer type, age at diagnosis, time since diagnosis, and year of diagnosis. Limitations include the unavailability of data on cancer stage at diagnosis, treatment, co-morbidities, and health-related lifestyle behaviors, which prevented us from exploring the role of these factors as potential mediators of the sex differences in survival.

Findings from population-based studies conducted in the United States (USA) [24], Canada [20], Europe [19, 21, 23, 25, 26], and Korea [22] are generally consistent with ours. A study using USA Surveillance, Epidemiology, and End Results (SEER) data found lower cancer-specific survival for men than for women for most cancers, while women had lower survival for bladder and tongue cancer [24]. Results from the Canadian Cancer Registry also confirmed a male disadvantage in cancer survival, with the greatest sex differences for melanoma and thyroid cancer; bladder cancer was the only cancer for which women had higher excess risk of death [20]. In a Swedish study, men had lower survival for 27 of 39 cancer types and women had lower survival for urinary and biliary tract cancers [19]. Similarly, the EURO-CARE-4 project reported a higher excess mortality rate for men for 15 cancer types except for bladder, biliary tract, and leukemia [25]. In contrast to these results, a study in Estonia did not find significant survival difference between men and women for cancers of colon, rectum, pancreas, and bladder [21]. In the Austrian and Korean studies, while men were observed to have a survival disadvantage for most cancers, lower survival for colorectal, kidney, and bladder cancers were observed for women, although these findings were not statistically significant in the Austrian study [22, 23].

The underlying reasons for male disadvantage in surviving from cancers are unknown, but several theories have been proposed. Sex hormones might explain the survival advantage in premenopausal women, possibly by influencing tumor characteristics and the immune system [22, 25]. Some studies have reported that genes on the X chromosome affect the function of the immune system, protecting women from cancer progression or metastasis [38, 39]. Better health literacy or awareness of cancer

symptoms by women and greater willingness to uptake screening or seek medical help may also contribute to their survival advantage due to earlier stage of disease at diagnosis [19, 20, 40]. Alternative theories point to differences by sex in treatment modalities or compliance with treatment, and differences in co-morbidity prevalence and health-related lifestyle behaviors, especially cigarette smoking and alcohol consumption [21, 24], but these are largely speculative.

For bladder cancer, women have consistently been found to have lower survival [15–18, 41, 42]. Recent reviews have concluded that women are more likely than men to be diagnosed at an advanced stage and with higher-grade tumors [43, 44]. Women with early signs and symptoms of bladder cancer are often misdiagnosed with cystitis and urinary tract infections, leading to later diagnosis [18, 45– 47]. In addition, there is some evidence that variabilities in treatment may contribute to the inferior outcome for women [47].

For the majority of cancer types we studied, the higher excess rate of death for men with cancer relative to their female counterparts was greatest at younger ages. Previous studies have detected a similar gradient of greater survival differences among individuals diagnosed at younger ages to minimal differences in older patients [20, 22, 23, 25]. The authors of the EUROCARE-4 and Canadian studies also noted a greater survival disadvantage for men diagnosed before age 55 years than those diagnosed after [20, 25]. Micheli *et al*. postulated that age at diagnosis is a surrogate for biological factors, particularly sex hormones, which differ between the sexes and change dramatically in women during menopause [25]. It has been suggested that influences of testosterone on cancer aggressiveness in young and middle-aged men may also contribute to women's survival advantage at younger ages [48].

We observed increasing male survival disadvantage with time since diagnosis for esophagus, colorectal, and kidney cancer. A recent analysis of Canadian Cancer Registry data showed a similar pattern for cancers of the colon and rectum, at some extent for esophagus and kidney cancer, although for these latter two less significant survival differences were reported in the 3- to 5-year interval post-diagnosis [20]. Also consistent with our findings was the observation in this Canadian study that women's survival disadvantage for bladder cancer was only present in the first year following diagnosis [20]. It is unclear why these patterns with time since diagnosis would differ by cancer type.

It is also unclear why sex differences in cancer survival would increase over time for bladder (increasingly lower for women) and thyroid cancers (increasingly lower for men). The trend for thyroid cancer could be related to increasingly higher overdiagnosis for women relative to men [49, 50]. The evidence of these trends was relatively weak, with deviation from linearity observed for bladder cancer. These trends require replication in independent populations. There was much stronger evidence of increasing male survival disadvantage relative to women for lung cancer, a finding consistent with those reported in a recent population-based study from Japan [4]. On closer examination, it appears that at least part of this trend is explained by differences by sex in temporal trends in the incidence of the

histological types of the disease. Since 1982, the incidence of adenocarcinoma, for which women had the greatest survival advantage relative to men, has more than tripled for women and less than doubled for men. Further, the incidence of squamous cell carcinoma, for which women survive no longer than men, [5] has remained stable over time for women, but decreased by more than half for men. Other potential explanations for this trend include sex differences over time by stage at diagnosis, histology, smoking habits, and treatment modalities [4, 5]. We did not have information on smoking status, which is strongly associated with histological type and expected survival, and its prevalence varies between the sexes [8]. Blakely and colleagues describe the 'non-comparability bias' that can arise in relative survival and EMRR estimates by not using smoking status-specific life tables in analyses of smoking-related cancers [37]. The majority of lung cancer patients are smokers and, therefore, have a higher risk of death due to other causes than the general population. This means that the excess risk of death due to lung cancer would be overestimated [37]. This bias could have contributed to the observed higher EMRR for men compared with women because proportionally more lung cancers in men than women are due to smoking [51].

In conclusion, the current study showed that in Australia, men generally fare worse with cancer than women. It is essential to unravel the mediating effects of stage at diagnosis, co-morbidities, treatment modalities and health-related lifestyle factors on these sex differences in cancer outcomes. Emerging new methods from the causal inference literature offer promise in this area, particularly as access to linked population-based cancer and other health-related datasets improves. Future national and international research should focus on identifying actionable factors to address inequalities in cancer outcomes, which may improve survival for both men and women.

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

**Ethics approval** Ethical approval to conduct the analyses of these data was granted by the Cancer Council Victoria Human Research Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** For this type of study formal consent is not required.

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## Chapter 8 . Differences in cancer survival by area-level socio-economic disadvantage: a population-based study using cancer registry data

In this chapter, an analysis of the Victorian Cancer Registry data was carried out to investigate differences in cancer patient survival by area-level socio-economic disadvantage.
This study was conceptualised and designed in consultation with Professor Dallas English, Professor Roger Milne and Professor Graham Giles. I led this study, conducted the analyses and drafted the manuscript. Helen Farrugia and Vicky Thursfield curated the data. All co-authors provided advice in the interpretation of results and reviewed the manuscript.

This chapter includes the author-accepted version of the paper.
The list of references is formatted according to the journal requirements, with separate numbering to the thesis reference list. Supplementary materials related to this publication are presented in Appendix E.

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**Differences in cancer survival by area-level socio-economic disadvantage: a population-based study using cancer registry data**

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**Abstract**

Despite overall improvements in cancer survival due to earlier diagnosis and better treatment, socio-economically disadvantaged people have lower cancer survival than more advantaged people. We aimed to examine differences in cancer survival by area-level socio-economic disadvantage in Victoria, Australia and assess whether these inequalities varied by year of diagnosis, age at diagnosis, time since diagnosis and sex. Cases diagnosed with a first primary cancer in 2001–2015 were identified using the Victorian Cancer Registry and followed to the end of 2016. Five-year net survival and the excess risk of death due to a cancer diagnosis were estimated. People living in more disadvantaged areas had lower five-year survival than residents of less disadvantaged regions for 21 of 29 cancer types: head and neck, oesophagus, stomach, colorectum, anus/anal canal, liver, gallbladder/biliary tract, pancreas, lung, melanoma, connective/soft tissue, female breast, ovary, prostate, kidney, bladder, brain and central nervous system, unknown primary, non-Hodgkin lymphoma, multiple myeloma and leukemia. The observed lower survival in more deprived regions persisted over time, except head and neck cancer, for which the gap in survival has widened. Socio-economic inequalities in survival decreased with increasing age at diagnosis for cancers of connective/soft tissue, bladder and unknown primary. For colorectal cancer, the observed survival disadvantage in lower socio-economic regions was greater for men than for women, while for brain and central nervous system tumours, it was larger for women. Cancer survival is generally lower for residents of more socio-economically disadvantaged areas. Identifying the underlying reasons for these inequalities is important and may help to identify effective interventions to increase survival for underprivileged cancer patients.

## 8.1. Introduction

Over recent decades, survival has increased for most cancer types due to earlier diagnosis and more effective treatments. [1, 2] In parallel, there is well-documented evidence that socio-economic inequalities in cancer survival exist in high-income countries, with disadvantaged cancer patients having lower survival than their counterparts with higher socio-economic position (SEP). [3-5] Even though Australia has a universal health care system, socio-economic differences in cancer survival exist. [6-8] In 2010–2014, five-year relative survival for all cancers combined was lower for patients living in the most disadvantaged areas (55%), relative to the least disadvantaged areas (67%). [9] The largest gaps were found for cancers of the head and neck, colorectum, cervix, kidney, prostate as well as non-Hodgkin lymphoma. [9]

Australian studies that have investigated socio-economic differences in cancer survival have not used socio-economic status-specific life tables to estimate relative survival [8, 10] and may have provided biased survival estimates by overestimating relative survival gaps, as the expected background mortality of more disadvantaged people is likely to be underestimated in general population life tables (i.e. more deaths than should have been were attributed to cancer).

Several studies, including one from Australia, have observed differences in cancer survival by sex; men generally have lower survival than women for most cancers, [11-15] but it is not clear whether socio-economic inequalities in cancer survival differ between men and women. Additionally, published studies have not examined socio-economic inequalities by age at diagnosis or time since cancer diagnosis. We aimed to assess differences in cancer survival by area-level socio-economic disadvantage using the Victorian Cancer Registry data. We investigated whether these inequalities are widening or narrowing over time and examined differences by age at diagnosis, time since diagnosis and sex.

## 8.2. Materials and methods

### *Data sources*

Our analyses of deidentified Victorian Cancer Registry (VCR) data was approved by the Cancer Council Victoria Human Research Ethics Committee.

Cases were identified from records of invasive cancers held by the VCR, a population-based registry in the state of Victoria, Australia which receives notifications from hospitals, pathology laboratories and cancer screening registries. Data items collected for each cancer include date of diagnosis, tumour anatomical location, morphology, grade and behaviour, as well as patient name, address, date of birth and sex. Information on vital status is routinely updated via linkage to the Victorian Registry of Births, Deaths and Marriages and the National Death Index at the Australian Institute of Health and Welfare.

The address of usual residence registered at the time of diagnosis was mapped and coded to the smallest geographical areas defined by the Australian Bureau of Statistics (ABS). For cancer cases diagnosed in

2009–2015 this was Statistical Area Level 1 (SA1; mean population size of 400 persons), [16] and for cases diagnosed in 2001–2008, this was Collection District (CD; mean of 225 dwellings). [17] An area-based measure of socio-economic disadvantage (Socio-Economic Indexes for Areas, SEIFA) was determined using the census-based Index of Relative Socio-economic Disadvantage (IRSD). [18] A low score on the IRSD indicates a high proportion of economically and socially disadvantaged people in an area (e.g. many households with low income, many people with no qualifications or in low-skill occupations). [18] The distribution of SEIFA index values across geographical areas in the Victorian population was used to define quintiles, and the order reversed so that quintile 1 included the least disadvantaged and quintile 5 the most disadvantaged.

The ABS constructed SEIFA-specific life tables by year, sex and single year of age for the period 2001–2015. Victorian population mortality rates at ABS Statistical Area Level 2 (SA2) were aggregated into quintiles. The mortality curves for all SEIFA quintiles were smoothed using the Hodrick-Prescott filter to reduce the variability of *qx* values (i.e. the probability of dying at age x). [19]

***Study cohort***

Patients were eligible if they were diagnosed with a first primary cancer of one of 29 types in the period from 1 January 2001 until 30 December 2015 and aged 15–99 at diagnosis (n = 331,419). We chose the 29 cancers for which at least 1,000 cases were reported to the VCR during the study period. Second primary neoplasms, *in situ* cancers, keratinocyte carcinomas and male breast cancers were not considered. We excluded patients notified only via autopsy or death certificate as well as those with missing data for area-level socio-economic disadvantage.

***Statistical analysis***

We used the Pohar-Perme method with SEIFA-specific Victorian population life tables to calculate five-year net survival and 95% confidence intervals (CIs) for each quintile of socio-economic disadvantage. [20, 21] Net survival was estimated by first calculating the ratio of each patient's observed survival relative to that expected for a member of the general population without cancer and of the same age, sex, calendar year and SEIFA quintile, and then averaging for all patients. [20] Expected survival was calculated using the Ederer II method. [22] To allow comparisons across socio-economic groups with differing distributions of age at diagnosis, we calculated age-standardised net survival using age-specific weights. For each cancer site, the weights were calculated based on the distribution of age at diagnosis of all cancers of that site using five age groups (15–44, 45–6, 65–74, and 75–99 years). Follow-up commenced at date of diagnosis and concluded five years later, on the date of death, or December 31, 2015, whichever came first. To avoid bias in the estimation of survival, one day of survival was given to cases with the same date of diagnosis and death. [23]

We modelled excess mortality rates due to cancer. [24] The excess mortality rate is the difference between the mortality rate for patients and the expected mortality rate for the general population. First,

we calculated observed and expected rates by calendar year, age, sex, and SEIFA category and collapsed the resulting data by period of diagnosis (2001–2005, 2006–2010, 2011–2015), age at diagnosis (15–44, 45–64, 65–74, and 75–99 years), time since diagnosis (1st, 2nd, 3rd, 4th and 5th year) and sex. We then modelled these data using Poisson regression with each covariate included in the model, together with interaction terms between age group and time since diagnosis, as elderly cancer patients have higher excess risk of death within two years following diagnosis. [25] The exponentiated parameter estimates from these models are excess mortality rate ratios (EMRR). To interpret the EMRR, consider an EMRR of 1.4 comparing the most disadvantaged patients with the least disadvantaged. This value indicates that the excess mortality rate due to the cancer is 1.4 times higher for the most disadvantaged than for the least disadvantaged.

To assess heterogeneity in the EMRR, four additional models were run, fitting interactions between pseudo-continuous SEIFA (the quintiles were treated as continuous with 5 integer values) and each of (i) year of diagnosis, (ii) age at diagnosis, (iii) time since diagnosis, and (iv) sex. We conducted these analyses for cancer types that showed consistent trends in socio-economic differences in survival. We also stratified on these covariates.

People residing outside major cities are generally more disadvantaged and have been reported to have lower cancer survival. [9] Because the measures of remoteness and socio-economic disadvantage available were both area-based (using the same geographical areas), rather than adjusting for remoteness, we conducted a sensitivity analysis restricted to cases living in major cities as an attempt to remove any potentially confounding effects of factors associated with remoteness such as access to services.

We used Pearson's goodness-of-fit statistic to compare models with different number of degrees of freedom. [26] A likelihood ratio test and a two-sided **p** value were applied to assess statistical significance. Stata/MP version 14.2 (Stata Corporation LP, College Station, TX, USA) was used to perform all statistical analyses.

### 8.3. Results

A total of 331,419 Victorian residents diagnosed between January 1, 2001 and December 30, 2015 with one of the 29 incident cancers considered were included in the analyses (Figure 8.1). The number of cases and deaths for each cancer type, by area-level socio-economic disadvantage, are listed in S8.1 Table. The mean age at diagnosis was 63.5 years for patients living in the least disadvantaged areas and 66.7 years for cases from the most disadvantaged regions.

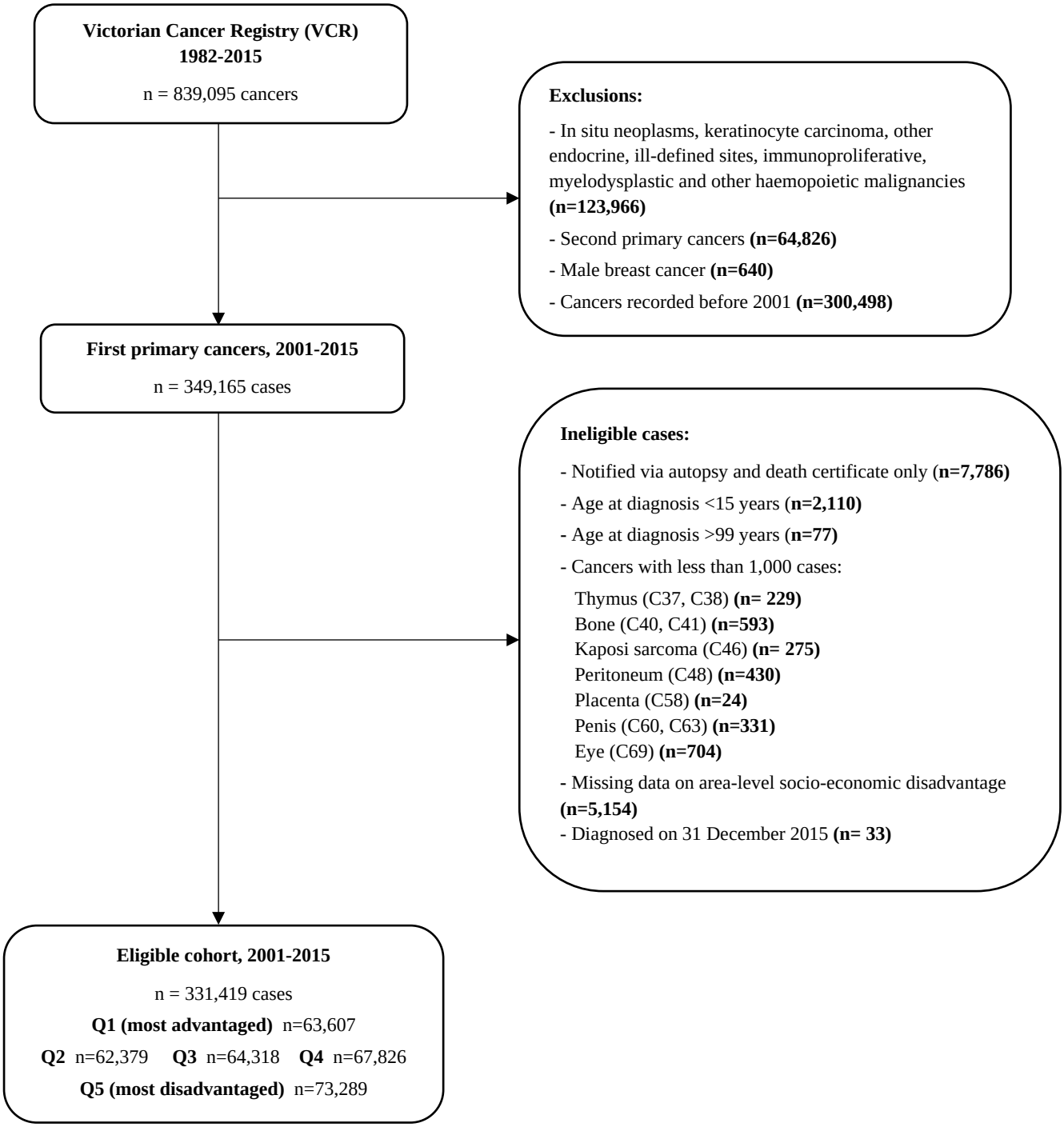


**Figure 8.1.** Case selection from the Victorian Cancer Registry

The EMRR and age-standardised five-year net survival estimates are presented in Figure 8.2 and S8.2 Table, respectively. For 21 of the 29 cancer types, a consistent trend of lower survival was observed for people living in more disadvantaged areas (p-trend <0.05 in Figure 8.2). The magnitude of these differences varied by cancer type (Figure 8.2), but was notable for the five most common cancers except lung cancer, with EMRR comparing the most with the least disadvantaged areas 1.40 (95%CI 1.32–1.49), 1.91 (95%CI 1.60–2.28), 1.76 (95%CI 1.55–1.99), 1.73 (95%CI 1.46–2.04) for colorectal cancer, melanoma, female breast and prostate cancer, respectively. The EMRR for the most relative to the least disadvantaged areas was also high for cancers of the head and neck (1.69; 95%CI 1.46–1.95), connective and soft tissue (1.60; 95% CI 1.20–2.14), kidney (1.34; 95%CI 1.15–1.56), bladder (1.32; 95%CI 1.15–1.52), unknown primary (1.33; 95%CI 1.22–1.45) and non-Hodgkin lymphoma (1.48; 95%CI 1.32–1.66). A similar pattern of lower survival in more disadvantaged areas was found for cancers of the oesophagus, stomach, anus/anal canal, liver, gallbladder/biliary tract, pancreas, lung, ovary, brain and central nervous system (CNS), multiple myeloma and leukaemia. For cancers of small intestine, mesothelioma, cervix, uterus, renal pelvis/ureter, thyroid and Hodgkin-lymphoma, there was some evidence of greater excess mortality in the most disadvantaged areas, but no clear trends across socio-economic groups (Figure 8.2). We observed no socio-economic differences in survival from cancer of vulva and vagina.

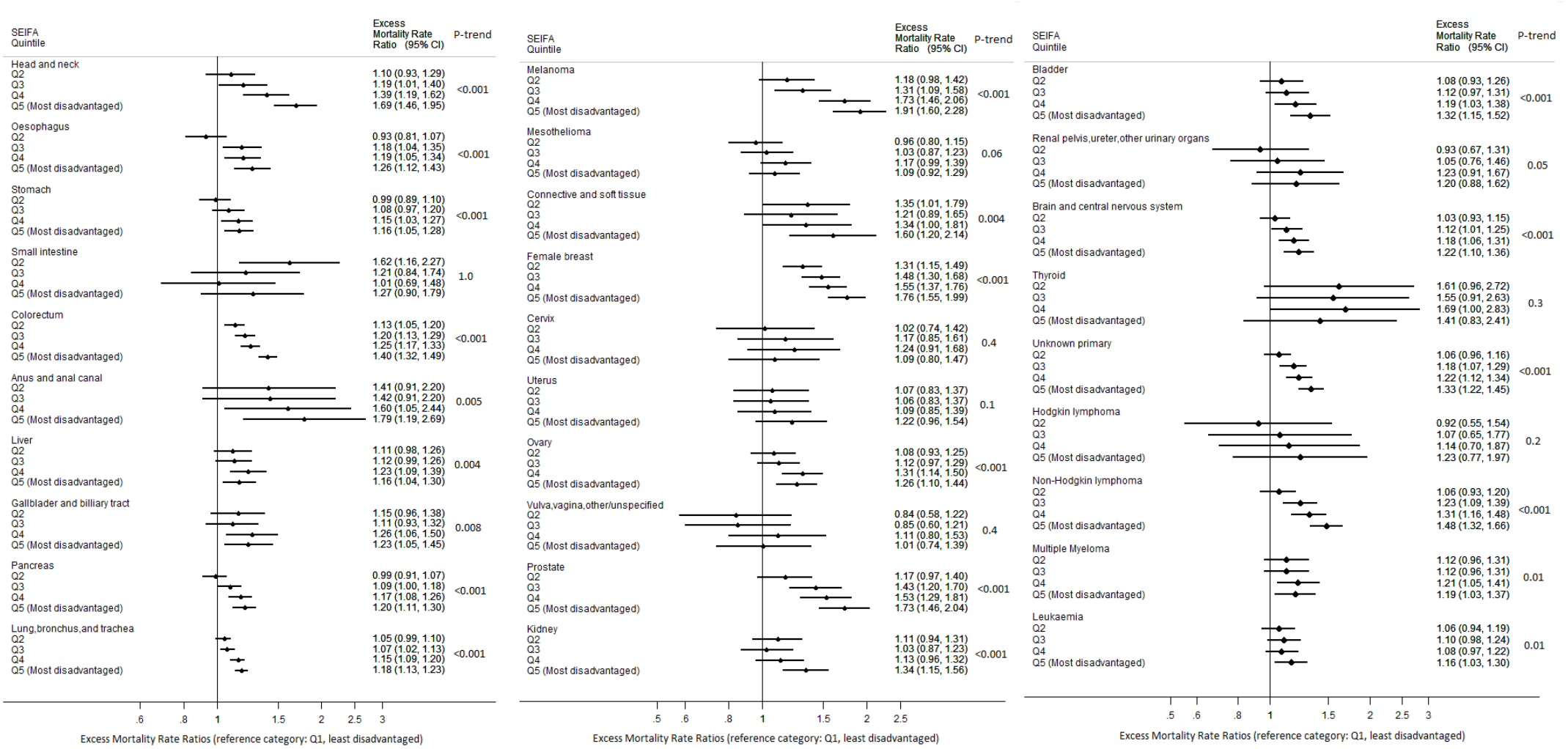


**Figure 8.2.** Excess Mortality Rate Ratios (EMRRs) within 5-year of diagnosis, by area-level socio-economic disadvantage, in Victoria, Australia, 2001–2015
Panel A: Cancer sites with ICD-10 C00-C34; Panel B: Cancer sites with ICD-10 C43-C63; Panel C: Cancer sites with ICD-10 C65-C96

There was no strong evidence of widening or narrowing gaps in survival over the study period except for head and neck cancer, for which differences in survival increased over time, from an EMRR per quintile increase in SEIFA-based disadvantage of 1.10 (95%CI 1.04–1.15) in 2001–2005 to 1.19 (95%CI 1.12–1.26) in 2011–2015 (S8.3 Table, Figure 8.3). Weak evidence of a similar pattern was noted for tumours of the brain and CNS. We also found weak evidence of decreasing differences in survival over time for non-Hodgkin lymphoma and oesophageal cancer (S8.3 Table).

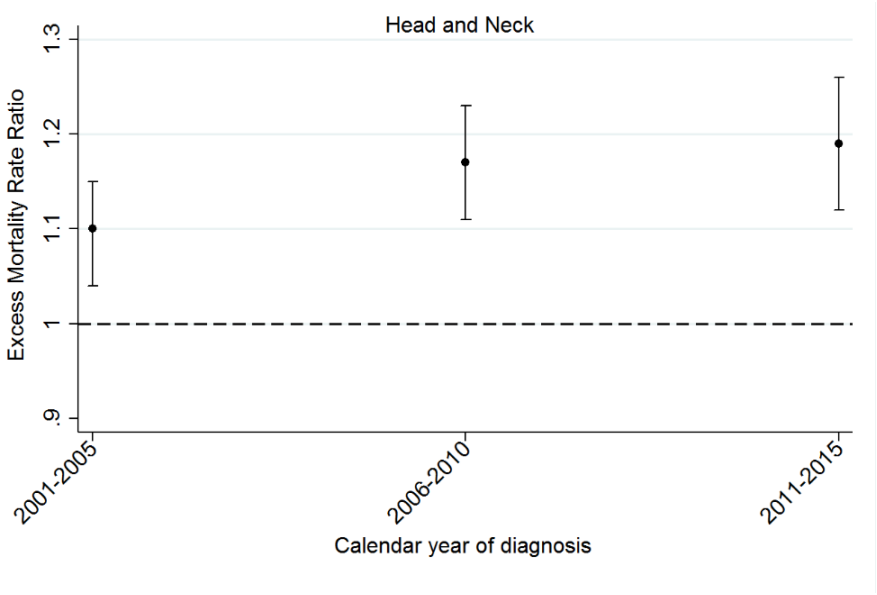


**Figure 8.3.** Five-year excess mortality rate ratios (EMRRs), by year of diagnosis, per quintile increase in socio-economic disadvantage (SEIFA)
The dashed line shows the reference value for the EMRR, representing no differences in survival between the least disadvantaged areas and more disadvantaged regions

For leukaemia and cancers of the pancreas and brain/CNS, lower survival for people living in more disadvantaged areas was mainly evident in the first year of diagnosis, while for lung and ovarian cancer, it was apparent within three years after diagnosis (S8.4 Table, Figure 8.4). For female breast cancer, socio-economic inequalities in survival decreased with time since diagnosis, but persisted over five years.

For unknown primary cancer and bladder cancer, the relative excess mortality for cases from more disadvantaged areas became smaller with increasing age at diagnosis (S8.5 Table, Figure 8.5). For prostate cancer, excess mortality varied inconsistently by age. For connective and soft tissue cancer, differences in survival were only observed for younger patients (<55 years).

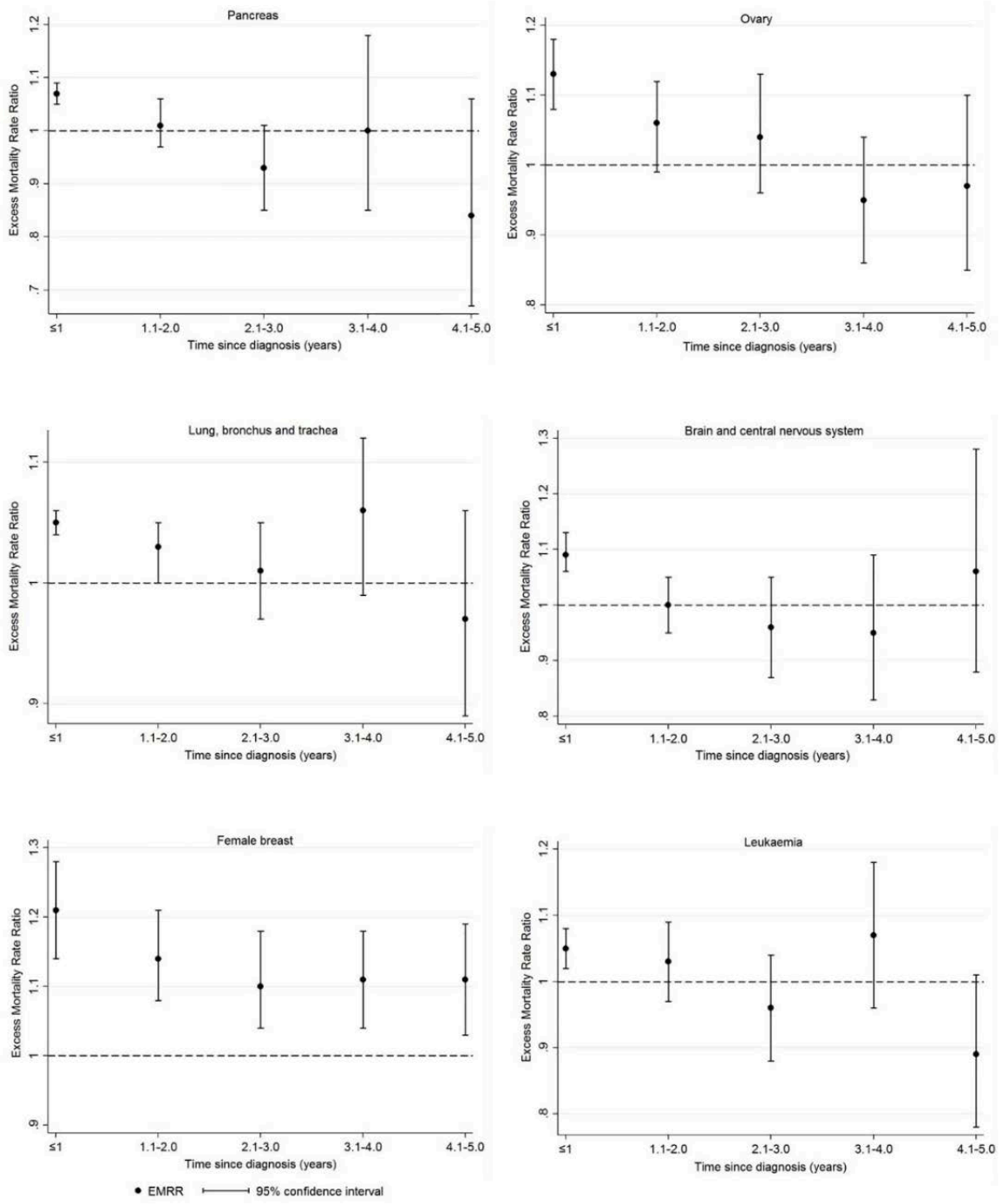


**Figure 8.4.** Excess mortality rate ratios (EMRRs), by time since diagnosis, per quintile increase in socio-economic disadvantage (SEIFA)
The dashed line shows the reference value for the EMRR, representing no differences in survival between the least disadvantaged areas and more disadvantaged regions

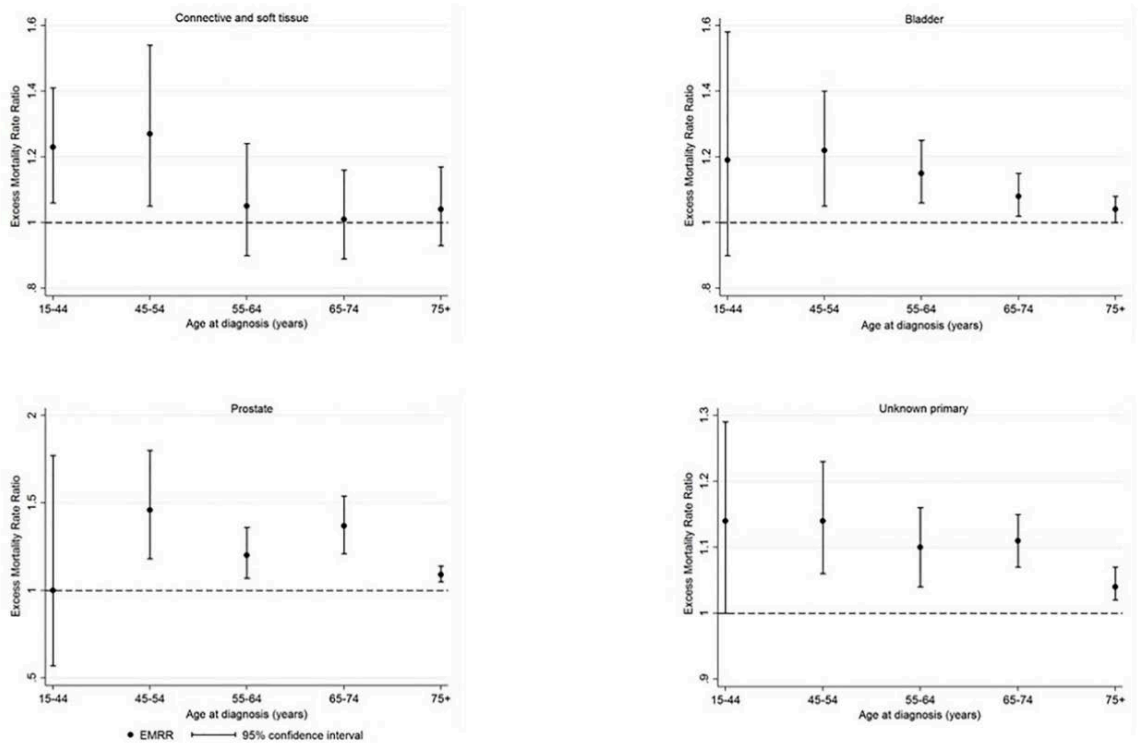


**Figure 8.5.** Five-year excess mortality rate ratios (EMRRs), by age at diagnosis, per quintile increase in socio-economic disadvantage (SEIFA)
The dashed line shows the reference value for the EMRR, representing no differences in survival between the least disadvantaged areas and more disadvantaged regions

Socio-economic differences in survival after colorectal cancer were larger for men (EMRR per quintile increase in SEIFA 1.10; 95%CI 1.08–1.12) than for women (EMRR 1.06; 95%CI 1.04–1.08). In contrast, for brain and CNS cancers, inequalities in survival were greater for women (S8.6 Table).

Excluding cases living outside major cities did not alter the EMRRs for most cancer types, except for stomach and kidney cancer, for which inequalities in survival diminished slightly, whereas for melanoma and mesothelioma, the observed gaps in survival widened slightly (S8.7 Table).

### 8.4. Discussion

Residents of more disadvantaged areas, relative to those residing in less disadvantaged regions, had lower survival for 21 of 29 cancer types, with inter-quintile EMRRs as high as 1.40 (95%CI 1.32–1.49), 1.91 (95%CI 1.60–2.28), 1.76 (95%CI 1.55–1.99), 1.73 (95%CI 1.46–2.04) for colorectal cancer, melanoma, female breast and prostate cancer, respectively. These inequalities persisted over the 15-year period for most cancers and widened for head and neck cancer. The gaps in survival were generally greater for younger individuals (aged <55 years) with cancers of bladder, connective/soft tissue and unknown primary.

For most cancers, socio-economic inequalities in survival generally remained unchanged after excluding cases living outside major cities, except for stomach and kidney cancer, for which the excess risk of death in more deprived areas decreased, whereas for melanoma and mesothelioma, it increased.

Strengths of this analysis include the use of SEIFA-specific life tables, the population-based design, and the large cohort of cases with complete follow up through national death registries that allowed us to examine variation in the EMRR by year of diagnosis, age at cancer diagnosis, time since diagnosis and sex. To the best of our knowledge, of the existing Australian studies of socio-economic inequalities in cancer survival, ours is the only study to use SEIFA-specific life tables. Socio-economically more disadvantaged people tend to have higher mortality due to other causes (i.e. non-cancer related deaths); [27] thus, using life tables not stratified by socio-economic disadvantage generates 'non-comparability' bias due to underestimation of expected mortality of more disadvantaged cancer patients and over estimation of their excess risk of death due to cancer. [25]

The main limitation was the unavailability of individual-level data on socio-economic position and the possibility of patients moving between areas with different socio-economic profiles, which could have underestimated the influence of SEP on cancer survival through misclassification. In addition, we did not have information regarding potential mediators of survival such as health-related lifestyle behaviours, stage at diagnosis, co-morbidities and cancer treatment. Thus, we were unable to investigate the potential role of these factors in explaining socio-economic inequalities in cancer survival. There is also a possibility of non-comparability bias for smoking-associated cancers as we lacked data on smoking and the life tables were not stratified by smoking status; therefore, we may have modestly overestimated socio-economic differences in survival. [25]

Our findings are consistent with those from other studies conducted in Australia, irrespective of how SEP was defined. A study using cancer registry data from New South Wales (NSW), Australia, found that with and without adjustment for stage at diagnosis, cancer patients living in more disadvantaged areas had lower survival compared with those residing in less disadvantaged areas. [28] The largest differences in survival were for melanoma and liver, prostate, lung, colorectum and breast cancer. The authors also noted that socio-economic inequalities in cancer survival had widened during the study period (1980–2008). [28] They postulated that variations in health-related behaviours, co-morbidities, and access to diagnostic and treatment facilities may explain these differences. [28] Other research conducted in NSW found persistent patterns over time of lower survival in more disadvantaged neighbourhoods, particularly for colorectal, prostate, breast, liver and stomach cancer. [10] Adjusting for a potential mediator, stage of disease, did not markedly change the results; therefore, the authors suggested quality of treatment and patient characteristics such as smoking, alcohol consumption and co-morbidities as other potential explanatory factors. [10]

Also consistent with these findings are those from studies in other Western countries. A study conducted in the United States, using the Surveillance, Epidemiology, and End Results cancer registry data, examined socio-economic inequalities in cancer survival and their temporal trends from 1950 to 2014. [29] Survival was lower for cancer patients living in more disadvantaged regions; these inequalities remained after adjusting for stage at diagnosis and widened over the six decades for colorectal, prostate and breast cancer. The authors postulated that higher prevalence of unhealthy behaviours such as smoking, excessive alcohol drinking, physical inactivity, poor diet, lower uptake of screening, lack of health insurance and limited access to healthcare and treatment services for cancer patients from lower socio-economic areas may explain the observed gaps in survival. [29] A population-based study from Canada found a similar pattern of lower cancer survival for cases from disadvantaged communities, relative to those from affluent regions, for breast, lung, colorectal and head and neck cancer. [30] The investigators observed, over 13 years, more gains in cancer survival for privileged people, which could increase inequalities in survival and proposed differences in use of screening and receiving optimal treatment as potential explanatory factors. [30] Findings from European and New Zealand research have also been consistent. A Danish study found differences between low-income and high-income patients in five-year survival for most cancers from 1987 to 2009, and that these had widened in the most recent five years, partly due to greater gains in cancer survival by affluent cases. [31] Similarly, a New Zealand study reported lower survival for low income cancer cases compared with high-income patients; the authors also found that the observed gaps in survival has widened over 13 years. [32] Another study from New Zealand observed socio-economic inequalities in cancer survival, which were only partly explained by extent of disease at diagnosis. [33] Research conducted in England and Wales [34] and Scotland [35] also found a deprivation gap in survival for several cancers comparing residents of more deprived areas with more affluent regions. Both studies observed an increase in these inequalities over 15 years. [34, 35]

Except for head and neck cancers, we observed a persistent pattern of lower survival in more disadvantaged areas over the past 15 years for most cancers, while other studies reported widening gaps over time, particularly for common cancers such as breast, prostate, colorectum and lung. [29–31, 34, 35] The causes of increasing gaps in survival are not well-understood, but it might be explained by greater improvements in cancer survival for advantaged individuals due to better access to diagnostic facilities and improved treatments, including clinical trials. [30, 36]

We found that socio-economic inequalities in survival were present across all age groups for most cancers, although the magnitude and pattern varied. A study from England examined the influence of age at diagnosis on socio-economic differences in survival from three common cancers including breast, lung and colon. [37] The authors found that the deprivation gap as measured by the absolute difference in 1-year relative survival increased with increasing age at diagnosis for breast cancer, while the opposite pattern was observed for 1- and 5-year relative survival for lung cancer. For colon cancer, it

appeared that short and longer-term survival was lower for older disadvantaged patients than younger counterparts. It is not clear why socio-economic inequalities in survival varied by age at diagnosis, but these patterns may be due to differential access to diagnostic services, screening and optimal treatment across age groups. [37]

For a few cancers (pancreas, ovary, lung, brain/CNS, female breast and leukaemia), the gaps in survival decreased with time following diagnosis, which might be explained if there are variations in receiving timely treatment across socio-economic groups. It is unclear why socio-economic differences in colorectal cancer survival would be greater for men, or those for brain and CNS cancers would be greater for women.

The observed socio-economic inequalities in survival from cancers of the cervix, colorectum and female breast might be partly due to variation in participation in screening programs by socio-economic disadvantage. People living in more disadvantaged areas have lower participation in the bowel and cervical cancer screening programs than those from less disadvantaged areas. [38, 39] Variation in participation in the breast screening program is smaller across socio-economic groups, although it is slightly lower for women from the most disadvantaged areas (51.8%) than for those living in the least disadvantaged regions (55.2%). [40] While Australia has no organised screening program for prostate cancer, the prostate-specific antigen test (PSA) is widely used, especially by men of higher socio-economic position. [41] At least part of the apparently higher survival from prostate cancer in areas of less socio-economic disadvantage is due to overdiagnosis of indolent cancers by PSA testing. [42]

Several studies have attempted to identify factors that mediate socio-economic inequalities in cancer survival, but the mediating effects of the identified factors are inconsistent within and between countries, mainly due to limitations of the data and applied methods and different health care systems. Further, the applied methods to identify mediators have been suboptimal. Most studies compared relative risk estimates with and without adjusting for intermediate variables in causal pathways. This approach fails in the presence of multiple mediators that affect and interact with each other and could produce biased results. [43, 44]

The International Agency for research on cancer (IARC) recently published a comprehensive review focusing on reducing social inequalities in cancer. [5] Higher prevalence of unhealthy lifestyle behaviours, lower screening participation, advanced stage at diagnosis, and inadequate access to diagnostic and cancer treatment services among underprivileged people were reported as major contributing factors to existing inequalities in cancer outcomes. [5] Another review on the influence of socio-economic position on access to clinical trials found that cancer patients from lower socio-economic backgrounds were underrepresented in cancer treatment trials and less likely to be eligible due to multiple barriers such as presence of co-morbidities and financial concerns. [36]

***Conclusion***

In summary, for most cancers, people residing in more socio-economically disadvantaged areas have lower survival relative to those living in less disadvantaged regions. Future research should focus on unravelling the influence of potential explanatory factors using innovative methods of mediation analysis, which may help to prioritise the factors that need to be changed to reduce inequalities in cancer survival.

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**Competing interests**

The authors have declared that no competing interests exist.

**Data Availability**

Potentially identifiable data from the Victorian Cancer Registry (VCR) was made available to the researchers with approval from the VCR Director and Cancer Council Victoria Human Research Ethics Committee, and under a memorandum of understanding that does not allow these data to be shared with third parties. Requests for access to VCR data can be made to the VCR Director: Professor Sue Evans, via (Sue.Evans@cancervic.org.au) or +61 3 9514 6216. The authors did not receive special access privileges to the data.

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## Chapter 9 . differences in cancer survival by remoteness of residence: an analysis of data from a population-based registry

In this chapter, an analysis of the Victorian Cancer Registry data was carried out to investigate differences in cancer patient survival by remoteness of residence.

This study was conceptualised and designed in consultation with Professor Dallas English and Professor Roger Milne. I led this study, conducted the analyses and drafted the manuscript. Helen Farrugia and Vicky Thursfield curated the data. Dr James Chamberlain generated population life tables stratified by socio-economic disadvantage and remoteness of residence. All co-authors provided advice in the interpretation of results and reviewed the manuscript.

This chapter includes the author-accepted version of the paper.

The list of references is formatted according to the journal requirements, with separate numbering to the thesis reference list. Supplementary materials related to this publication are presented in Appendix F.

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**Differences in cancer survival by remoteness of residence: an analysis of data from a population-based registry**

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**Keywords:** Rural; urban; inequalities; cancer survival; excess mortality; survival analysis

**Abstract**

**Purpose:** Cancer survival is generally lower for rural compared with urban residents, but findings have been inconsistent. We aimed to assess inequalities in cancer survival by remoteness of residence in Victoria, Australia.

**Methods:** Incident cancer cases diagnosed in 2001-2015 with 30 cancer types (N=331,302) were identified through the Victorian Cancer Registry and followed to the end of 2015 through death registries. Five-year net survival was estimated using the Pohar-Perme method and differences assessed by excess mortality rate ratios (EMRRs) using Poisson regression, adjusting for sex, age and year of diagnosis. EMRRs adjusted for socio-economic disadvantage were also estimated.

**Results:** People living outside major cities had lower survival for 11 cancers: oesophagus, stomach, colorectum, liver, gallbladder/biliary tract, pancreas, lung, connective/soft tissue, ovary, prostate, kidney. No differences in survival were found for cancers of uterus, small intestine and mesothelioma. After adjusting for socio-economic disadvantage, the observed differences in survival decreased for most cancers and disappeared for colorectal cancer, but they remained largely unchanged for cancers of oesophagus, stomach, liver, pancreas, lung, connective/soft tissue, ovary and kidney.

**Conclusion:** People with cancer residing outside major cities had lower survival from some cancers, which is partly due to the greater socio-economic disadvantage of rural residents.

## 9.1. Introduction

Cancer survival is increasing in Western countries because of earlier diagnosis and more effective treatment, and Australia is among the four high-income countries with the highest survival for most cancers. [1,2] Our recent systematic review showed that several studies have reported inequalities in cancer survival between rural and urban residents, while others have observed little or no difference, possibly due to variation in the definition of urban and rural regions and the variables accounted for in the analyses. [3] In Australia, cancer survival for people residing in more rural or remote areas is generally lower than that for residents of major cities, which could be partly due to one or more of these factors: socio-economic disadvantage, size of the indigenous population, and access to cancer care services. [4] In 2010-2014, the observed five-year cancer survival was highest in major cities (62%) and lowest in very remote areas (55%). [4]

Inequalities in cancer survival have also been observed by sex and socio-economic position (SEP); people living in more disadvantaged areas generally have lower survival. [5-10] Several Australian studies have reported lower survival for rural cancer patients relative to their urban counterparts, [11-13] but few studies have explored the influence of socio-economic disadvantage on these inequalities [5,14,15] and whether differences in survival between rural and urban areas are changing over time; it is also not well understood how remoteness of residence, sex, and SEP interact to influence cancer survival.

In this study, we investigated differences in cancer survival by patients' remoteness of residence at time of cancer diagnosis, using data from the population-based Victorian Cancer Registry. We also sought to assess the change in association after adjusting for area-level socio-economic disadvantage; and whether association of remoteness of residence with survival varied by sex, age at diagnosis, year of diagnosis and time since diagnosis.

## 9.2. Materials and Methods

### *Data sources*

Cases of incident cancer were identified by the Victorian Cancer Registry (VCR), a population-based registry for the State of Victoria, Australia. The VCR routinely collects demographic details (sex, date of birth, usual residential address, country of birth, Indigenous status) and tumour characteristics (date of diagnosis, site, grade, histology, behaviour). VCR records are linked monthly to the Victorian Registry of Births, Deaths and Marriages, and annually to the National Death Index, in order to update vital status.

For each registrant, the usual residential address at the time of diagnosis was geocoded to precise latitude and longitude coordinates using the Geocoded National Address File, [16] and these coordinates were then mapped to Statistical Area Level 1 (SA1; mean population size of 400 persons) defined by

the Australian Bureau of Statistics (ABS). SA1s were then grouped into 'major cities' and 'outside major cities' using the ABS remoteness structure, which classifies remoteness of geographical areas based on relative access (road distance) to the closest service centres. [17] The life tables provided by the ABS stratified remoteness into 'major cities' and other areas; therefore, we grouped inner regional, outer regional and remote areas into one category to define 'outside major cities'. The ABS Index of Relative Socio-Economic Disadvantage was used to measure area-level socio-economic disadvantage (Socio-Economic Indexes for Areas, SEIFA), grouped into quintiles. [18]

Life tables for residents of major cities and for those residing outside major cities (combining inner regional, outer regional and remote) were produced by the ABS for each year from 2001-2015 by sex and single years of age. These life tables were constructed by aggregating Victorian population death rates at Statistical Area Level 2 (SA2) geography into the two defined areas. The mortality rates for each area were smoothed to reduce the variability of $q_x$, the probability of dying at age $x$.

***Study cohort***

Eligible cases were aged 15 to 99 years when diagnosed with a first primary cancer between 1 January 2001 and 30 December 2015. We excluded subsequent primary tumours, *in situ* neoplasms, keratinocyte carcinomas and male breast cancer. Cases notified via autopsy and death certificate only or diagnosed on the last day of follow-up, 31 December 2015, were also excluded. Cancer types for which fewer than 1,000 cases occurred during the study period (thymus, bone, Kaposi sarcoma, peritoneum, placenta, penis and eye) were not included. The study cohort comprised 331,302 cases and 30 individual cancer types defined according to the International Statistical Classification of Disease and Related Health Problems, tenth revision (ICD-10). [19] We classified lymphoma and leukemia based on the revised World Health Organization (WHO) classification of neoplastic diseases of the hematopoietic and lymphoid tissue, [20] in accordance with the recommendations of the Australasian Association of Cancer Registries and Australian Blood Cancer Registry. [21]

***Statistical analysis***

Follow-up started at date of cancer diagnosis and ended five years following diagnosis, on death, or on 31 December 2015, whichever occurred first. We gave one day of survival to cases with the same date of diagnosis and death to include them in the statistical analyses; excluding these cases could have biased the survival estimates. [22] Five-year net survival and 95% confidence intervals (CIs) were estimated separately for major cities and outside major cities by the Pohar-Perme method, [23] using the life tables described above. Age-standardised net survival estimates were generated using cancer site-specific weights calculated from the distribution of cases across defined age-groups (15-44, 45-64, 65-74, and 75-99 years).

We estimated the excess risk of death due to cancer for people residing outside major cities, relative to those residing in major cities by calculating excess mortality rate ratios (EMRRs). The excess mortality

rate is the additional hazard of death due to a cancer diagnosis. We first estimated expected 5-year survival for each person using the Ederer II method [24], then collapsed these estimates by time since diagnosis, age and sex, and then modelled the excess mortality rates using Poisson regression. [25] The main model (Model 1) included: remoteness of residence (major cities and outside major cities), age at diagnosis (15-44, 45-64, 65-74, and 75-99 years), year of diagnosis (2001-2005, 2006-2010, 2011-2015), time since cancer diagnosis (1st, 2nd, 3rd, 4th and 5th year of follow-up), and sex. We also fitted an interaction between time since cancer diagnosis and age group to account for higher excess risk of death for older cancer patients during the first two years after diagnosis. [26] To assess the influence of socio-economic position on survival differences for particular cancer types, we added SEIFA (quintiles) to the main model (Model 2). Heterogeneity in the EMRR was assessed by comparing models with and without an interaction term between remoteness of residence and each of SEIFA (Model 3), year of diagnosis (Model 4), time since diagnosis (Model 5), and sex (Model 6). We also conducted analyses stratified by SEIFA, age at diagnosis, year of diagnosis, time since cancer diagnosis and sex.

Because the life tables were not stratified by SEIFA quintile, we conducted a sensitivity analysis using derived life tables for the 10 strata formed by combinations of two separate lifetables by remoteness of residence (in and outside major cities) and SEIFA (quintiles); see supplementary material for details.

We evaluated goodness-of-fit using the Pearson statistic. [27] Stata/MP version 14.2 (Stata Corporation LLC, College Station, TX, USA) was used to conduct all statistical analyses.

The analyses of these data were approved by the Cancer Council Victoria Human Research Ethics Committee.

**9.3. Results**

Of 331,302 eligible Victorians diagnosed between 1 January 2001 and 30 December 2015 with one of the 30 cancers considered (Figure 9.1), 221,449 lived in major cities and 109,853 resided outside major cities (Table 9.1). Their mean age at cancer diagnosis was 64.8 years and 65.6 years, respectively. Of eligible cases, 993 (0.3%) were Indigenous, of whom 447 of resided in major cities.

For 23 of the 30 cancer types considered, the estimated excess mortality within five years following diagnosis was greater for cases living outside major cities (i.e., EMRR > 1.0). For 11 of these cancers, the 95% confidence interval excluded the null (Figure 9.2A): oesophagus, stomach, colorectum, liver, gallbladder/biliary tract, pancreas, lung, connective/soft tissue, ovary, prostate, and kidney. The EMRR was greatest (1.20 or greater) for cancers of the oesophagus, stomach, liver, connective/soft tissue, prostate, and testis, although the confidence interval for testis was wide and included the null. The EMRR was between 1.10 and 1.20 for cancers of the anus/anal canal, gallbladder/biliary tract, pancreas, cervix, ovary, kidney and renal pelvis or ureter, although for cancers of the anus/anal canal, cervix and renal pelvis/ureter, the confidence intervals included the null. The EMRR was between 1.05 and 1.09 for cancers of the colorectum, lung, vulva or vagina, bladder, and brain/CNS and for multiple myeloma

and leukaemia, but only colorectal and lung cancer had confidence intervals that excluded the null. For no cancer was survival substantially better for cases residing outside major cities than for their major city-dwelling counterparts. For mesothelioma and cancers of the uterus and small intestine, we observed no evidence of differences in survival between major cities and outside major cities.

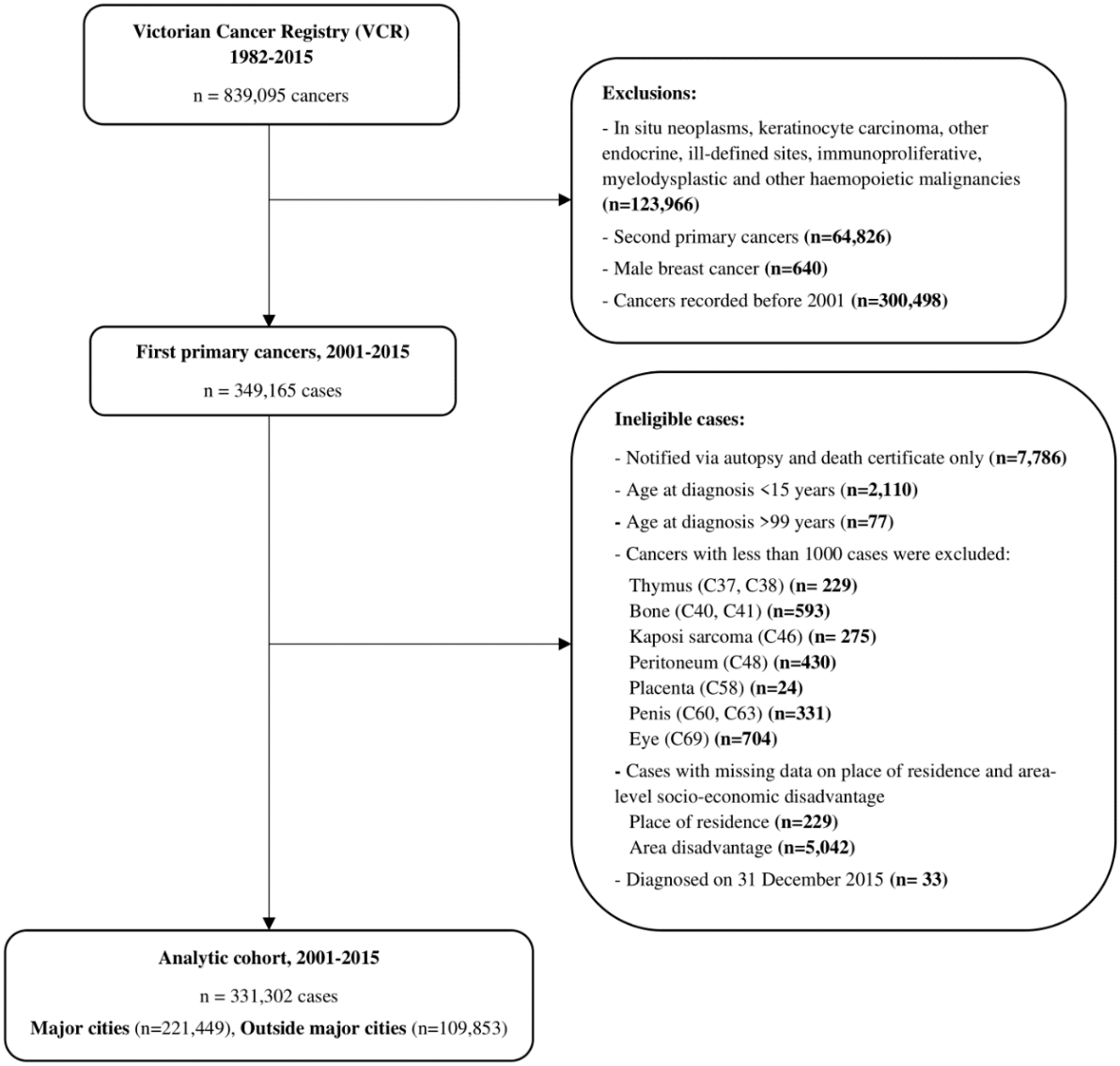


**Figure 9.1.** Flowchart of case selection from the Victorian Cancer Registry for the analysis in the study.

***Adjustment for area-level socio-economic disadvantage***

We considered socio-economic position as a confounder and investigated whether at least part of these associations could be due to greater socio-economic disadvantage for those residing outside major cities (Supplementary Figure 1). After adjusting for area-level socio-economic disadvantage (SEIFA), the observed survival disadvantage for cancer patients residing outside major cities was decreased, but persisted for most cancers, while it disappeared for colorectal cancer (Figure 9.B). The EMRRs were substantially attenuated for prostate and anus/anal canal cancer, and moderately decreased for cancers of oesophagus, connective/soft tissue, ovary and renal pelvis/ureter. After accounting for area-level socio-economic disadvantage, we found some evidence of higher survival for outside major cities residents for cancers of head and neck, melanoma, unknown primary and Hodgkin lymphoma, while for female breast cancer and non-Hodgkin lymphoma, observed association changed to better survival for cases residing outside major cities.

When stratified by SEIFA quintile, the EMRRs for cancers of stomach, kidney and brain/CNS were higher for cases with higher SEIFA, indicating that the lower survival outside major cities, relative to major cities, was more pronounced when comparing areas with greater socio-economic disadvantage. In contrast, for head and neck cancer, the survival advantage outside major cities was greater when considering less disadvantaged regions (Supplementary Table 1).

**Table 9.1.** Number of cases and deaths, and five-year age-standardised net survival for cancer cases residing in major cities and outside major cities, Victoria, Australia, 2001-2015

| ICD-10 | Cancer site | Major cities | | Outside major cities | | Major cities | Outside major cities | P-value^ |
|---|---|---|---|---|---|---|---|---|
| | | Cases | Deaths | Cases | Deaths | Net survival* (%) (95% CI) | Net survival* (%) (95% CI) | |
| C00-14, C30-32 | Head and neck | 7,061 | 2,731 | 4,148 | 1,614 | 73.4 (71.8 to 75.0) | 74.8 (72.7 to 76.8) | 0.4 |
| C15 | Oesophagus | 2,464 | 1,925 | 1,497 | 1,218 | 22.8 (20.8 to 24.9) | 17.3 (15.0 to 19.8) | <0.001 |
| C16 | Stomach | 4,754 | 3,418 | 2,074 | 1,545 | 30.5 (28.9 to 32.2) | 25.5 (22.9 to 28.2) | <0.001 |
| C17 | Small intestine | 837 | 371 | 368 | 164 | 62.3 (58.0 to 66.4) | 64.2 (57.2 to 70.5) | 0.9 |
| C18-20 | Colorectum | 28,839 | 13,183 | 15,656 | 7,345 | 69.2 (68.3 to 70.0) | 67.7 (66.6 to 68.9) | 0.001 |
| C21 | Anus and anal canal | 733 | 288 | 349 | 149 | 70.5 (65.7 to 74.8) | 67.0 (60.0 to 73.2) | 0.3 |
| C22 | Liver | 3,358 | 2,602 | 1,188 | 952 | 18.1 (16.6 to 19.7) | 15.4 (12.7 to 18.4) | <0.001 |
| C23-24 | Gallbladder and biliary tract | 1,566 | 1,216 | 628 | 497 | 22.4 (19.9 to 24.9) | 18.9 (15.2 to 23.0) | 0.03 |
| C25 | Pancreas | 5,261 | 4,604 | 2,482 | 2,210 | 9.2 (8.3 to 10.2) | 6.4 (5.3 to 7.8) | <0.001 |
| C33-34 | Lung, bronchus and trachea | 18,950 | 15,566 | 10,022 | 8,396 | 16.6 (16.0 to 17.3) | 15.2 (14.3 to 16.0) | <0.001 |
| C43 | Melanoma | 18,036 | 3,877 | 10,618 | 2,212 | 92.8 (91.9 to 93.7) | 93.3 (91.9 to 94.4) | 0.3 |
| C45 | Mesothelioma | 1,116 | 1,003 | 600 | 548 | 6.6 (5.0 to 8.5) # | 6.2 (4.1 to 8.9) # | 1.0 |
| C47-49 | Connective and soft tissue | 1,331 | 508 | 622 | 291 | 70.7 (66.9 to 74.1) | 61.3 (55.7 to 66.3) | 0.003 |
| C50 | Female breast | 32,792 | 6,383 | 14,731 | 3,011 | 90.8 (90.2 to 91.3) | 90.6 (89.7 to 91.4) | 0.5 |
| C53 | Cervix | 1,704 | 452 | 664 | 206 | 76.1 (73.8 to 78.3) | 72.6 (68.5 to 76.3) | 0.1 |
| C54-55 | Uterus | 5,036 | 1,140 | 2,248 | 504 | 86.2 (84.7 to 87.5) | 86.6 (84.3 to 88.6) | 0.9 |
| C56 | Ovary | 2,996 | 1,786 | 1,311 | 831 | 42.5 (40.5 to 44.4) | 39.6 (36.7 to 42.5) | 0.001 |
| C51-52, C57 | Vulva | 1,021 | 422 | 507 | 222 | 68.8 (64.1 to 72.9) | 62.5 (56.4 to 68.0) | 0.5 |
| C61 | Prostate | 38,158 | 9,072 | 19,076 | 5,333 | 95.1 (94.5 to 95.7) | 93.2 (92.2 to 94.0) | <0.001 |
| C62 | Testis | 1,912 | 54 | 715 | 32 | 98.6 (97.5 to 99.2) | 97.4 (95.3 to 98.5) | 0.4 |
| C64 | Kidney | 5,471 | 1,893 | 2,770 | 1,055 | 73.4 (71.8 to 74.9) | 72.0 (69.7 to 74.2) | 0.004 |

| ICD-10 | Cancer site | Major cities | | Outside major cities | | Major cities | Outside major cities | P-value^ |
|---|---|---|---|---|---|---|---|---|
| | | Cases | Deaths | Cases | Deaths | Net survival* (%) (95% CI) | Net survival* (%) (95% CI) | |
| C67 | Bladder | 4,538 | 2,535 | 2,143 | 1,208 | 56.1 (53.8 to 58.4) | 54.3 (50.1 to 58.3) | 0.2 |
| C65-66, C68 | Renal pelvis, ureter, other/unspecified | 761 | 463 | 368 | 224 | 47.6 (42.6 to 52.3) | 40.5 (33.8 to 47.2) | 0.3 |
| C70-72 | Brain and central nervous system | 3,566 | 2,601 | 1,705 | 1,286 | 23.8 (22.4 to 25.2) | 25.0 (23.0 to 27.1) | 0.05 |
| C73 | Thyroid | 4,060 | 332 | 1,328 | 170 | 95.4 (94.3 to 96.4) | 93.9 (91.7 to 95.6) | 0.2 |
| C80 | Unknown primary | 4,539 | 3,990 | 2,464 | 2,149 | 13.7 (12.5 to 14.9) | 16.9 (14.9 to 18.9) | 0.3 |
| C81 | Hodgkin Lymphoma | 1,410 | 196 | 631 | 112 | 88.4 (86.4 to 90.1) | 88.0 (85.3 to 90.3) | 0.5 |
| C82-86 | Non-Hodgkin Lymphoma | 9,984 | 3,573 | 4,508 | 1,737 | 74.9 (73.6 to 76.4) | 73.6 (71.7 to 75.4) | 0.4 |
| C90 | Multiple Myeloma | 3,371 | 1,888 | 1,645 | 973 | 49.7 (47.4 to 51.9) | 47.8 (44.5 to 51.0) | 0.3 |
| C91-95 | Leukemia | 5,824 | 2,938 | 2,787 | 1,487 | 54.3 (52.6 to 56.0) | 53.7 (51.2 to 56.1) | 0.2 |

CI, confidence interval; ^ Wald test; *****net survival estimates were adjusted for year of diagnosis, age and sex; [#] non-age-standardised (age-standardised net survival cannot be estimated)

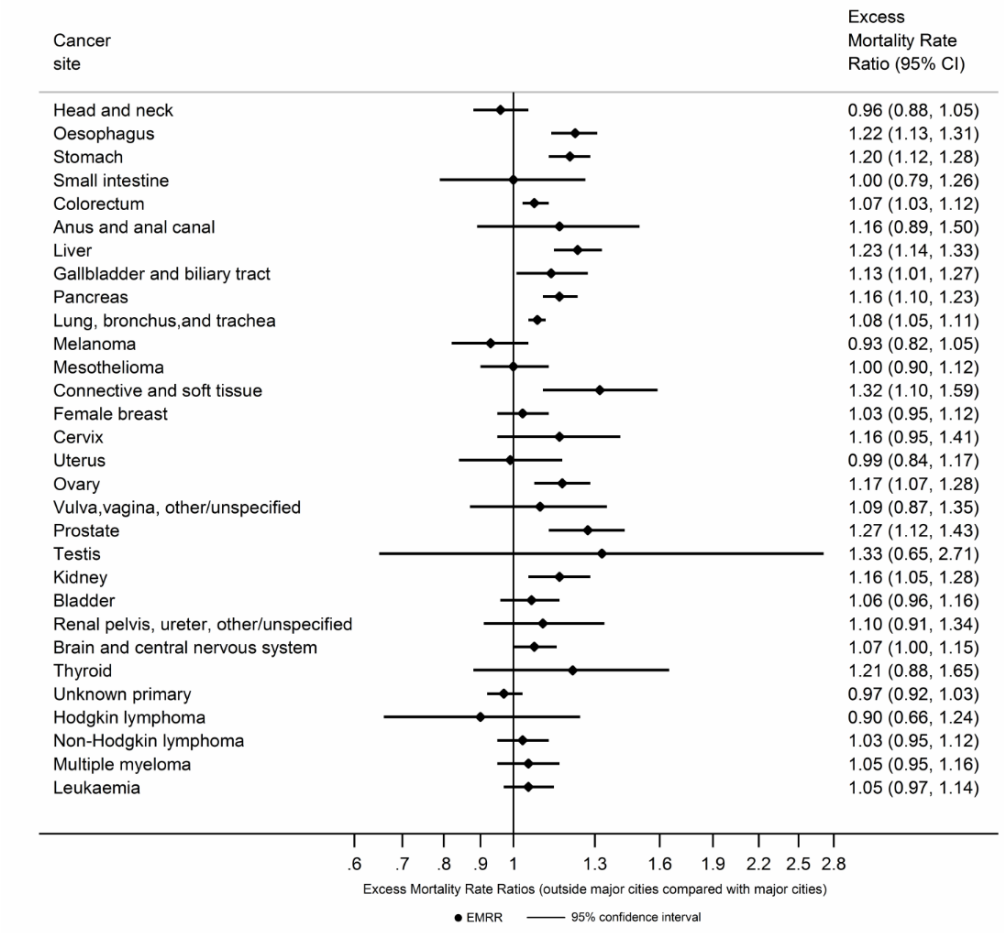


**Figure 9.2A.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis for cancer cases residing outside major cities compared with those residing in major cities, Victoria, Australia, 2001–2015

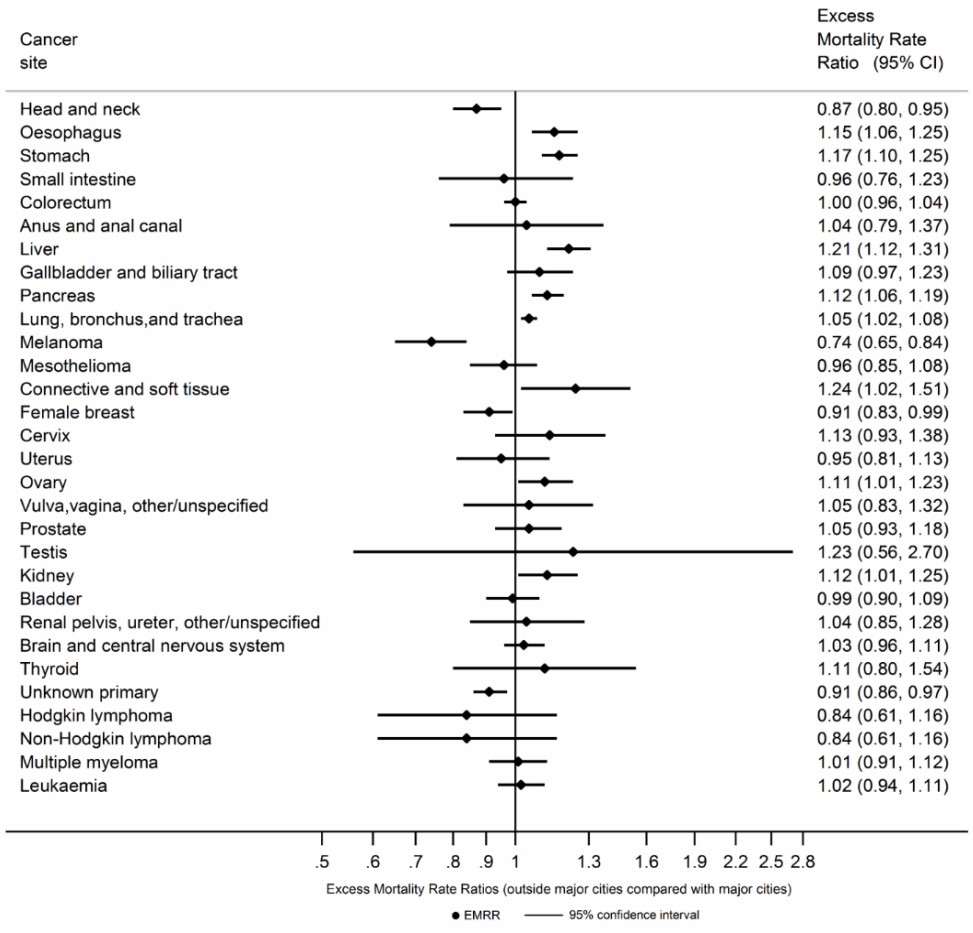


**Figure 9.2B.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis for cancer cases residing outside major cities compared with those residing in major cities (adjusted for area-level socio-economic disadvantage), Victoria, Australia, 2001–2015

***Trends over time***

Analyses stratified by period of diagnosis provided some evidence that the lower survival from oesophageal and pancreatic cancer experienced by those residing outside major cities decreased over time (Table 9.2). In contrast, for prostate cancer, the survival inequality between those residing in and outside major cities increased over time.

***Time since diagnosis***

We found no consistent trends in the EMRRs by time since diagnosis, except for brain and CNS tumours and leukaemia, for which the survival disadvantage for cases residing outside major cities was only evident in the first year following diagnosis (Table 9.3).

***Associations by age and sex***

For unknown primary cancer and cancer of connective or soft tissue, the observed survival disadvantage for those residing outside major cities was greater for younger cases (Table 9.4); while for brain and CNS tumours, it was greater for older cases (≥75 years).

For melanoma, we found strong evidence of differences in the EMRRs by sex; the higher survival experienced by those who resided outside major cities was greater for women than for men. For cancers of the renal pelvis or ureter, it appears that the lower survival for those who resided outside major cities was only evident for men (Supplementary Table 2).

***Sensitivity analysis***

The EMRRs were not substantially changed by using derived life tables specific to both remoteness of residence and SEIFA, with the exception of prostate cancer, for which the EMRR diminished from 1.27 (95% CI 1.12-1.43) to 1.14 (95% CI 1.03-1.26), and testicular cancer for which the EMRR increased from 1.33 (95% CI 0.65-2.71) to 1.46 (95% CI 0.75-2.83) (Supplementary Table 3).

**Table 9.2.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis, by year of diagnosis, for cancer cases residing outside major cities compared with those residing in major cities, 2001-2015

| Year of diagnosis, adjusted for area-level socio-economic disadvantage | | | | | | |
|---|---|---|---|---|---|---|
| | 2001-2005 | 2006-2010 | 2011-2015 | Change in EMRR per calendar year | p-trend^ | p-departure from linearity^ |
| **Cancer site** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | | |
| Head and neck | 0.84 (0.73, 0.98) | 0.89 (0.77, 1.03) | 0.86 (0.72, 1.03) | 1.01 (0.98, 1.03) | 0.6 | 0.5 |
| Oesophagus | 1.23 (1.07, 1.41) | 1.26 (1.10, 1.44) | 0.97 (0.83, 1.13) | 0.98 (0.96, 1.00) | 0.02 | 0.3 |
| Stomach | 1.20 (1.08, 1.34) | 1.20 (1.07, 1.34) | 1.10 (0.97, 1.25) | 0.99 (0.98, 1.01) | 0.3 | 0.1 |
| Small intestine | 1.48 (0.93, 2.35) | 0.59 (0.39, 0.88) | 1.15 (0.76, 1.75) | 1.00 (0.94, 1.06) | 0.9 | 0.04 |
| Colorectum | 1.02 (0.95, 1.09) | 1.03 (0.96, 1.10) | 0.93 (0.85, 1.01) | 0.99 (0.98, 1.00) | 0.1 | 0.005 |
| Anus and anal canal | 0.91 (0.56, 1.48) | 1.08 (0.68, 1.72) | 1.24 (0.74, 2.08) | 1.00 (0.94, 1.08) | 0.9 | 0.04 |
| Liver | 1.33 (1.14, 1.55) | 1.10 (0.96, 1.25) | 1.26 (1.10, 1.44) | 0.99 (0.97, 1.01) | 0.2 | 0.02 |
| Gallbladder and biliary tract | 1.04 (0.85, 1.28) | 1.11 (0.91, 1.35) | 1.07 (0.87, 1.33) | 1.01 (0.98, 1.04) | 0.6 | 0.7 |
| Pancreas | 1.24 (1.13, 1.37) | 1.09 (0.99, 1.19) | 1.06 (0.96, 1.17) | 0.99 (0.98, 1.00) | 0.05 | 0.2 |
| Lung, bronchus and trachea | 1.04 (0.99, 1.10) | 0.99 (0.95, 1.04) | 1.11 (1.05, 1.17) | 1.00 (1.00, 1.01) | 0.3 | <0.001 |
| Melanoma | 0.80 (0.64, 1.00) | 0.70 (0.57, 0.85) | 0.77 (0.59, 1.00) | 1.00 (0.97, 1.03) | 1.0 | 0.1 |
| Mesothelioma | 0.92 (0.76, 1.11) | 1.07 (0.87, 1.31) | 0.85 (0.68, 1.06) | 1.00 (0.97, 1.03) | 0.9 | 0.8 |
| Connective and soft tissue | 1.29 (0.92, 1.82) | 1.19 (0.86, 1.65) | 1.23 (0.86, 1.76) | 1.00 (0.95, 1.05) | 1.0 | 0.01 |
| Female breast | 0.90 (0.79, 1.03) | 0.88 (0.77, 1.02) | 0.97 (0.80, 1.18) | 1.01 (0.99, 1.03) | 0.4 | 0.2 |
| Cervix | 1.09 (0.77, 1.53) | 0.98 (0.71, 1.35) | 1.37 (0.94, 2.01) | 1.02 (0.97, 1.07) | 0.4 | 0.7 |

| | 2001-2005 | 2006-2010 | 2011-2015 | Change in EMRR per calendar year | p-trend^ | p-departure from linearity^ |
|---|---|---|---|---|---|---|
| **Cancer site** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | | |
| Uterus | 0.97 (0.73, 1.29) | 0.96 (0.72, 1.29) | 0.96 (0.71, 1.29) | 0.98 (0.95, 1.03) | 0.5 | 0.4 |
| Ovary | 0.98 (0.83, 1.15) | 1.23 (1.06, 1.44) | 1.22 (1.00, 1.49) | 1.02 (1.00, 1.05) | 0.07 | 0.8 |
| Vulva, vagina, other/unspecified | 0.92 (0.57, 1.50) | 1.08 (0.73, 1.58) | 1.15 (0.79, 1.68) | 1.00 (0.94, 1.05) | 0.9 | 0.8 |
| Prostate | 0.99 (0.84, 1.17) | 1.07 (0.86, 1.33) | 1.35 (0.97, 1.87) | 1.04 (1.00, 1.08) | 0.03 | 0.001 |
| Testis | 0.96 (0.36, 2.53) | 2.27 (0.71, 7.29) | 0.36 (0.02, 5.33) | 1.04 (0.88, 1.23) | 0.6 | 0.1 |
| Kidney | 1.17 (0.98, 1.39) | 1.13 (0.95, 1.35) | 1.04 (0.85, 1.27) | 0.99 (0.97, 1.02) | 0.5 | 0.7 |
| Bladder | 0.98 (0.82, 1.16) | 0.93 (0.80, 1.09) | 1.08 (0.91, 1.29) | 1.01 (0.99, 1.03) | 0.5 | 0.04 |
| Renal pelvis, ureter, other/unspecified | 1.44 (1.01, 2.07) | 0.89 (0.62, 1.27) | 0.94 (0.65, 1.34) | 0.98 (0.93, 1.03) | 0.3 | 0.3 |
| Brain and central nervous system | 1.05 (0.93, 1.19) | 1.04 (0.92, 1.17) | 1.00 (0.88, 1.14) | 1.00 (0.98, 1.01) | 0.6 | 0.5 |
| Thyroid | 1.09 (0.59, 2.01) | 1.28 (0.75, 2.18) | 1.03 (0.59, 1.80) | 1.03 (0.96, 1.11) | 0.4 | 0.1 |
| Unknown primary | 0.90 (0.82, 0.98) | 0.89 (0.81, 0.99) | 0.96 (0.86, 1.08) | 1.01 (0.99, 1.02) | 0.5 | 0.001 |
| Hodgkin lymphoma | 0.87 (0.52, 1.46) | 0.81 (0.46, 1.42) | 0.90 (0.49, 1.66) | 1.03 (0.95, 1.12) | 0.5 | 0.1 |
| Non-Hodgkin lymphoma | 0.90 (0.78, 1.03) | 0.95 (0.83, 1.10) | 1.00 (0.85, 1.19) | 1.01 (0.99, 1.04) | 0.2 | 0.4 |
| Multiple myeloma | 0.98 (0.82, 1.16) | 1.02 (0.87, 1.20) | 1.03 (0.83, 1.28) | 1.00 (0.98, 1.03) | 0.9 | 0.2 |
| Leukaemia | 0.98 (0.86, 1.11) | 1.01 (0.89, 1.16) | 1.13 (0.97, 1.32) | 1.01 (0.99, 1.03) | 0.3 | 0.07 |

CI, confidence interval; ^ likelihood ratio test

**Table 9.3.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis, by time since diagnosis, for cancer cases residing outside major cities compared with those residing in major cities, 2001-2015

| Time since diagnosis (years), adjusted for area-level socio-economic disadvantage | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | Change in EMRR per year after diagnosis | p-trend^ | p-departure from linearity^ |
| Cancer site | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | | |
| Head and neck | 0.87 (0.76, 0.98) | 0.97 (0.81, 1.15) | 0.76 (0.57, 1.00) | 0.94 (0.67, 1.32) | 0.68 (0.45, 1.03) | 0.99 (0.92, 1.07) | 0.8 | 0.3 |
| Oesophagus | 1.16 (1.06, 1.28) | 1.17 (0.98, 1.41) | 1.13 (0.81, 1.58) | 1.09 (0.62, 1.90) | 0.66 (0.27, 1.60) | 1.00 (0.90, 1.10) | 0.9 | 0.9 |
| Stomach | 1.22 (1.13, 1.32) | 1.05 (0.91, 1.23) | 1.25 (0.96, 1.63) | 0.80 (0.49, 1.32) | 0.75 (0.37, 1.51) | 0.93 (0.86, 1.01) | 0.1 | 0.4 |
| Small intestine | 0.92 (0.68, 1.25) | 0.73 (0.41, 1.31) | 1.40 (0.63, 3.11) | 1.36 (0.53, 3.44) | NA | 1.04 (0.82, 1.32) | 0.8 | 0.4 |
| Colorectum | 1.05 (0.99, 1.11) | 0.95 (0.87, 1.04) | 0.92 (0.82, 1.04) | 0.99 (0.85, 1.17) | 0.89 (0.71, 1.12) | 0.96 (0.93, 1.00) | 0.06 | 0.4 |
| Anus and anal canal | 0.85 (0.54, 1.32) | 1.60 (0.98, 2.63) | 1.06 (0.55, 2.05) | 0.55 (0.22, 1.40) | 1.63 (0.23, 11.56) | 0.94 (0.74, 1.19) | 0.6 | 0.2 |
| Liver | 1.21 (1.10, 1.33) | 1.34 (1.09, 1.63) | 1.01 (0.72, 1.42) | 1.11 (0.69, 1.78) | 1.02 (0.57, 1.81) | 0.97 (0.89, 1.06) | 0.5 | 0.6 |
| Gallbladder and biliary tract | 1.05 (0.91, 1.21) | 1.03 (0.79, 1.35) | 2.07 (1.36, 3.15) | 0.83 (0.40, 1.76) | 1.54 (0.46, 5.13) | 1.07 (0.94, 1.22) | 0.3 | 0.01 |
| Pancreas | 1.13 (1.06, 1.20) | 1.02 (0.88, 1.18) | 1.41 (1.04, 1.91) | 1.28 (0.75, 2.19) | 1.84 (0.84, 4.02) | 1.00 (0.92, 1.09) | 1.0 | 0.4 |
| Lung, bronchus and trachea | 1.04 (1.01, 1.08) | 1.10 (1.02, 1.18) | 1.05 (0.93, 1.20) | 0.94 (0.78, 1.14) | 0.87 (0.66, 1.15) | 0.98 (0.94, 1.01) | 0.2 | 0.3 |
| Melanoma | 0.73 (0.59, 0.90) | 0.69 (0.53, 0.90) | 0.57 (0.41, 0.78) | 1.35 (0.95, 1.91) | 0.74 (0.43, 1.30) | 1.05 (0.95, 1.16) | 0.3 | 0.005 |
| Mesothelioma | 0.95 (0.82, 1.10) | 1.01 (0.79, 1.27) | 0.84 (0.54, 1.29) | 0.87 (0.42, 1.80) | 1.07 (0.43, 2.70) | 1.01 (0.89, 1.14) | 0.9 | 0.7 |
| Connective and soft tissue | 1.11 (0.85, 1.45) | 1.59 (1.08, 2.34) | 1.81 (0.98, 3.35) | 0.59 (0.22, 1.59) | 1.11 (0.47, 2.60) | 1.04 (0.88, 1.22) | 0.7 | 0.2 |
| Female breast | 1.02 (0.86, 1.20) | 0.81 (0.68, 0.98) | 0.89 (0.74, 1.07) | 0.80 (0.65, 0.99) | 1.06 (0.84, 1.32) | 0.98 (0.92, 1.04) | 0.4 | 0.06 |
| Cervix | 0.91 (0.68, 1.22) | 1.22 (0.84, 1.77) | 1.85 (1.09, 3.15) | 1.70 (0.89, 3.25) | 0.66 (0.21, 2.04) | 1.16 (0.99, 1.38) | 0.07 | 0.3 |
| Uterus | 0.99 (0.78, 1.25) | 0.93 (0.66, 1.30) | 0.94 (0.60, 1.47) | 1.10 (0.62, 1.95) | 0.57 (0.19, 1.75) | 0.99 (0.86, 1.14) | 0.9 | 0.8 |
| Ovary | 1.09 (0.95, 1.25) | 1.21 (0.99, 1.47) | 1.26 (0.98, 1.63) | 1.04 (0.76, 1.43) | 0.76 (0.49, 1.19) | 0.94 (0.87, 1.01) | 0.09 | 0.3 |

| | 1 | 2 | 3 | 4 | 5 | Change in EMRR per year after diagnosis | p-trend^ | p-departure from linearity^ |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | | |
| | 1.01 (0.73, 1.39) | 1.05 (0.65, 1.70) | 0.87 (0.44, 1.71) | 1.92 (0.89, 4.18) | 0.98 (0.34, 2.83) | 1.05 (0.87, 1.26) | 0.6 | 0.3 |
| Prostate | 1.03 (0.86, 1.23) | 1.26 (0.97, 1.63) | 1.04 (0.77, 1.42) | 1.27 (0.85, 1.89) | 0.55 (0.31, 0.95) | 0.96 (0.87, 1.05) | 0.4 | 0.08 |
| Testis | 1.23 (0.36, 4.22) | 2.27 (0.66, 7.76) | 0.56 (0.06, 5.36) | 3.75 (0.27, 51.94) | 6.54 (0.19, 227.69) | 1.20 (0.66, 2.18) | 0.6 | 0.6 |
| Kidney | 1.17 (1.03, 1.33) | 1.04 (0.78, 1.37) | 1.04 (0.75, 1.45) | 0.99 (0.60, 1.62) | 1.02 (0.59, 1.78) | 0.95 (0.87, 1.05) | 0.3 | 1.0 |
| Bladder | 1.02 (0.90, 1.16) | 0.99 (0.81, 1.21) | 0.88 (0.64, 1.20) | 1.08 (0.71, 1.64) | 0.61 (0.30, 1.24) | 0.97 (0.88, 1.06) | 0.5 | 0.7 |
| Renal pelvis, ureter, other | 1.00 (0.76, 1.32) | 1.17 (0.76, 1.80) | 1.15 (0.68, 1.95) | 1.03 (0.44, 2.44) | 0.46 (0.05, 4.55) | 1.04 (0.86, 1.26) | 0.7 | 0.8 |
| Brain and central nervous system | 1.12 (1.02, 1.22) | 0.89 (0.76, 1.03) | 0.77 (0.57, 1.03) | 0.94 (0.62, 1.41) | 0.98 (0.56, 1.72) | 0.87 (0.80, 0.95) | 0.001 | 0.09 |
| Thyroid | 1.15 (0.79, 1.67) | 1.60 (0.63, 4.08) | 1.93 (0.40, 9.33) | NA | 3.47 (0.79, 15.22) | 1.04 (0.78, 1.40) | 0.8 | 0.9 |
| Unknown primary | 0.93 (0.87, 0.99) | 0.79 (0.63, 0.99) | 0.77 (0.49, 1.21) | 0.72 (0.40, 1.30) | 0.97 (0.45, 2.12) | 0.92 (0.82, 1.02) | 0.1 | 0.5 |
| Hodgkin lymphoma | 0.81 (0.53, 1.23) | 0.75 (0.34, 1.65) | 0.77 (0.17, 3.47) | 0.80 (0.31, 2.01) | 3.66 (0.79, 16.94) | 1.10 (0.84, 1.43) | 0.5 | 0.4 |
| Non-Hodgkin lymphoma | 0.96 (0.86, 1.06) | 1.00 (0.81, 1.22) | 0.85 (0.61, 1.17) | 0.91 (0.61, 1.36) | 0.60 (0.35, 1.02) | 0.96 (0.88, 1.04) | 0.3 | 0.8 |
| Multiple myeloma | 1.00 (0.86, 1.17) | 1.00 (0.80, 1.26) | 0.85 (0.65, 1.10) | 1.24 (0.92, 1.68) | 1.11 (0.77, 1.58) | 1.01 (0.93, 1.08) | 0.9 | 0.3 |
| Leukaemia | 1.10 (1.00, 1.22) | 0.94 (0.78, 1.13) | 0.64 (0.47, 0.88) | 1.04 (0.74, 1.45) | 0.92 (0.60, 1.42) | 0.91 (0.84, 0.98) | 0.01 | 0.04 |

CI, confidence interval; ^ likelihood ratio test; NA (not available, cannot be estimated)

**Table 9.4.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis, by age at diagnosis, for cancer cases residing outside major cities compared with those residing in major cities, 2001-2015

| Age at diagnosis (years), adjusted for area-level socio-economic disadvantage | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 15-44 | 45-54 | 55-64 | 65-74 | 75+ | Change in EMRR per age group | p-trend^ | p-departure from linearity^ |
| Cancer site | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | | |
| Head and neck | 0.69 (0.44, 1.07) | 0.87 (0.68, 1.10) | 0.95 (0.81, 1.12) | 0.86 (0.73, 1.02) | 0.81 (0.66, 0.99) | 0.98 (0.91, 1.06) | 0.7 | 0.3 |
| Oesophagus | 0.80 (0.44, 1.46) | 1.43 (1.08, 1.88) | 1.11 (0.93, 1.33) | 1.20 (1.03, 1.40) | 1.15 (1.01, 1.30) | 0.96 (0.90, 1.03) | 0.3 | 0.4 |
| Stomach | 1.16 (0.86, 1.58) | 1.07 (0.85, 1.33) | 1.13 (0.97, 1.32) | 1.23 (1.08, 1.39) | 1.16 (1.04, 1.29) | 1.02 (0.96, 1.08) | 0.5 | 0.6 |
| Small intestine | 2.58 (1.00, 6.67) | 0.86 (0.38, 1.95) | 1.17 (0.68, 2.00) | 1.04 (0.66, 1.65) | 0.66 (0.43, 1.02) | 0.86 (0.71, 1.04) | 0.2 | 0.4 |
| Colorectum | 1.08 (0.88, 1.31) | 1.01 (0.89, 1.15) | 0.97 (0.88, 1.06) | 1.04 (0.96, 1.13) | 0.98 (0.91, 1.05) | 0.99 (0.96, 1.03) | 0.7 | 0.5 |
| Anus and anal canal | 1.74 (0.53, 5.71) | 1.24 (0.68, 2.25) | 0.69 (0.38, 1.24) | 1.13 (0.64, 2.00) | 1.21 (0.70, 2.09) | 1.00 (0.81, 1.25) | 1.0 | 0.4 |
| Liver | 1.35 (0.84, 2.15) | 1.38 (1.11, 1.72) | 1.11 (0.94, 1.31) | 1.21 (1.04, 1.40) | 1.22 (1.06, 1.40) | 0.98 (0.91, 1.05) | 0.6 | 0.6 |
| Gallbladder and biliary tract | 0.56 (0.19, 1.66) | 0.96 (0.61, 1.51) | 0.97 (0.73, 1.28) | 1.31 (1.06, 1.62) | 1.02 (0.85, 1.22) | 1.03 (0.92, 1.15) | 0.6 | 0.3 |
| Pancreas | 1.30 (0.87, 1.95) | 1.26 (1.04, 1.53) | 1.14 (1.00, 1.29) | 1.08 (0.98, 1.20) | 1.12 (1.03, 1.22) | 0.98 (0.94, 1.04) | 0.5 | 0.7 |
| Lung, bronchus, and trachea | 1.28 (1.01, 1.63) | 0.99 (0.90, 1.11) | 1.09 (1.02, 1.16) | 1.06 (1.01, 1.12) | 1.02 (0.97, 1.07) | 0.98 (0.95, 1.01) | 0.1 | 0.09 |
| Melanoma | 0.59 (0.43, 0.80) | 0.75 (0.56, 1.00) | 0.75 (0.59, 0.96) | 0.92 (0.70, 1.21) | 0.67 (0.46, 0.98) | 1.10 (0.99, 1.21) | 0.07 | 0.6 |
| Mesothelioma | 7.54 (0.60, 94.46) | 1.10 (0.64, 1.88) | 0.94 (0.72, 1.23) | 0.93 (0.76, 1.14) | 0.95 (0.79, 1.14) | 0.95 (0.84, 1.07) | 0.4 | 1.0 |
| Connective and soft tissue | 1.71 (1.12, 2.61) | 1.96 (1.15, 3.34) | 0.89 (0.54, 1.48) | 1.32 (0.85, 2.05) | 1.07 (0.73, 1.57) | 0.87 (0.76, 0.98) | 0.03 | 0.3 |
| Female breast | 0.93 (0.76, 1.13) | 0.99 (0.84, 1.17) | 0.97 (0.81, 1.15) | 0.69 (0.55, 0.87) | 0.85 (0.68, 1.07) | 0.97 (0.91, 1.03) | 0.3 | 0.1 |
| Cervix | 1.92 (1.25, 2.94) | 0.94 (0.59, 1.47) | 0.97 (0.62, 1.52) | 1.27 (0.81, 1.98) | 0.98 (0.62, 1.55) | 0.89 (0.77, 1.02) | 0.08 | 0.2 |

| | 15-44 | 45-54 | 55-64 | 65-74 | 75+ | Change in EMRR per age group | p-trend^ | p-departure from linearity^ |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | | |
| Uterus | 1.25 (0.49, 3.15) | 0.63 (0.38, 1.05) | 1.17 (0.87, 1.58) | 0.93 (0.68, 1.27) | 0.95 (0.67, 1.34) | 1.02 (0.88, 1.18) | 0.8 | 0.4 |
| Ovary | 1.10 (0.73, 1.65) | 1.07 (0.81, 1.42) | 1.33 (1.07, 1.64) | 1.01 (0.83, 1.22) | 1.13 (0.97, 1.32) | 1.00 (0.93, 1.08) | 1.0 | 0.5 |
| Vulva, vagina, other/unspecified | 0.41 (0.07, 2.23) | 1.16 (0.54, 2.51) | 0.80 (0.46, 1.39) | 1.33 (0.88, 2.02) | 0.99 (0.68, 1.45) | 1.05 (0.87, 1.28) | 0.6 | 0.2 |
| Prostate | 0.53 (0.08, 3.39) | 1.21 (0.69, 2.11) | 0.79 (0.57, 1.11) | 1.60 (1.21, 2.11) | 0.99 (0.85, 1.16) | 0.96 (0.85, 1.09) | 0.5 | 0.002 |
| Testis | 1.89 (0.78, 4.49) | 1.32 (0.32, 5.36) | 0.97 (0.10, 9.19) | NA | NA | 0.93 (0.52, 1.66) | 0.8 | 0.4 |
| Kidney | 1.11 (0.70, 1.76) | 1.38 (1.03, 1.84) | 1.13 (0.92, 1.41) | 1.24 (1.00, 1.55) | 0.98 (0.82, 1.17) | 0.94 (0.87, 1.02) | 0.1 | 0.5 |
| Bladder | 0.74 (0.31, 1.76) | 1.11 (0.72, 1.69) | 0.98 (0.76, 1.25) | 0.98 (0.82, 1.18) | 1.00 (0.87, 1.14) | 0.97 (0.88, 1.07) | 0.5 | 0.8 |
| Renal pelvis, ureter, other/unspecified | 2.58 (0.14, 47.01) | 3.19 (0.94, 10.77) | 1.20 (0.63, 2.28) | 1.03 (0.71, 1.50) | 0.99 (0.75, 1.32) | 0.85 (0.68, 1.05) | 0.1 | 0.6 |
| Brain and central nervous system | 0.84 (0.66, 1.07) | 0.98 (0.81, 1.17) | 1.05 (0.91, 1.22) | 1.00 (0.87, 1.15) | 1.13 (0.98, 1.31) | 1.06 (1.01, 1.12) | 0.03 | 0.8 |
| Thyroid | 4.61 (0.72, 29.58) | 0.95 (0.24, 3.81) | 1.31 (0.66, 2.59) | 0.69 (0.36, 1.30) | 1.34 (0.79, 2.29) | 0.79 (0.60, 1.04) | 0.09 | 0.7 |
| Unknown primary | 1.22 (0.83, 1.80) | 0.85 (0.68, 1.07) | 1.23 (1.05, 1.43) | 1.02 (0.90, 1.14) | 0.82 (0.76, 0.88) | 0.89 (0.85, 0.94) | <0.001 | 0.004 |
| Hodgkin lymphoma | 1.16 (0.50, 2.71) | 1.38 (0.42, 4.56) | 0.93 (0.37, 2.34) | 0.55 (0.30, 1.02) | 1.22 (0.71, 2.09) | 1.00 (0.79, 1.27) | 1.0 | 0.4 |
| Non-Hodgkin lymphoma | 1.01 (0.70, 1.46) | 0.89 (0.67, 1.19) | 1.05 (0.86, 1.29) | 0.85 (0.72, 1.01) | 0.95 (0.84, 1.08) | 0.99 (0.93, 1.07) | 0.9 | 0.6 |
| Multiple myeloma | 1.77 (0.81, 3.87) | 1.37 (0.93, 2.02) | 1.12 (0.88, 1.43) | 0.91 (0.75, 1.10) | 0.98 (0.84, 1.14) | 0.93 (0.84, 1.02) | 0.1 | 0.3 |
| Leukaemia | 1.30 (0.98, 1.72) | 0.96 (0.71, 1.29) | 1.14 (0.94, 1.40) | 0.86 (0.74, 1.01) | 1.06 (0.94, 1.20) | 0.96 (0.90, 1.02) | 0.2 | 0.1 |

CI, confidence interval; ^ likelihood ratio test; NA (not available, cannot be estimated)

### 9.4. Discussion

For 23 of 30 cancer types, cases residing outside major cities had lower estimated five-year survival than those residing in major cities, with 11 of these 23 estimates having a 95% confidence interval excluding the null. The survival gap between cases residing in and outside major cities decreased for most cancers after adjusting for area-based socio-economic disadvantage, particularly for prostate and anus or anal canal cancer, and it disappeared for colorectal cancer. For melanoma, unknown primary, Hodgkin lymphoma and head and neck cancers, the higher survival observed for cases residing outside major cities increased. For non-Hodgkin lymphoma and female breast cancer, the weak evidence of lower survival for cases residing outside major cities changed to increased survival after adjusting for area-level socio-economic disadvantage.

Residing in rural and more socio-economically disadvantaged areas appeared to be particularly disadvantageous for survival following a diagnosis with stomach, kidney or brain and CNS cancer. For prostate cancer, the observed survival disadvantage outside major cities increased over time. In contrast, for oesophageal and pancreatic cancer, inequalities in survival by remoteness of residence reduced over time. For unknown primary and cancer of connective or soft tissue, the lower survival of cases residing outside major cities, relative to their counterparts in major cities, was more pronounced at younger ages. For brain and CNS cancer, the lower survival for cases residing outside major cities was only observed for older cases and in the first year following diagnosis. For melanoma, the survival for cases residing outside major cities was higher for women than for men, whereas men residing outside major cities had lower survival than women from renal or ureter cancer.

Strengths of the present study are its population-based design and the large sample size with complete follow-up, allowing an assessment of heterogeneity in the excess mortality rates by sex, socio-economic disadvantage, age at diagnosis, year of diagnosis and time since cancer diagnosis. People in areas outside major cities generally experience more socio-economic disadvantage, and our sensitivity analysis in which we created lifetables stratified by remoteness and socio-economic disadvantage adds further strength to our findings, although it would have been preferable if these lifetables had been constructed by the Australian Bureau of Statistics from raw mortality data.

The main limitations of this study were unavailability of information in the VCR data about health-related behaviours such as smoking or alcohol drinking. Because the population life tables were not stratified by socio-economic disadvantage, indigeneity or smoking status, we cannot rule out the possibility of non-comparability bias due to variations in the background mortality rate, which could influence the estimation of relative or net survival and EMRRs for particular sub-populations. [26] We were unable to assess trends in survival with increasing distance from major cities as life tables by more refined categories of remoteness of residence (i.e. inner regional, outer regional and remote areas) were not available. Further, most non-metropolitan Victorian residents with cancer live in inner regional

areas, with only 6% and 0.6% residing in outer regional and remote areas, respectively. We had no information about change of place of residence after diagnosis. If patients moved from rural areas to more urban areas to be closer to services, the observed rural-urban differences would be underestimated. Additionally, there is a possibility of misclassification of individual-level socio-economic disadvantage using an area-level based measure.

The lower survival from colorectal, lung and prostate cancer for cases living outside major cities generally accords with other population-based studies. Most studies from Australia [5,11,28] and the United States (US) [29,30] have reported lower survival from colorectal cancer in non-urban areas, relative to urban regions, while some found no differences. [7, 31, 32] Conversely, a German study of females with colorectal cancer reported higher survival for rural residents than for urban residents. [33] Australian research regarding rural and urban differences in lung cancer survival reported a similar pattern of lower survival outside major cities. [11,28] Other Australian studies that investigated the association of remoteness of residence with prostate cancer survival have reported lower survival in rural and regional areas than in urban areas. [13,28,34]

After adjusting for area-based socio-economic disadvantage, we observed higher survival following diagnosis with melanoma or female breast cancer for residents of non-metropolitan areas. Studies conducted in the US reported no inequality in survival from breast cancer in rural and urban regions regardless of whether adjustment was made for SEP. [35,36] While some Australian studies not accounting for SEP reported an association between rural residence and lower survival, [11,28] others that adjusted for area-based measures of socio-economic disadvantage found strong evidence of lower survival from breast cancer in non-urban regions relative to urban regions. [14,37] In contrast, a study from Norway observed a survival advantage for females living in non-urban areas. [38] For melanoma, one Australian study from New South Wales found no differences in survival, [28] while one from Queensland reported lower survival from melanoma in rural regions; [39] neither adjusted for SEP. A systematic review of studies of prostate cancer found that after adjusting for SEP, survival was generally lower in rural regions. [40]

We found an increasing trend over time in the excess risk of death due to prostate cancer outside major cities, which might be due to the higher prevalence of prostate specific antigen testing in major cities in recent years. [41] Population-based studies from Australia showed that differences in prostate cancer survival by remoteness of residence widened over time, which was partly explained by lower prevalence of PSA testing and radical prostatectomy in non-urban areas. [41,42]

Our recent systematic review of 45 observational studies found that people residing in non-urban areas generally have lower cancer survival than their urban counterparts; variations in cancer stage at diagnosis and the treatment received appeared to explain part of these inequalities. [3] Other reviews have reported inadequate access to primary health care, diagnostic and treatment services as well as

higher prevalence of health-adverse behaviours and co-morbidities as potential contributing factors to lower cancer survival experienced by cases residing outside major cities. [43-45]

For most cancers we examined, the observed differences in survival between major cities and other areas decreased after adjusting for area-level socio-economic disadvantage. Some studies have shown that rural residents are more disadvantaged and have lower educational attainment than people living in urban regions, [10,46,47] which is associated with less use of health care services and more unhealthy behaviours such as poor diet, physical inactivity, smoking and excessive alcohol drinking. [48-53] Other research has reported socio-economic position as a strong determinant of co-morbidity and all-cause mortality. [52-55] However, it is not clear the degree to which socio-economic disadvantage and its associated factors might contribute to the association between remoteness of residence and cancer survival due to limitations of the applied methods and the variables accounted for in the analyses. Most studies that have attempted to assess differences in cancer survival between rural and urban areas either did not adjust for SEP or controlled for both socio-economic position and at least one variable in the causal pathway, which may have masked any direct influence of socio-economic disadvantage and potential mediators on rural and urban differences in cancer survival. [3]

***Conclusion***

People living with cancer and residing outside major cities had lower survival from some cancers when compared with those residing in major cities, partly due to their higher socio-economic disadvantage. There is strong and well-documented evidence that people at a lower socio-economic position have higher mortality from all causes; therefore, it is necessary to take socio-economic factors into account when comparing cancer outcomes by remoteness of residence. Further work is needed to disentangle the potential mediating effect of screening uptake, stage at diagnosis, co-morbid conditions, treatment modalities, and health-related lifestyle behaviours, which may help to establish effective interventions to minimise these inequalities.

**Ethics approval**

Ethical approval to conduct the analyses of these data was granted by the Cancer Council Victoria Human Research Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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**Conflict of interest** The authors declare no conflict of interest.

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## Chapter 10 . Factors explaining socio-economic inequalities in survival from colon cancer: a causal mediation analysis

In this chapter, an analysis of the linked population-based health data has been carried out to identify factors explaining socio-economic inequalities in colon cancer survival. This study was conceptualised and designed in consultation with Professor Dallas English and Professor Roger Milne as part of a collaborative project between Cancer Council Victoria and the Victorian Department of Health and Human Services (DHHS) that has recently linked the Victorian Cancer Registry (VCR) with hospital and other treatment datasets. The analysis was restricted to a common cancer i.e. colon cancer with strong socio-economic differences in survival and with good data availability. Because the new methods of causal mediation analysis cannot incorporate net or relative survival methods using population life tables, cancer-specific survival i.e. death from colon cancer was considered as the outcome in this study. I led this study, conducted the analyses and drafted the manuscript. Helen Farrugia, Vicky Thursfield, Kathryn Whitfield and Dr Luc te Marvelde curated the data. Professor Tony Blakely and Dr Ghazaleh Dashti provided expert and methodological advice. Dr Andrew Haydon provided clinical advice. All co-authors provided advice in the interpretation of results and reviewed the manuscript.

The list of references is formatted according to potential journal requirements, with separate numbering to the thesis reference list. Supplementary materials related to this publication are presented in Appendix F.

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**Factors explaining socio-economic inequalities in survival from colon cancer: a causal mediation analysis**

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**Key words** Cancer survival; Socio-economic position; Deprivation; Disadvantage; Inequality

**Abbreviations** CI: Confidence interval; IDE: interventional direct effect; IIE: interventional indirect effect; IRSD: Index of Relative Socio-Economic Disadvantage; SEIFA, socio-economic indexes for areas; SEP: Socio-economic position; TE: total effect; VAED: Victorian Admitted Episodes Dataset; VCR: Victorian Cancer Registry

**Abstract**

**Background:** Socio-economic inequalities in colon cancer survival exist in high-income countries, but little is known about why. We aimed to assess the mediating effects of stage at diagnosis, co-morbidities and treatment on survival from colon cancer.

**Methods:** We identified 5,374 people aged 15-79 years with first primary colon cancer diagnosed in Victoria in 2008-2011. Clinical information was obtained from hospital records. Deaths to the end of 2016 were identified from Victorian and national death registries. Socio-economic disadvantage was determined based on residential address at diagnosis; we decomposed its total effect into direct and indirect effects using interventional mediation analysis.

**Results:** Socio-economic inequalities in colon cancer survival were greater for men than women and were not explained by stage. For stage III, there were 161 (95%CI 67, 256) additional deaths per 1,000 cases in the five years following diagnosis for the most disadvantaged men compared with the least disadvantaged. The indirect effects through co-morbidities and chemotherapy explained 5 (95%CI -9, 20) and 18 (95%CI -10, 45) per 1,000 of these additional deaths, respectively. Surgery and substage did not explain the excess deaths for disadvantaged men.

**Conclusions:** Socio-economically disadvantaged men had poorer survival from colon cancer that was not explained by stage at diagnosis. For men with stage III disease, the poorer survival for those living in the most disadvantaged areas is only partly explained by having co-morbid conditions and not receiving chemotherapy.

## 10.1. Introduction

Socio-economic position (SEP) is associated with survival from colon cancer in high-income countries, with higher excess mortality for people with lower SEP. [1,2] In Australia, colon cancer is the second most common cancer diagnosed in both men and women, and the second most common cause of cancer-related deaths. [3] Previous Australian studies observed lower survival for disadvantaged people with colorectal cancer and reported that disease stage and other tumour characteristics did not explain the observed gaps in survival. [4-7] In contrast, studies conducted in the United States, Europe and New Zealand suggested that cases from more socio-economically disadvantaged backgrounds present with more advanced stage. [8-12] Few studies have assessed the potential role of health-related behaviours, co-morbidities and treatment in inequalities in cancer survival. [13,14] Interpreting the findings of studies that have attempted to identify the underlying reasons for socio-economic inequalities in colorectal cancer survival is difficult because most compared the effect of SEP on survival with and without controlling for mediators, which can give biased results, particularly in the presence of multiple mediators influencing or interacting with each other. [15,16] We aimed to identify factors explaining socio-economic inequalities in colon cancer survival by applying causal mediation analysis to linked population-based health data.

## 10.2. Methods

### *Data sources*

We identified colon cancer cases using the population-based Victorian Cancer Registry (VCR). All hospitals and pathology laboratories in Victoria are required to notify the registry of new malignant invasive neoplasms. The VCR collects demographic and tumour details [17] and derives TNM summary stage at diagnosis from information on pathology reports and from hospital notifications. [18] Information about co-morbidities and the treatment received was obtained via record linkage between the VCR and the Victorian Admitted Episodes Dataset (VAED). [19] The VAED comprises demographic, clinical and administrative data for every admission to Victorian public and private hospitals, including rehabilitation centres, extended care facilities and day procedure centres. [19]

### *Participants*

We included cases diagnosed with first primary colon cancer at age 15-79 years from 2008 to 2011. We excluded cases diagnosed with colon and rectal cancer on the same day or diagnosed via autopsy or death certificate only. We also excluded indigenous cases and those with missing data on socio-economic disadvantage, disease stage or co-morbidities. Follow-up was complete to 31 December 2016.

### *Socio-economic disadvantage*

The Index of Relative Socio-Economic Disadvantage (IRSD), constructed by the Australian Bureau of Statistics, was used to define an aggregated composite measure of socio-economic disadvantage known

as socio-economic indexes for areas (SEIFA). [20] For each case, this was based on the smallest geographical area of their usual residential address at the census closest to their year of diagnosis. For individuals diagnosed between 2009 and 2011, addresses were geocoded and mapped to precise latitude and longitude, and then mapped according to statistical area level 1, which have a mean population size of approximately 400 persons; [21] for individuals diagnosed in 2008, addresses were geocoded and mapped using collection district, which have a mean of 225 dwellings. [22] SEIFA quintiles were defined based on the assigned IRSD scores for each geographical area. A lower score represents more socio-economically disadvantaged areas with households with lower income and people in less skilled occupations or with lower education. [20] The most and least socio-economically disadvantaged areas were defined as the fifth and first quintiles of SEIFA, respectively. Hereafter, we use the word 'disadvantage' for this variable.

***Mortality***

Deaths and causes of deaths were identified by linkage to the Victorian Registry of Births, Deaths and Marriages and the National Death Index (NDI). Causes of deaths were coded by the VCR staff using information from several medical records such as death certificate, each person's history of cancer diagnosis/diagnoses, recent hospital admission for recurrent or metastatic disease. The interstate causes of deaths were notified by the NDI, which uses the Australian Bureau of Statistics coding. We defined the outcome as death from colon cancer, and the few cases died of other causes were considered alive.

***Co-morbidities and treatment***

We defined co-morbidities using the Charlson Co-morbidity Index [23] dichotomised into absence or presence of any co-morbidity. Substage was categorized as 3A/3B and 3C; Surgical resection and intravenous adjuvant chemotherapy were defined dichotomously (yes/no) according to the Victorian optimal care pathway recommendations; [24] surgery was defined as occurring within 4 weeks after diagnosis and chemotherapy within 8 weeks following surgery.

***Other mediators***

For mediation analyses restricted to cases who received surgery within 6-months of diagnosis, other potential mediators were emergency presentation 0–7 days prior to diagnosis (no/yes), type of hospital in which surgery was done (private or public), median number of colon cancer surgeries performed at the hospital (≥32 or <32, 32 being the median across hospitals in Victoria) [25] as a measure for hospital caseload, and number of nodes taken during surgery (≥12 or <12) as a proxy measure for quality of surgery.

***Statistical analysis***

Analyses were restricted to the most and least disadvantaged categories to assist with the interpretation of the estimated mediating effects. One- and five-year net survival was estimated by stage, sex and

socio-economic disadvantage using the Pohar-Perme method, [26] based on Victorian population life tables stratified by year, age, sex, and SEIFA quintile.

Mediation analysis was performed for stage III disease, with death from colon cancer as the outcome. Cases with stage I colon cancer were not included in mediation analyses because of their high survival. Those with stage II disease were also excluded because the competing risk of death was high. Individuals with stage IV disease were not included, as death within the first 3 months following diagnosis was substantially higher for cases living in the most disadvantaged areas than for their counterparts from the least disadvantaged regions, suggesting that disadvantaged cases were more likely to die before they could receive treatment.

We fitted logistic regression models to assess associations between disadvantage and the outcome, between disadvantage and potential mediators, and between the mediators and the outcome (death from colon cancer). For the causal mediation analyses, we used a multiple mediator interventional approach to decompose the total effect (TE) of socio-economic disadvantage on survival into interventional direct (IDE), not through any of the mediators, and indirect (IIE) effects, [27] estimated as risk differences. This method requires the averaging of effects across Monte-Carlo draws; we used 600,000 draws. Confidence intervals were obtained from 1,000 bootstrap samples.

Our hypothesised causal structure for the effects of socio-economic disadvantage on survival were based on existing literature (see Supplementary Figure 1). [1,14,28] For stage III disease, potential mediators were co-morbidities, substage, receiving surgery within 4 weeks of diagnosis and chemotherapy within 8 weeks following surgery; for the subset of cases who received surgery within 6 months of diagnosis, mediators were co-morbidities, substage, receiving chemotherapy within 8 weeks after surgery, emergency presentation prior to diagnosis, surgical hospital type, surgical volume of a hospital, and number of nodes taken.

The models to estimate IIEs for men and women were i) logistic regression of co-morbidities conditional on disadvantage and age; ii) logistic regression of substage conditional on disadvantage and age; iii) logistic regression of surgery conditional on disadvantage and age; iv) logistic regression of chemotherapy conditional on disadvantage and age; v) logistic regression of the outcome (death from colon cancer) conditional on disadvantage, all mediators and age. A similar approach was used to define models estimating the mediating effects of emergency presentation, hospital type, surgical volume and number of nodes taken. We repeated mediation analysis that allowed for potential exposure-mediator interactions, but only included interaction term between exposure and mediators that did not create combinations with sparse data (i.e. a sufficient number of at least 30 cases in each category).

People residing in non-metropolitan areas are generally more disadvantaged and have lower cancer survival. [3] Because area-level socio-economic disadvantage and remoteness of residence were defined based on same geographical areas, rather than adjusting for rurality, we conducted a sensitivity analysis

restricted to cases residing in major cities to remove any potential confounding effects of factors associated with rurality.

All analyses were performed using Stata/MP version 14.2 (Stata Corporation LP, College Station, TX, USA). Approval to conduct the analyses was granted by the data custodians at the Victorian Department of Health and Human Services and the Cancer Council Victoria Human Research Ethics Committee.

### 10.3. Results

We identified 5,374 eligible colon cancer cases (Figure 10.1). The characteristics of cases are summarised in Table 10.1. Cases residing in the most disadvantaged areas were diagnosed at older ages. There was no notable difference in the distribution of stage at diagnosis between the least and most disadvantaged areas (Table 10.2; $P$=0.4).

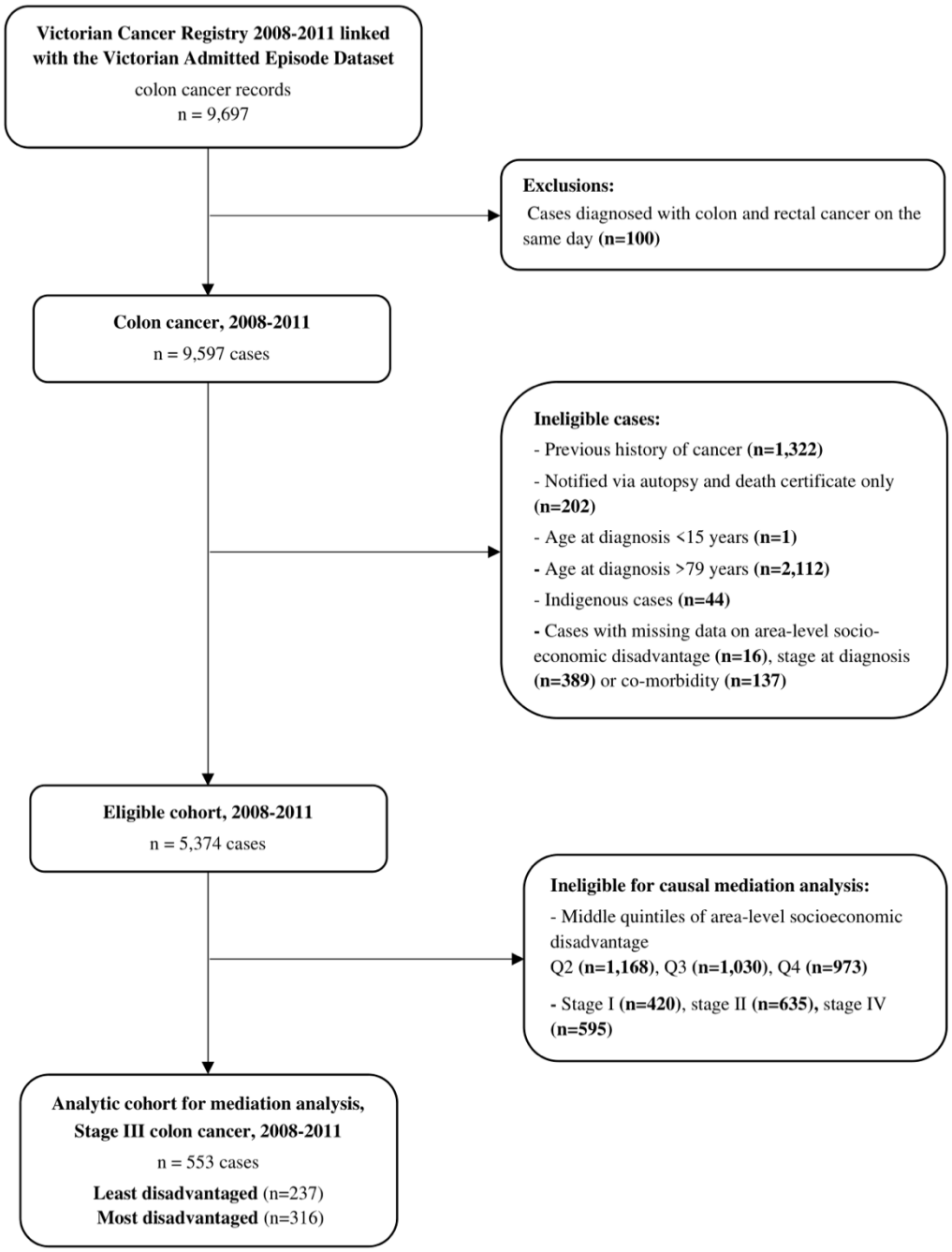


**Figure 10.1.** Case selection from the linked dataset

### *Survival from colon cancer*

For stage I disease, five-year net survival was close to 100%, while for stage II, it was lower for the most disadvantaged cases, relative to the least disadvantaged (Table 10.3). For stage III disease, one-year survival did not differ between those residing in the least and most disadvantaged areas; however, five-year survival was 13% lower for the most disadvantaged areas. The gap in survival was greater for men than women. Of cases with stage IV disease, those residing in the most disadvantaged areas had

lower one- and five-year survival than their counterparts residing in the least disadvantaged areas, although the difference in five-year survival was restricted to men (Table 10.3).

***Exposure–outcome association***

With respect to the association between socio-economic disadvantage and death from stage III colon cancer, the results of the logistic regression analyses were consistent with the results of the net survival analyses (Supplementary Table 1).

***Exposure–mediator and mediator–outcome associations***

Of men with stage III colon cancer, those residing in the most disadvantaged areas were more likely to have co-morbid conditions than those living in the least disadvantaged regions; we observed no association for women (Supplementary Table 2). Residents of the most disadvantaged areas were more likely not to receive surgery within 4 weeks of diagnosis and chemotherapy within 8 weeks after surgery and were more likely to have an emergency presentation prior to diagnosis and receive surgery at public hospitals than the least disadvantaged cases (Supplementary Table 2).

Cases with co-morbidities or those having emergency presentation prior to diagnosis were more likely to die from colon cancer (Supplementary Table 3). Not receiving chemotherapy within 8 weeks after surgery was associated with lower survival from stage III colon cancer. The probability of dying within five years after diagnosis was greater for cases with late stage III cancer compared with earlier stages (IIIA and B). Men with stage III disease who received surgery in public hospitals were more likely to die within five years of diagnosis than their counterparts having surgery in private hospitals. There was no evidence of association between survival and surgical volume of the hospital for stage III disease. Results for receiving surgery within 4 weeks of diagnosis and the number of nodes taken in surgery for cases with stage III disease were too imprecise to be informative (Supplementary Table 3).

**Table 10.1.** Characteristics of individuals diagnosed with first primary colon cancer in Victoria, Australia, 2008-2011

| **Stage I colon cancer** | Least disadvantaged | | | Most disadvantaged | | |
|---|---|---|---|---|---|---|
| | Total n=169 | Men n=87 | Women n=82 | Total n=251 | Men n=140 | Women n=111 |
| **Age at diagnosis, years; median (interquartile range)** | 65 (57 – 72) | 65 (58 – 72) | 65 (56 – 71) | 67 (60 – 74) | 68 (60 – 74) | 66 (60 – 74) |
| **Died within 1 year of diagnosis** | | | | | | |
| colon cancer deaths (%) | 0 (0) | 0 (0) | 0 (0) | 1 (0.4) | 1 (1) | 0 (0) |
| other causes deaths (%) | 1 (0.6) | 0 (0) | 1 (1) | 2 (0.8) | 2 (1) | 0 (0) |
| **Died within 5 years of diagnosis** | | | | | | |
| colon cancer deaths (%) | 2 (1) | 2 (2) | 0 (0) | 9 (4) | 5 (4) | 4 (4) |
| other causes deaths (%) | 7 (4) | 2 (2) | 5 (6) | 22 (9) | 14 (10) | 8 (7) |
| **Stage II colon cancer** | Least disadvantaged | | | Most disadvantaged | | |
| | Total n=245 | Men n=134 | Women n=111 | Total n=390 | Men n=195 | Women n=195 |
| **Age at diagnosis, years; median (interquartile range)** | 65 (58 – 74) | 64 (55 – 72) | 69 (60 – 75) | 69 (62 – 74) | 69 (63 – 74) | 69 (62 – 74) |
| **Died within 1 years of diagnosis** | | | | | | |
| colon cancer deaths (%) | 2 (0.8) | 2 (2) | 0 (0) | 10 (3) | 4 (2) | 6 (3) |
| other causes deaths (%) | 3 (1.2) | 3 (2) | 0 (0) | 9 (2) | 6 (3) | 3 (2) |
| **Died within 5 years of diagnosis** | | | | | | |
| colon cancer deaths (%) | 14 (6) | 5 (4) | 9 (11) | 39 (10) | 23 (12) | 16 (8) |
| other causes deaths (%) | 8 (3) | 8 (6) | 0 (0) | 34 (9) | 23 (12) | 11 (6) |
| **Stage III colon cancer** | Least disadvantaged | | | Most disadvantaged | | |
| | Total n=237 | Men n=129 | Women n=108 | Total n=316 | Men n=167 | Women n=149 |
| **Age at diagnosis, years; median (interquartile range)** | 64 (55 – 72) | 63 (54 – 72) | 65 (58.5 – 73) | 68 (59 – 75) | 67 (58 – 74) | 69 (59 – 75) |
| **Died within 1 year of diagnosis** | | | | | | |
| colon cancer deaths (%) | 11 (4.6) | 6 (5) | 5 (5) | 12 (4) | 7 (4) | 5 (4) |
| other causes deaths (%) | 1 (0.4) | 1 (1) | 0 (0) | 5 (2) | 3 (2) | 2 (1) |
| **Died within 5 year of diagnosis** | | | | | | |
| colon cancer deaths (%) | 49 (21) | 19 (15) | 30 (28) | 100 (32) | 53 (32) | 47 (32) |

| | | | | | | |
|---|---|---|---|---|---|---|
| other causes deaths (%) | 7 (3) | 5 (4) | 2 (2) | 22 (7) | 11 (7) | 11 (7) |
| **At least one co-morbidity** | | | | | | |
| yes (%) | 12 (5) | 7 (5) | 5 (5) | 27 (9) | 21 (13) | 6 (4) |
| **Had late stage III cancer (substage)** | | | | | | |
| 3C (%) | 39 (16) | 24 (19) | 15 (14) | 54 (17) | 24 (14) | 30 (20) |
| **Received surgery within 4 weeks of diagnosis** | | | | | | |
| yes (%) | 213 (90) | 116 (90) | 97 (90) | 248 (78) | 128 (77) | 120 (81) |
| **Received chemotherapy within 8 weeks after surgery^** | | | | | | |
| yes (%) | 176 (74) | 94 (73) | 82 (76) | 164 (52) | 83 (50) | 81 (54) |
| **Received surgery within 6 months of diagnosis** | | | | | | |
| yes (%) | 233 (98) | 128 (99) | 105 (97) | 309 (98) | 163 (98) | 146 (98) |
| **Received chemotherapy within 6 months of diagnosis^** | | | | | | |
| yes (%) | 192 (81) | 104 (81) | 88 (81) | 212 (67) | 111 (66) | 101 (68) |
| **Stage III colon cancer**<br>Patients who received surgery within 6 months after diagnosis* | Least disadvantaged<br>Total<br>n=233 | <br>Men<br>n=128 | <br>Women<br>n=105 | Most disadvantaged<br>Total<br>n=309 | <br>Men<br>n=163 | <br>Women<br>n=146 |
| **Age at diagnosis, years; median (interquartile range)** | 64 (55 – 72) | 63 (54 – 72) | 65 (59 – 73) | 68 (59 – 75) | 67 (58 – 74) | 69 (59 – 75) |
| **Died within 1 year of diagnosis** | | | | | | |
| colon cancer deaths (%) | 10 (4.3) | 5 (4) | 5 (5) | 12 (4) | 7 (4) | 5 (4) |
| other causes deaths (%) | 1 (0.4) | 1 (1) | 0 (0) | 5 (2) | 3 (2) | 2 (1) |
| **Died within 5 years of diagnosis** | | | | | | |
| colon cancer deaths (%) | 47 (20) | 18 (14) | 29 (28) | 98 (32) | 52 (32) | 46 (32) |
| other causes deaths (%) | 7 (3) | 5 (4) | 2 (2) | 22 (7) | 11 (7) | 11 (7) |
| **At least one co-morbidity** | | | | | | |
| yes (%) | 11 (5) | 7 (5) | 4 (4) | 27 (9) | 21 (13) | 6 (4) |
| **Had late stage III cancer (substage)** | | | | | | |
| 3C (%) | 38 (16) | 23 (18) | 15 (14) | 51 (17) | 24 (15) | 27 (18) |
| **Emergency presentation** | | | | | | |
| yes (%) | 37 (16) | 20 (16) | 17 (16) | 70 (23) | 34 (21) | 36 (25) |
| **Hospital type** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Private (%) | 150 (64) | 81 (63) | 69 (66) | 73 (24) | 38 (23) | 35 (24) |
| Public (%) | 83 (36) | 47 (37) | 36 (34) | 236 (76) | 125 (77) | 111 (76) |
| **Surgical volume of hospital (median number of colon surgeries per year)** | | | | | | |
| ≥32 (%) | 216 (93) | 120 (94) | 96 (91) | 277 (90) | 149 (91) | 128 (88) |
| <32 (%) | 17 (7) | 8 (6) | 9 (9) | 32 (10) | 14 (9) | 18 (12) |
| **Number of nodes taken at surgery** | | | | | | |
| ≥12 (%) | 208 (89) | 114 (89) | 94 (89) | 275 (89) | 142 (87) | 133 (91) |
| <12 (%) | 20 (9) | 11 (9) | 9 (9) | 21 (7) | 13 (8) | 8 (6) |
| Missing (%) | 5 (2) | 3 (2) | 2 (2) | 13 (4) | 8 (5) | 5 (3) |
| **Stage IV colon cancer** | Least disadvantaged | | | Most disadvantaged | | |
| | Total n=228 | Men n=128 | Women n=100 | Total n=367 | Men n=209 | Women n=158 |
| **Age at diagnosis, years; median (interquartile range)** | 64 (54.5 – 73.5) | 67 (55 – 75) | 63 (53.5 – 72) | 66 (58 – 74) | 68 (59 – 74) | 64 (57 – 73) |
| **Died within 1 year of diagnosis** | | | | | | |
| colon cancer deaths (%) | 78 (34) | 42 (33) | 36 (36) | 174 (48) | 100 (48) | 74 (47) |
| other causes deaths (%) | 0 (0) | 0 (0) | 0 (0) | 8 (2) | 7 (3) | 1 (1) |
| **Died within 5 year of diagnosis** | | | | | | |
| colon cancer deaths (%) | 171 (75) | 94 (73) | 77 (77) | 300 (82) | 172 (82) | 128 (81) |
| other causes deaths (%) | 7 (3) | 2 (2) | 5 (5) | 16 (4) | 13 (6) | 3 (2) |

* 11 cases who did not receive surgery were excluded; ^ Does not include oral chemotherapy

**Table 10.2.** Stage distribution, by area-level socio-economic disadvantage, for individuals diagnosed with first primary colon cancer in Victoria, Australia, 2008-2011

| Stage at diagnosis | SOCIO-ECONOMIC INDEXES FOR AREA (SEIFA) QUINTILES | |
|---|---|---|
| | Least disadvantaged N (%) | Most disadvantaged N (%) |
| 1 | 169 (19) | 251 (19) |
| 2 | 245 (28) | 390 (29) |
| 3 | 237 (27) | 316 (24) |
| 4 | 228 (26) | 367 (28) |

N; number of cases

### *Mediation analyses*

The excess number of deaths in the most disadvantaged areas was notably higher for men than for women. Co-morbidities and surgery did not play any role for women, and the estimated IE through substage and chemotherapy was 18 (95%CI -13, 48) and 13 (95%CI -8, 33) per 1,000 cases, respectively. For men, we estimated that there were 161 (95%CI 67, 256) additional deaths from colon cancer per 1,000 with stage III disease in the five years after diagnosis in the most disadvantaged areas relative to the least disadvantaged (Figure 10.2). The estimated DE (not through the mediators) was 150 (95%CI 48, 252) per 1,000. Surgery and substage did not contribute to the observed excess deaths for men residing in the most disadvantaged areas. The estimated number of additional deaths per 1,000 among men residing in the most disadvantaged areas was 5 (95%CI -9, 20) through co-morbidities and 18 (95%CI -10, 45) through chemotherapy (Figure 10.2).

Given the larger survival gap for men than for women with stage III colon cancer, which was not explained by co-morbidities, substage, surgery or chemotherapy, we further investigated whether emergency admission prior to diagnosis, the type of hospital in which surgery was done (public or private), surgical volume of the hospital or the number of nodes taken during surgery (as a measure of quality) explained the observed difference in survival for men. Of the 142 (95%CI 48, 235) additional deaths per 1,000 for men receiving surgery within 6 months of diagnosis and residing in the most disadvantaged areas relative to their counterparts in the least disadvantages areas, 31 (95%CI -15, 77) per 1,000 of excess deaths were explained through receiving surgery at a public hospital (Figure 10.3). There were no mediating effects through surgical volume or number of nodes taken.

Adding interactions between the exposure and the mediators did not markedly change any results (Supplementary Figures 2 and 3). Excluding cases residing outside major cities did not alter the results for men, although the mediating effect of co-morbidities and chemotherapy was greater in major cities (Supplementary Figures 4 and 5). For women, the gap in survival and the mediating effect of substage and chemotherapy was greater in major cities (Supplementary Figures 4).

**Table 10.3.** One- and five-year net survival for individuals diagnosed with first primary colon cancer in Victoria, Australia, 2008-2011

| | | Stage I | | | Stage II | | |
|---|---|---|---|---|---|---|---|
| | | All | Men | Women | All | Men | Women |
| **Period** | **Socio-economic index for area (SEIFA)** | **Net survival % (95% CI)** | | | **Net survival % (95% CI)** | | |
| One year following diagnosis | Least disadvantaged | 100.4 (100.4 – 100.4) | 101.2 (101.2 – 101.2) | 99.5 (56.4 – 100) | 99.0 (94.0 – 99.8) | 97.4 (91.0 – 99.3) | 101.0 (101.0 – 101.0) |
| | Most disadvantaged | 101.0 (101.0 – 101.0) | 99.9 (0 – 100) | 101.1 (101.1 – 101.1) | 96.8 (93.7 – 98.4) | 97.0 (91.5 – 98.9) | 96.6 (91.9 – 98.6) |
| Five years following diagnosis | Least disadvantaged | 99.9 (0 – 100) | 101.9 (101.9 – 101.9) | 97.8 (77.1 – 99.8) | 96.7 (89.6 – 98.9) | 96.4 (84.5 – 99.2) | 97.1 (82.0 – 99.6) |
| | Most disadvantaged | 97.0 (86.7 – 99.3) | 98.2 (51.1 – 99.9) | 95.5 (82.3 – 98.9) | 90.1 (84.8 – 93.7) | 87.0 (78.2 – 92.4) | 93.3 (85.5 – 97.0) |
| | | **Stage III** | | | **Stage IV** | | |
| | | **All** | **Men** | **Women** | **All** | **Men** | **Women** |
| **Period** | **Socio-economic index for area (SEIFA)** | **Net survival % (95% CI)** | | | **Net survival % (95% CI)** | | |
| One year following diagnosis | Least disadvantaged | 95.9 (91.9 – 97.9) | 95.6 (89.3 – 98.2) | 96.2 (89.3 – 98.7) | 66.4 (59.7 – 72.2) | 67.9 (58.9 – 75.4) | 64.4 (54.1 – 73.0) |
| | Most disadvantaged | 96.1 (92.6 – 98.0) | 95.8 (90.1 – 98.3) | 96.5 (90.8 – 98.7) | 51.1 (45.8 – 56.1) | 49.7 (42.6 – 56.3) | 53.0 (44.8 – 60.5) |
| Five years following diagnosis | Least disadvantaged | 80.4 (73.9 – 85.5) | 86.2 (77.0 – 91.9) | 73.6 (63.2 – 81.5) | 22.8 (17.5 – 28.6) | 26.3 (18.8 – 34.5) | 18.3 (11.3 – 26.5) |
| | Most disadvantaged | 67.4 (61.0 – 72.9) | 69.1 (59.9 – 76.5) | 65.5 (56.2 – 73.3) | 14.9 (11.3 – 18.9) | 12.4 (8.1 – 17.6) | 18.1 (12.4 – 24.7) |

CI; confidence interval

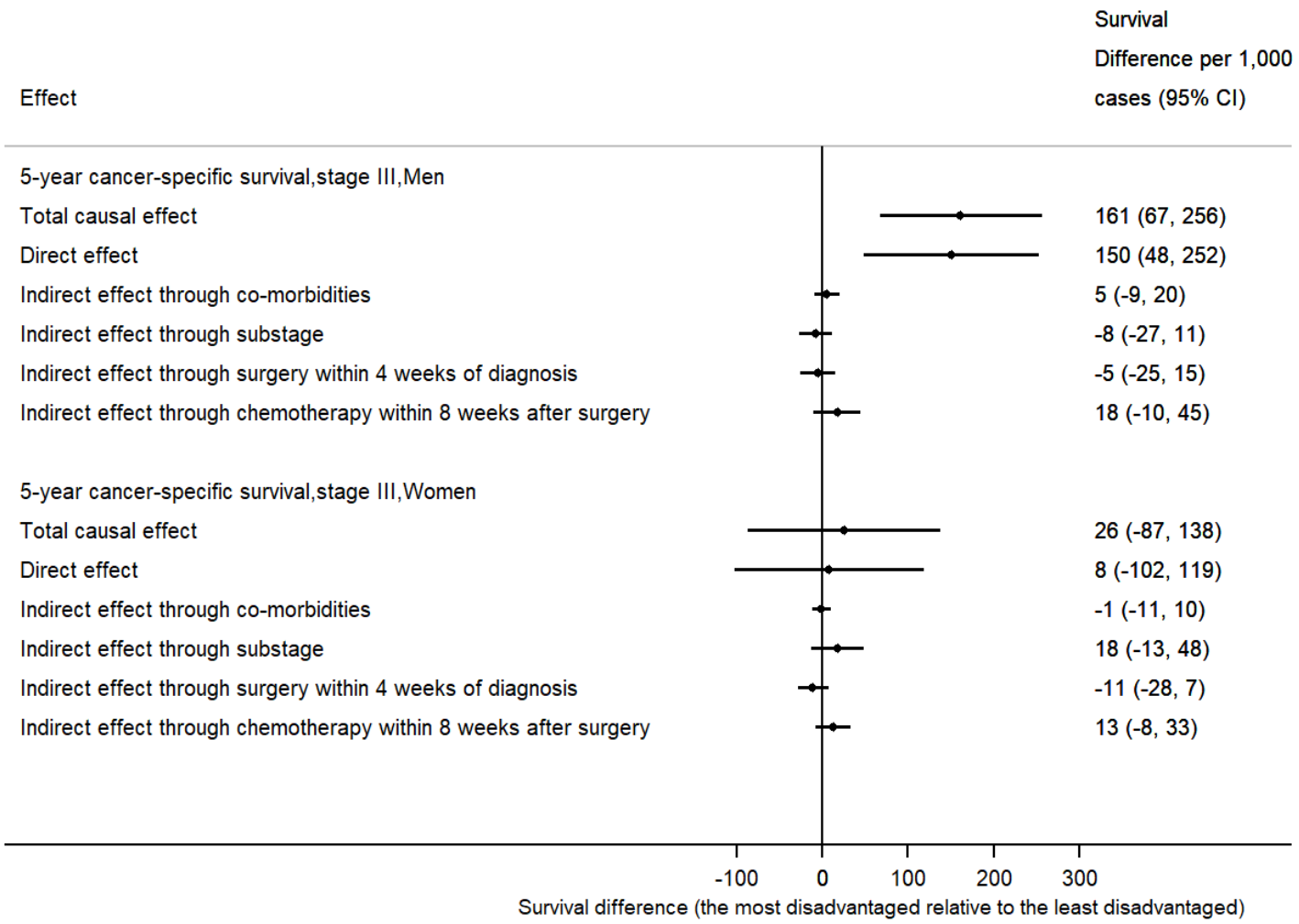


**Figure 10.2.** Results of interventional mediation analysis with co-morbidities, substage, receiving surgery within 4 weeks of diagnosis and intravenous chemotherapy within 8 weeks after surgery as mediators of interest, and area-level socio-economic disadvantage and death from colon cancer within 5 years of diagnosis, Victoria, Australia, 2008-2011

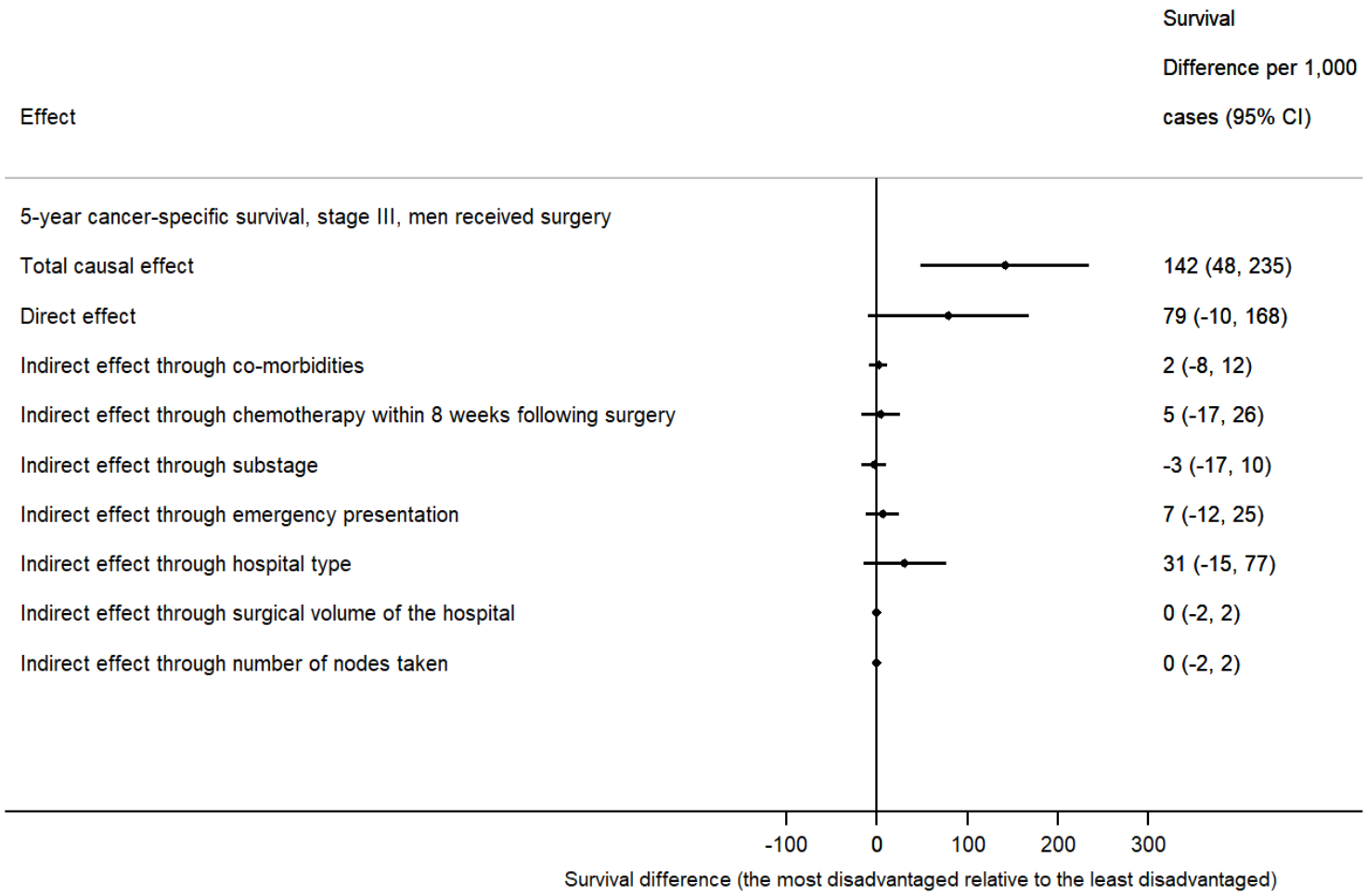


**Figure 10.3.** Results of interventional mediation analysis with co-morbidities, receiving chemotherapy within 6 months after diagnosis, substage, emergency presentation, hospital type, surgical volume of the hospital, and number of nodes taken during surgery as mediators of interest, and area-level socio-economic disadvantage and death from colon cancer within 5 years of diagnosis, Victoria, Australia, 2008-2011

### 10.4. Discussion

We observed socio-economic inequalities in colon-cancer survival that were greater for men than women. The stage distribution could not explain the differences in survival because it did not differ by disadvantage. Lower five-year survival from stage III colon cancer for cases residing in the most disadvantaged areas, relative to the least disadvantaged regions, was not explained by differential surgical treatment. Co-morbidities and chemotherapy contributed very little to the observed differences; however, lower survival for men living in the most disadvantaged areas may be partly mediated through receiving surgery at public hospitals. Emergency presentation prior to diagnosis, while more common for patients from the most disadvantaged areas, explained very little of the gap in survival. Surgical volume of the hospital and number of nodes taken, as markers of hospital and surgical quality, did not explain the observed socio-economic inequalities in survival from stage III colon cancer.

To the best of our knowledge, of the few existing studies that have investigated the underlying reasons for inequalities in colorectal cancer-specific survival by educational level or SEP, [4,8,11,29,30] our study is the first to use novel methods of causal mediation analysis. Interventional mediation analysis enabled us to disentangle and quantify indirect effects through multiple interrelated mediators. [27] Another advantage of this method is the ability to include exposure-mediator interactions in the models. [27] Another strength of our study is the population-based design and the linkage to inpatient hospital data, which allowed us to assess the role of treatment and co-morbidities in socio-economic inequalities in survival from stage III colon cancer. The main limitation of this method is that we used an area-based measure of socio-economic position rather than an individual-based measure, which could have resulted in misclassification and underestimation of the influence of SEP on colon cancer survival. We did not have information on health-related lifestyle behaviours or oral chemotherapy, which is an issue for older cases with stage III disease, who are more likely to receive oral chemotherapy. Also, co-morbidities were underreported, as they were only recorded when related to the hospital admission. Moreover, we defined surgery and chemotherapy as binary variables which could have diluted their indirect effects and increased the direct effects.

Findings from previous Australian studies are generally consistent with our results. One Australian study showed that stage at diagnosis did not explain the observed socio-economic inequalities in survival from colorectal cancer. [4] The other study from Australia, found that differential stage at diagnosis, co-morbidities, treatment, patient characteristics or tumour characteristics did not contribute to the shorter survival of cases with colorectal cancer residing in the most disadvantaged areas. [30] A Swedish study reported that variation in surgery type (elective or emergency) and hospital location (urban or rural) did not explain the higher excess death from colon cancer among cases with low educational level. [8] In contrast, studies from New Zealand and England found that tumour stage and treatment partly contributed to socio-economic inequalities in survival from colorectal cancer. [11,29] The

inconsistency between countries in the estimated effects of these mediators might be due to differences in health care systems or to limitations of the data or the methods applied.

A recent review by the International Agency for research on cancer (IARC) reported higher prevalence of unhealthy diet, smoking, heavy alcohol intake, physical inactivity among individuals with low levels of income and education as potential contributing factors to inequalities in cancer survival. [28] Differences in screening uptake, stage at diagnosis and access to diagnostic and treatment services across socio-economic groups have also been highlighted as other explanatory factors. [28]

It is unclear why worse survival of underprivileged men with stage III disease appeared to be partly explained by having surgery in public rather than private hospitals. This observation might be due to other unmeasured characteristics of disadvantaged men receiving surgery in public hospitals rather than to the public or private hospitals themselves, as we found that the observed gap in survival was not explained by differences in surgical volume of the hospital or the number of nodes taken, i.e. quality of hospital and surgical resection.

In summary, despite Australia's universal health care system, we observed lower survival from stage III colon cancer for cases residing in the most disadvantaged areas, which was barely explained by differences in co-morbidities, chemotherapy, emergency presentation or surgical hospital type. It is essential that future studies identify the potential role of other explanatory factors such as health-related lifestyle behaviours, completion of and compliance to chemotherapy and access to clinical trials, which may lead to changes in current cancer control policies and interventions, and improving survival equally for all colon cancer patients.

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**Conflict of interest**

The authors declare no conflict of interest.

**Data Availability Statement** Potentially identifiable data from the Victorian Cancer Registry and the Victorian Admitted Episodes Dataset was made available to the researchers with approval from the data custodians at the Victorian Department of Health and Human Services and the Cancer Council Victoria Human Research Ethics Committee, and under a memorandum of understanding that does not allow these data to be shared with third parties.

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# Chapter 11 . Discussion

## 11.1. Overview

The aims of this thesis were to investigate trends and inequalities in cancer survival by sex, area-level socio-economic disadvantage and remoteness of residence in Victoria, Australia and to identify factors contributing to socio-economic inequalities in colon cancer survival. These objectives were addressed by conducting systematic reviews, estimating five-year net/relative survival and excess mortality rate ratios from first primary cancers using data from the Victorian Cancer Registry, and applying causal mediation to population-based linked health data.

This chapter has four main sections:

- The first section summarises and interprets the key findings of results chapters 7-10, with sub-sections comparing the findings with previous studies that have assessed differences in cancer survival by sex, socio-economic position and rural-urban residence, including studies that have attempted to identify the underlying reasons for these inequalities.
- The second section presents the strengths and limitations of this thesis.
- The third section presents potential areas for future research.
- The fourth section presents the overall conclusions.

## 11.2. Summary of findings, comparison with previous studies and interpretations

In this section, an overall summary of major findings from each of the results chapters and comparison with other research is given, with the aim of minimising repetition.

### 11.2.1 Differences in cancer survival by sex

#### 11.2.1.1 Summary of findings

Net survival analyses of 412,471 people aged 15-99 years and diagnosed with one of 25 first primary cancers between 1982 and 2015 (chapter 7, published in *Cancer Causes and Control*) showed that, in Victoria, Australia, men generally had lower five-year survival than women for most cancers. The largest difference was found for melanoma, with two times higher excess mortality in men compared with women. A similar pattern was observed for cancers of the colorectum, lung, head and neck, oesophagus, pancreas, bone and cartilages, kidney, and thyroid, as well as for mesothelioma and non-Hodgkin lymphoma, with 4% to 47% higher excess risk of death due to cancer in men. In contrast, women had a survival disadvantage for cancers of the bladder, renal pelvis or ureter. The observed gap in cancer survival between men and women was generally greater at younger ages. The sex differences in survival from colorectal and pancreatic cancer decreased over time, whereas those for lung cancer widened over the last 18 years.

#### 11.2.1.2 Comparison with other studies and interpretations

This is the first population-based study in Australia that has comprehensively investigated the magnitude and temporal and age-related patterns of survival differences between men and women. Its findings are generally in line with studies from other countries. The EUROCARE-4 study [81] and other population-based studies conducted in the United States (US), [82] Canada [11] and Korea [83] found that men typically have lower survival for most cancers compared with women, while women with bladder cancer have a higher excess risk of death than men. The finding of a greater cancer survival gap by sex for people diagnosed at younger ages is also consistent with previous studies. [11, 81, 83, 84] The underlying mechanisms for the observed survival disadvantage for men are not well known, but several researchers have proposed a plausible protective role of genes on the X chromosome affecting immune system function, as well as the influence of other biological factors such as sex hormones in cancer progression, aggressiveness and metastasis. [81, 83, 85, 86] Other research has suggested that earlier diagnosis in women due to greater awareness of cancer symptoms and willingness to seek medical help may partly explain their higher survival. [10, 11, 87] Further, higher prevalence of smoking, alcohol drinking, obesity and co-morbid conditions in men have been postulated as other potential contributing factors. [82, 88] For bladder cancer, several studies and recent comprehensive reviews found that women are more likely to be diagnosed later than men due to confusing the signs and symptoms of the disease with urinary tract infections or cystitis, [89-93] which may explain women's worse survival.

### 11.2.2 Differences in cancer survival by area-level socio-economic disadvantage

#### 11.2.2.1 Summary of findings

Analyses of 331,419 Victorians, aged 15-99 years, diagnosed with first primary cancers between 2001 and 2015 (chapter 8, published in *PLOS ONE*) showed that people living in more socio-economically disadvantaged areas had lower five-year survival than their counterparts living in less disadvantaged regions for 21 of 29 cancer types. A consistent pattern of lower survival for cases living in more disadvantaged areas was observed for common cancers including colorectal, melanoma, female breast and prostate cancer, with 40% to 73% higher excess mortality compared with those residing in less disadvantaged areas. For lung cancer, the gap in survival was smaller, with 15% to 18% higher excess risk of death for cases living in more disadvantaged regions. These inequalities have persisted over the last 15 years for most cancers, and for head and neck cancer the gap in survival has increased. For most cancers, socio-economic inequalities in survival were present across all age groups, although the size and pattern differed by cancer type.

#### 11.2.2.2 Comparison with other studies and interpretations

To the best of my knowledge, this study is the only Australian study that used socio-economic status-specific life tables (i.e. SEIFA-specific life tables) based on Statistical Areas Level 2 mortality data to

investigate socio-economic inequalities in cancer survival. Moreover, no other published study has assessed socio-economic inequalities in cancer patient survival by sex or age at diagnosis.

Other Australian research has also found strong evidence of socio-economic inequalities in cancer survival for melanoma and cancers of the breast, liver, stomach, and prostate. [34, 94] Other large population-based studies conducted in developed countries such as the US, [95] Canada, [96] Denmark, [97] New Zealand, [98, 99] England/Wales [100] and Scotland [101] found lower survival for more disadvantaged cancer patients, irrespective of how socio-economic position was defined. Most studies reported an increase in these inequalities over recent decades, partly due to greater improvements in survival for advantaged people. [96, 102] Comprehensive reviews by Kogevinas and Porta (1997) and Woods *et al* (2005) reported late stage at diagnosis as the primary reason for socio-economic inequalities in cancer survival, while the potential role of treatment was unclear. [103, 105] The findings of my systematic review (chapter 3) suggest that stage, other tumour characteristics, co-morbid diseases, health-related lifestyle behaviours and the treatment received are the major contributing factors to these inequalities. The mediating effects of these factors differed for each cancer type and between countries, possibly because most studies applied the traditional difference method of mediation analysis, which has major limitations in the presence of multiple mediators, to quantify the effects of potential mediators (discussed in chapters 3 and 6).

### 11.2.3 Differences in cancer survival by remoteness of residence

#### 11.2.3.1 Summary of findings

Analyses of 331,302 eligible cancer cases diagnosed in 2001-2015 in Victoria (chapter 9, published in cancer causes & control) showed that living outside major cities, relative to major cities, was associated with lower five-year survival for 23 of 30 cancer types studied. The excess risk of death was 20% to 32% higher for people with cancers of the oesophagus, stomach, liver, prostate and connective or soft tissue who were living outside major cities, while for colorectal and lung cancer, the excess mortality rate was 7-8% higher relative to those living in major cities. In contrast, a survival advantage was found for cases residing outside major cities with cancers of the head and neck, unknown primary, melanoma, and Hodgkin lymphoma.

For most cancers, the gaps in survival decreased after adjusting for socio-economic disadvantage and disappeared for colorectal cancer; however, the observed lower survival among residents of outside major cities remained largely unchanged for cancers of oesophagus, stomach, liver, pancreas, lung, connective/soft tissues, ovary and kidney. The relative difference in excess mortality between in and outside major cities decreased over time for oesophageal and pancreatic cancer, whereas it increased for prostate cancer.

#### 11.2.3.2 Comparison with other studies and interpretations

Research conducted in Australia and the USA reported lower survival from colorectal cancer for cases residing in rural than urban regions, regardless of whether adjustment was made for socio-economic position, [105-109] although some studies that have accounted for SEP or income observed no differences. [32, 33, 110] For lung and prostate cancer, Australian studies found lower survival in non-urban areas. [106, 109, 111] The higher prevalence of PSA testing and radical prostatectomy in major cities might explain their observed widening gap in survival from prostate cancer in recent years. [112, 113]

Contrary to previous studies, including Australian research, higher survival from melanoma and female breast cancer was observed for cancer cases residing outside major cities. Previous American studies reported no differences in breast cancer survival comparing rural with urban areas, [114, 115] while most of the other studies conducted in Australia found lower survival from breast cancer in regional and rural areas, regardless of whether adjustment was made for socio-economic position. [106, 109, 116, 117] For melanoma, one Australian study from NSW reported no difference in survival between rural and urban areas, [109] whereas another study conducted in Queensland observed lower survival from melanoma in rural regions. [113] It is unclear why melanoma and cancers of the female breast, unknown primary and head and neck showed a pattern of higher survival for cases residing outside major cities after adjusting for area-based measure of socio-economic disadvantage. These findings require replication by other population-based studies.

Although findings have been inconsistent within and between countries, potentially due to differences in health care systems, my systematic review of 45 studies (chapter 4) found that cases residing in rural and remote areas generally have lower survival from most cancer types, relative to their counterparts residing in urban regions, [118] which is at least partly due to higher prevalence of socio-economic disadvantage in rural regions. [5] Differences in stage at diagnosis, treatment modalities, access to health care services as well as higher prevalence of co-morbidities, obesity and unhealthy behaviours such as smoking, and alcohol drinking are cited as potential contributing factors to these inequalities. [5, 41, 119-123]

### 11.2.4 Factors explaining socio-economic inequalities in colon cancer survival

#### 11.2.4.1 Summary of findings

Victorian residents diagnosed with first primary colon cancer at age 15-79 years between 2008 and 2011 in Victoria were identified from the population-based Victorian Cancer Registry. Inequalities in colon cancer-specific survival between cases residing in the most and least disadvantaged areas were notably greater for men than women. Stage at time of diagnosis did not explain the observed differences in survival (chapter 10). Lower five-year survival from stage III colon cancer for men living in the most disadvantaged areas, relative to their counterparts residing in the least disadvantaged regions, was not explained by surgical treatment. Differences in co-morbidities and intravenous adjuvant chemotherapy explained very little of the observed gap in survival from stage III, although receiving surgery at a

public hospital appeared to partly explain lower survival for men residing in the most disadvantaged areas. Emergency presentation 0-7 days prior to diagnosis was more common in men from the most disadvantaged areas, but it explained very little of the gap in survival. Surgical volume of the hospital and number of nodes taken during surgery (the latter two considered as markers of hospital and surgical quality, respectively) did not contribute to these inequalities. It is unclear why receiving colon cancer surgery at public hospitals partly contributes to lower survival among disadvantaged men, but it might be due to other unmeasured characteristics of disadvantaged men receiving surgery in public hospitals.

#### 11.2.4.2 Comparison with other studies and interpretations

To the best of my knowledge, this study is the first to use interventional causal mediation analysis to identify the reasons for socio-economic inequalities in colon cancer survival. Previous studies applied the more traditional difference method (chapter 6), comparing regression models with and without adjusting for intermediate variables, which could provide biased results in the presence of multiple interrelated mediators. [76, 124] Studies conducted in Australia and Sweden that have assessed colon cancer-specific survival found that disease stage, other tumour characteristics (e.g. tumour differentiation and grade), co-morbidities, treatment, surgical type (elective or emergency) and hospital location (rural or urban) did not explain the observed gap in survival across socio-economic groups. [7, 32, 125] Other studies from New Zealand and England reported stage at diagnosis and treatment as contributing factors. [98, 126] The mediating effects of the above factors might be country-specific due to differences in health care systems. Discrepancies in the findings might also be due to limitations of the data or the applied suboptimal methods.

## 11.3. Strengths and limitations

### 11.3.1 Strengths

Key strengths of these studies were using high-quality population-based data for all Victorian residents diagnosed with invasive cancers during the period of each study as well as complete follow-up through record linkage to the Victorian Registry of Births, Deaths and Marriages and the National Death Index. The large sample size allowed assessment of heterogeneity in the excess mortality rates by age at diagnosis, time since diagnosis, year of diagnosis and sex (where applicable). Further, using Victorian population life tables stratified either by socio-economic disadvantage (i.e. SEIFA) or remoteness of residence (discussed in chapter 6 and chapters 8-9) is an advantage as these life tables provided better estimates of expected background mortality and therefore minimised bias in the estimation of net or relative survival and excess mortality rates.

Another major strength of this thesis was the linkage of colon cancer incidence data in the Victorian Cancer Registry to inpatient hospital data, which enabled the investigation of the potential mediating role of stage, co-morbidities and the treatment received in socio-economic inequalities in colon cancer survival. Further, using the novel method of interventional causal mediation analysis allowed me to

disentangle and quantify the indirect effects through multiple interrelated mediators without assuming an order in which they operate.

### 11.3.2 Limitations

The Victorian Cancer Registry does not collect data on health-related lifestyle behaviours such as smoking status, alcohol intake, diet and physical activity, nor for most cancers on stage at diagnosis except for colorectal, breast and prostate cancer, for which the registry has only collected data since the late 2000s. Therefore, it was not possible to explore the contribution of these factors to the observed inequalities in cancer survival by sex, socio-economic disadvantage and remoteness of residence.

Non-comparability bias is another key limitation of this thesis; this systematic error can occur when the expected risk of mortality used in relative and net survival analyses is not comparable with the cancer group due to the influence of other factors such as race or ethnicity, socio-economic position, rurality, and smoking. [67, 72] For example, people with smoking-related cancers such as lung, head and neck or bladder cancer have higher expected background mortality than the general population due to greater exposure to smoking and having other chronic conditions such as cardiovascular or respiratory diseases. [67, 73] Thus, using general population life tables to estimate relative survival leads to underestimation of the expected background mortality and overestimation of excess risk of death due to cancer. [67, 73] To minimise 'non-comparability' bias, two separate life tables containing the mortality data of Victorian population by socio-economic disadvantage and remoteness of residence were obtained from the Australian Bureau of Statistics. These life tables have some limitations. First, they were not stratified by indigenous status, although less than 1% of the Victorian population identify as indigenous, i.e. Aboriginal or Torres Strait Islander people. [127] Second, the lifetables were not stratified by smoking status; even if such tables were available, the cancer registry does not collect smoking-status data. Third, life tables by remoteness of residence had two categories: major cities and outside major cities (i.e. inner regional, outer regional and remote regions), which precluded assessing trends in cancer survival with increasing inaccessibility to service centres. Further, life tables by remoteness were not stratified by socio-economic disadvantage which could have influenced the estimation of net or relative survival and excess mortality rates as residents of outside major cities are generally more disadvantaged. [5] To address this problem, a sensitivity analysis was conducted by creating new life tables combining Victorian population life tables by remoteness and socio-economic disadvantage (see chapter 9).

Area-based measures of socio-economic position are frequently used in population-based cancer registries as individual-level measures are usually not available, and the Victorian Cancer Registry is not an exception. Using a measure of area-level socio-economic disadvantage (SEIFA) may have led to misclassification and therefore underestimation of the role of socio-economic position in cancer survival, although SEIFA was defined based on small areas with a mean population size of 400 persons or a mean of 225 dwellings. [31, 38] Another potential source of bias was the high correlation between socio-economic disadvantage and remoteness of residence, as these measures are both area-based and

they were defined using the same geographical areas. Under this condition, adjusting for SEIFA when assessing the association between remoteness of residence and cancer survival may not be ideal; therefore, the results were reported with and without including SEIFA in the models. Similarly, a sensitivity analysis was conducted excluding cases living outside major cities to remove potential confounding effects of factors associated with rurality on the association between socio-economic disadvantage and cancer survival.

Unfortunately, co-morbid conditions were greatly underreported and only recorded if they affected management of the patient during a hospital admission. Thus, people were systematically misclassified as not having co-morbidities (chapter 10). Another potential source of bias applying to colon cancer-linked data project (chapter 10) was misclassification of cause of death due to the theoretical issue of deaths as consequences of cancer diagnosis or cancer treatment; therefore, a cancer-specific death could be incorrectly classified as death due to another cause on the death certificate. [67] Competing risk is another major issue for estimating cancer-specific survival (chapter 10), a bias that could have been introduced when cases who died of other causes had different risk of death from cancer than those who did not die of other causes. For example, disadvantaged cancer patients are more likely to die of other causes and of cancer than advantaged cases. [67]

In any observational epidemiological study, confounding is a potential concern. Directed acyclic graphs were used to present causal assumptions, including potential confounding and mediating variables based on the existing literature. All net survival estimates were age-standardised and excess mortality rates were adjusted for time since diagnosis (i.e. follow-up time), age at diagnosis, sex (where applicable), and year of diagnosis to allow comparison between sub-populations. Sex-specific analyses were also conducted as cancer survival is known to be different between men and women. [11, 81-83] Despite controlling for potential confounders, residual confounding may still exist through unknown and known variables such as psychological factors or socio-economic position over the life course.

Other limitations of this thesis were the impact of overdiagnosis and lead-time or length-time bias on survival estimates of screen-detectable cancers. Accordingly, screen-detected cases show better survival than non-screen detected, although their life expectancy might not be changed. Also, the treatment data available through the Victorian Admitted Episode Dataset was crude and we did not have data on oral chemotherapy; therefore, the treatment that stage III colon cancer patients received was defined as binary (i.e. receiving or not receiving intravenous chemotherapy and surgery), which might have underestimated the effect of treatment.

### 11.4. Future research directions

Understanding and minimising inequalities in cancer survival is a global challenge and a priority for many countries. The International Agency for Research on Cancer recently published a report about reducing social inequalities in cancer as a foundation for collaborative research and priorities for future studies. [128] Current evidence regarding lower cancer survival in rural than in urban areas, as well as

worse outcomes in men relative to women, is also concerning. This section highlights potential areas for future research.

There is well-documented evidence that people with lower levels of income and education have less awareness about the adverse effect of unhealthy lifestyle behaviours; accordingly, the prevalence of smoking, heavy alcohol drinking, unhealthy diet and physical inactivity is higher among disadvantaged people. [128, 129] Similar patterns have been observed in rural or remote areas. [41, 119, 121, 123] Moreover, systematic reviews have found that lower heath literacy and awareness was associated with lower levels of engagement in health care and uncertainty in decision-making. [130, 131] Therefore, use of shared decision-making or patient decision aids programs has been found to be highly effective in improving health outcomes. [130, 131] Other research on the psychological factors of socio-economic inequalities in cancer screening participation and attitudes towards cancer noted that individuals from lower socio-economic background have more negative beliefs about cancer screening, early detection and treatment such as worrying and not willing to know if they have cancer, as they believe cancer is a death sentence or cancer treatment is worse than cancer itself. [132, 133] The contribution of health-related behaviours and social psychological determinants to inequalities in cancer survival has not been systematically and explicitly investigated. Therefore, access to population-based cancer registries data linked to other clinical and health-related data needs to be improved and facilitated to enable future studies to conduct a more expansive program of research identifying modifiable factors and quantifying their contributions to these inequalities.

The New South Wales Cancer Registry includes a measure of spread of disease at diagnosis; however, most cancer registries in Australia do not record stage for all cancer sites, which is a major limitation as differences in stage at diagnosis is cited as one of the major reasons for the observed inequalities in cancer survival, potentially due to lower rates of screening uptake and less access to diagnostic services for disadvantaged people. [128] Several studies have reported socio-economic inequalities in cancer screening participation for colorectal, breast and cervical cancer resulting in late diagnosis, [134-136] although stage at diagnosis did not explain socio-economic inequality in colon cancer survival in Victoria, Australia. Delay in seeking help has also been reported due to limited knowledge about early signs and symptoms of cancer, fear and social/cultural or emotional barriers. [137] Providing financial support for population-based cancer registries for recording stage for all cancer types and improving quality of the data is essential in understanding the mediating effect of stage on inequalities in cancer patient survival. Moreover, it is important to acquire more in-depth knowledge about the effects of psychological factors and social support on seeking medical advice and cancer survival, as it can be translated into targeted interventions, educational campaigns, resource allocation and/or cancer control policies.

A review on access to cancer treatment trials across socio-economic groups found that disadvantaged cancer patients were underrepresented due to several barriers such as presence of co-morbidities, travel

distance to and from clinics and financial concerns. [138] Other research found an increasing gap between advantaged and disadvantaged patients regarding access to novel targeted cancer treatments such as immunotherapy. [139] In addition, a review found that cancer cases with co-morbidities are more likely to be diagnosed at an advanced stage depending on the severity of their co-morbid condition and cancer type, and less likely to receive optimal cancer treatment or comply and adhere to prescribed treatment. [140] Evidence in this area is limited due to poor quality of the data, i.e. underreporting of co-morbidities in medical records and population-based health-related datasets.[140] Similarly, systematic reviews on differences in cancer patient survival between rural and urban regions have reported inadequate access to primary health care, diagnostic and treatment services as potential contributing factors to lower cancer survival for people living in rural regions. [142-144] Higher prevalence of co-morbidities and unhealthy lifestyle behaviours have been suggested as other potential explanatory factors to these inequalities. [41, 118-120, 123, 126] More research is needed regarding cancer care pathways and quality of care such as the timeliness of diagnosis and referral to the specialist/oncologist as well as access to screening, diagnostic services, treatment and clinical cancer trials in rural areas and across socio-economic groups. We also have limited knowledge about the biological, social, cultural and psychological mechanisms behind sex differences in cancer survival; understanding the effects of these factors could provide useful information for developing new treatments and improving health promotion, cancer control policies and interventions to reduce inequalities in cancer survival between men and women.

Given that cancer survival is a main indicator of treatment efficacy, health services performance and cancer control plans, it is important to improve utilisation and interpretation of net survival estimates and excess mortality rates by clinicians, policy makers and public health organisations. Increasing their understanding of the strengths and limitations of population-based linked data and the applied methods would assist the funding of research projects and the complex processes of cancer policy decision-making.

**Overall conclusions**

In this thesis, inequalities and trends in cancer survival by sex, area-level socio-economic disadvantage and remoteness of residence were assessed using a new net survival analytical approach, the Pohar-Perme method, as well as established statistical methods such as modelling excess mortality rates. Interventional causal mediation analysis was applied to population-based linked data to identify the potential underlying reasons for socio-economic inequalities in colon cancer-specific survival.

Findings from analysing the Victorian Cancer Registry data suggest that cases living in more socio-economically disadvantaged areas or outside major cities generally have lower five-year survival than their counterparts living in less disadvantaged regions or major cities. In addition, men showed lower survival from most cancers than women. The observed socio-economic inequalities in colon cancer survival were not explained by variations in stage at diagnosis or surgery. Not receiving chemotherapy within 8 weeks after surgery, emergency admission prior to diagnosis and receiving surgery at a public

hospital appeared to partly contribute to lower survival for men with stage III colon cancer living in the most disadvantaged areas, although this observation might be due to unmeasured characteristics of disadvantaged men receiving surgery in public hospitals rather than the public/private hospitals themselves. Not having access to national pharmaceutical prescription data prevented me from comprehensively exploring the mediating effect of oral and intravenous chemotherapy such as the type and dosage cases received, as well as completion of and compliance to prescribed treatment.

The study has shown that inequalities in cancer survival by sex, area-level socio-economic disadvantage and remoteness of residence exist and have persisted over time, even though Australia has a universal health care system. Monitoring the magnitude of inequalities in cancer survival and conducting high-quality research to identify the underlying causes of these disparities is important for prioritising actionable factors to improve cancer outcomes for all patients. Additional financial support for existing cancer registries will enable them to increase data collection and quality and surveillance. Increasing funding for quantitative and qualitative research on differences in health-related risk factors, healthcare utilisation, cancer care pathways and access to diagnostic and treatment services across subpopulations should be a priority for researchers, public health organisations, governments and stakeholders to decrease the gap in cancer survival.

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## Appendices

**Appendix A** descriptions of each variable considered for inclusion in one of the 2016 indexes

*Income variables*

| | |
|---|---|
| INC_LOW | % PEOPLE WITH STATED ANNUAL HOUSEHOLD EQUIVALISED INCOME BETWEEN $1 AND $25,999 (approx. 1st and 2nd deciles)<br>▪ number of people living in classifiable occupied private dwellings with stated annual household equivalised income between $1 and $25,999 [HIED = 02–05]<br>▪ number of people living in classifiable occupied private dwellings with stated household \equivalised income [HIED = 01–15] |
| INC_HIGH | % PEOPLE WITH STATED ANNUAL HOUSEHOLD EQUIVALISED INCOME GREATER THAN $78,000 (approx. 9th and 10th deciles)<br>▪ number of people living in classifiable occupied private dwellings with stated annual household equivalised income greater than $78,000 [HIED = 11–15]<br>▪ number of people living in classifiable occupied private dwellings with stated household equivalised income [HIED = 01–15] |

*Education variables*

| | |
|---|---|
| ATSCHOOL | % PEOPLE AGED 15 YEARS AND OVER WHO ARE STILL ATTENDING SECONDARY SCHOOL<br>▪ number of people aged 15 years and over who are still attending secondary school [AGEP > 14 and TYPP = 31, 32 33]<br>▪ number of people aged 15 years and over (excluding educational institution attendance not stated) [AGEP > 14 and TYPP ne &&, VV] |
| ATUNI | % PEOPLE AGED 15 YEARS AND OVER AT A UNIVERSITY OR OTHER TERTIARY INSTITUTION<br>▪ number of people aged 15 years and over at university or other tertiary institution [AGEP > 14 and TYPP = 50]<br>▪ number of people aged 15 years and over (excluding educational institution attendance not stated) [AGEP > 14 and TYPP ne &&, VV] |
| CERTIFICATE | % PEOPLE AGED 15 YEARS AND OVER WHOSE HIGHEST LEVEL OF EDUCATION IS A CERTIFICATE III or IV QUALIFICATION<br>▪ number of people aged 15 years and over with a certificate III or IV qualification [HEAP = 51]<br>▪ number of people aged 15 years and over (excluding highest level of education not stated) [HEAP ne 001, @@@, VVV, &&&] |
| DEGREE | % PEOPLE AGED 15 YEARS AND OVER WHOSE HIGHEST LEVEL OF EDUCATION IS A BACHELOR DEGREE OR HIGHER<br>▪ number of people aged 15 years and over whose highest level of education is a bachelor degree or higher [HEAP = 1–3]<br>▪ number of people aged 15 years and over (excluding highest level of education not stated) [HEAP ne 001, @@@, VVV, &&&] |
| DIPLOMA | % PEOPLE AGED 15 YEARS AND OVER WHOSE HIGHEST LEVEL OF EDUCATION IS AN ADVANCED DIPLOMA OR DIPLOMA<br>▪ number of people aged 15 years and over whose highest level of education is an advanced diploma or diploma [HEAP = 4]<br>▪ number of people aged 15 years and over (excluding highest level of education not stated) [HEAP ne 001, @@@, VVV, &&&] |
| NOEDU | % PEOPLE AGED 15 YEARS AND OVER WHO HAVE NO EDUCATIONAL ATTAINMENT<br>▪ number of people aged 15 years and over whose highest level of education is no educational attainment [HEAP = 998]<br>▪ number of people aged 15 years and over (excluding highest level of education not stated) [HEAP ne 001, @@@, VVV, &&&] |
| NOYEAR12ORHIGHER | % PEOPLE AGED 15 YEARS AND OVER WHOSE HIGHEST LEVEL OF EDUCATION IS YEAR 11 OR LOWER<br>▪ number of people aged 15 years and over whose highest level of education is year 11 or lower (includes certificate I and II qualifications; excludes those still at secondary school) [HEAP = 613, 621, 720, 721, 811, 812, 998 and TYPP ne 31, 32, 33]<br>▪ number of people aged 15 years and over (excluding highest level of education not stated) [HEAP ne 001, @@@, VVV, &&&] |

*Employment variables*

UNEMPLOYED — % PEOPLE (IN THE LABOUR FORCE) WHO ARE UNEMPLOYED
- number of people aged 15 years and over who are unemployed and looking for work [LFSP = 4–5]
- number of people aged 15 years and over in the labour force [LFSP = 1–5]

UNEMPLOYED1 — % PEOPLE AGED 15 YEARS AND OVER WHO ARE UNEMPLOYED
- number of people aged 15 years and over who are unemployed and looking for work [LFSP = 4–5]
- number of people aged 15 years and over (excluding labour force status not stated) [LFSP = 1–6]

*Occupation variables*

OCC_DRIVERS — % EMPLOYED PEOPLE CLASSIFIED AS MACHINERY OPERATORS AND DRIVERS
- number of employed people classified as Machinery Operators and Drivers [OCCP = 7]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_LABOUR — % EMPLOYED PEOPLE CLASSIFIED AS LABOURERS
- number of employed people classified as Labourers [OCCP = 8]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_MANAGER — % EMPLOYED PEOPLE CLASSIFIED AS MANAGERS
- number of employed people classified as Managers [OCCP = 1]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_PROF — % EMPLOYED PEOPLE CLASSIFIED AS PROFESSIONALS
- number of employed people classified as Professionals [OCCP = 2]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_SALES_L — % EMPLOYED PEOPLE CLASSIFIED AS LOW-SKILL SALES WORKERS
- number of employed people classified as Low-Skill Sales Workers [OCCP = 6 and Skill Level = 5]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_SERVICE_L — % EMPLOYED PEOPLE CLASSIFIED AS LOW-SKILL COMMUNITY AND PERSONAL SERVICE WORKERS
- number of employed people classified as Low-Skill Community and Personal Service Workers [OCCP = 4 and Skill Level = 4–5]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_SKILL1 — % EMPLOYED PEOPLE WHO WORK IN A SKILL LEVEL 1 OCCUPATION
- number of employed people who work in a Skill Level 1 occupation [Skill Level = 1]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_SKILL2 — % EMPLOYED PEOPLE WHO WORK IN A SKILL LEVEL 2 OCCUPATION
- number of employed people who work in a Skill Level 2 occupation [Skill Level = 2]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_SKILL4 — % EMPLOYED PEOPLE WHO WORK IN A SKILL LEVEL 4 OCCUPATION
- number of employed people who work in a Skill Level 4 occupation [Skill Level = 4]
- number of employed people with a stated occupation [OCCP = 1–8]

OCC_SKILL5 — % EMPLOYED PEOPLE WHO WORK IN A SKILL LEVEL 5 OCCUPATION
- number of employed people who work in a Skill Level 5 occupation [Skill Level = 5]
- number of employed people with a stated occupation [OCCP = 1–8]

*Housing variables*

FEWBED — % CLASSIFIABLE OCCUPIED PRIVATE DWELLINGS WITH ONE OR NO BEDROOMS
- number of classifiable occupied private dwellings with one or no bedrooms [BEDD = 00,01 and HHCD = 11–32]
- number of classifiable occupied private dwellings with a stated number of bedrooms [BEDD ne &&, @@ and HHCD = 11–32]

GROUP — % OCCUPIED PRIVATE DWELLINGS THAT ARE GROUP OCCUPIED PRIVATE DWELLINGS
- number of classifiable occupied private dwellings that are occupied by group households [HHCD = 32 and HHCD = 11–32]
- number of classifiable occupied private dwellings [HHCD = 11–32]

HIGHBED — % OCCUPIED PRIVATE DWELLINGS WITH FOUR OR MORE BEDROOMS
- number of classifiable occupied private dwellings with four or more bedrooms [BEDD = 04–30 and HHCD = 11–32]
- number of classifiable occupied private dwellings with a stated number of bedrooms [BEDD ne &&, @@ and HHCD = 11–32]

HIGHMORTGAGE — % OCCUPIED PRIVATE DWELLINGS PAYING MORE THAN $2,800 PER MONTH IN MORTGAGE REPAYMENTS

- number of mortgaged classifiable occupied private dwellings with monthly mortgage repayments greater than $2,800 [MRED = 2801–9999, HHCD = 11–32 and TEND = 1-7]
- number of classifiable occupied private dwellings (excluding those with tenure not stated, mortgage not stated and rent not stated) [TEND ne &, @, MRED ne &&&&, RNTD ne &&&& and HHCD = 11–32]

HIGHRENT — % OCCUPIED PRIVATE DWELLINGS PAYING MORE THAN $470 PER WEEK IN RENT

- number of rented classifiable occupied private dwellings with rent payments greater than $470 per week [RNTD = 471–9999, HHCD = 11–32 and TEND = 1-7]
- number of classifiable occupied private dwellings (excluding those with tenure not stated, mortgage not stated and rent not stated) [TEND ne &, @, MRED ne &&&&, RNTD ne &&&& and HHCD = 11–32]

LOWRENT — % OCCUPIED PRIVATE DWELLINGS PAYING LESS THAN $215 PER WEEK IN RENT (EXCLUDING $0 PER WEEK)

- number of rented classifiable occupied private dwellings with rent payments less than $215 per week (excluding rent-free and renting from employer) [RNTD = 1–214 and HHCD = 11–32 and LLDD ne 51, 52]
- number of classifiable occupied private dwellings (excluding those with tenure not stated, mortgage not stated and rent not stated) [TEND ne &, @, MRED ne &&&&, RNTD ne &&&& and HHCD = 11–32]

OVERCROWD — % OCCUPIED PRIVATE DWELLINGS REQUIRING ONE OR MORE EXTRA BEDROOMS (BASED ON CANADIAN NATIONAL OCCUPANCY STANDARD)

- number of classifiable occupied private dwellings needing one or more extra bedrooms (based on Canadian National Occupancy Standard) [HOSD = 01-04 and HHCD = 11–32]
- number of classifiable occupied private dwellings (excluding dwellings where housing utilisation cannot be determined or is not stated) [HOSD ne 10, &&, @@ and HHCD = 11–32]

OWNING — % OCCUPIED PRIVATE DWELLINGS OWNING THE DWELLING THEY OCCUPY (WITHOUT A MORTGAGE)

- number of households owning the dwelling they occupy without a mortgage [TEND = 1 and HHCD = 11–32]
- number of classifiable occupied private dwellings (excluding tenure not stated) [TEND ne &, @ and HHCD = 11–32]

MORTGAGE — % OCCUPIED PRIVATE DWELLINGS OWNING THE DWELLING THEY OCCUPY (WITH A MORTGAGE)

- number of mortgaged classifiable occupied private dwellings [TEND = 2, 3, 6 and HHCD = 11–32]
- number of classifiable occupied private dwellings (excluding tenure not stated) [TEND ne &, @ and HHCD = 11–32]

SPAREBED — % OCCUPIED PRIVATE DWELLINGS WITH ONE OR MORE SPARE BEDROOMS (BASED ON CANADIAN NATIONAL OCCUPANCY STANDARD)

- number of classifiable occupied private dwellings with one or more spare bedrooms (based on Canadian National Occupancy Standard) [HOSD= 06-09 and HHCD = 11–32]
- number of classifiable occupied private dwellings (excluding dwellings where housing utilisation cannot be determined or is not stated) [HOSD ne 10, &&, @@ and HHCD = 11–32]

LONE — % OCCUPIED PRIVATE DWELLINGS THAT ARE LONE PERSON OCCUPIED PRIVATE DWELLINGS

- number of classifiable occupied private dwellings that are occupied by lone person households [HHCD = 31]
- number of classifiable occupied private dwellings [HHCD = 11–32]

*Other indicators of advantage or disadvantage*

*Cars*

HIGHCAR — % OCCUPIED PRIVATE DWELLINGS WITH THREE OR MORE CARS

- number of classifiable occupied private dwellings which had 3 or more registered motor vehicles at or near the dwelling [VEHD = 03–30 and HHCD = 11–32]
- number of classifiable occupied private dwellings (excluding number of vehicles not stated) [VEHD ne &&, @@ and HHCD = 11–32]

NOCAR — % OCCUPIED PRIVATE DWELLINGS WITH NO CARS

- number of classifiable occupied private dwellings which did not have a registered motor vehicle at or near the dwelling [VEHD = 00 and HHCD = 11–32]
- number of classifiable occupied private dwellings (excluding number of vehicles not stated) [VEHD ne &&, @@ and HHCD = 11–32]

*Internet*

**NONET** — % OCCUPIED PRIVATE DWELLINGS WITH NO INTERNET CONNECTION
- number of classifiable occupied private dwellings with no internet connection [NEDD = 2 and HHCD = 11–32]
- number of classifiable occupied private dwellings (excluding internet connection not stated) [NEDD ne &, @ and HHCD = 11–32]

*Other*

**CHILDJOBLESS** — % FAMILIES WITH CHILDREN UNDER 15 YEARS OF AGE AND JOBLESS PARENTS
- number of families with children aged under 15 and jobless parents [FMCF = 21, 31 and LFSF = 16, 17, 19, 25, 26]
- number of families (excluding not applicable and not stated) [FMCF ne @@@@ and LFSF ne 06, 11, 15, 18, 20, 21, 27, @@]

**DISABILITYU70** — % PEOPLE AGED UNDER 70 WHO NEED ASSISTANCE WITH CORE ACTIVITIES
- number of people aged under 70 years needing assistance in one or more of the three core activity areas of self-care, mobility and communication, because of a disability, long term health condition (lasting six months or more) or old age [AGEP < 70 and ASSNP = 1]
- number of people aged under 70 years (excluding need for assistance not stated) [AGEP < 70 and ASSNP = 1–2]

**ENGLISHPOOR** — % PEOPLE WHO DO NOT SPEAK ENGLISH WELL
- number of people aged 5 years and over who speak English either not well or not at all [AGEP > 4 and ENGLP = 4, 5]
- number of people aged 5 years and over (excluding those who did not state their English proficiency or main language) [AGEP > 4 and ENGLP = 1–5]

**ONEPARENT** — % FAMILIES THAT ARE ONE PARENT FAMILIES WITH DEPENDENT OFFSPRING ONLY
- number of families that are one parent families with dependent offspring only [FMCF = 3112, 3122, 3212]
- number of families [FMCF ne @@@@]

**SEPDIVORCED** — % PEOPLE AGED 15 AND OVER WHO ARE SEPARATED OR DIVORCED
- number of people aged 15 years and over who are separated or divorced [MSTP = 3, 4]
- number of people aged 15 years and over [MSTP = 1–5]

**UNINCORP** — % OCCUPIED PRIVATE DWELLINGS WITH AT LEAST ONE PERSON WHO IS THE OWNER OF AN UNINCORPORATED ENTERPRISE
- number of classifiable occupied private dwellings where at least one usual resident is the owner of an unincorporated enterprise [SIEMP = 5, 6, UAICP = 1 and HHCD = 11– 32]
- number of classifiable occupied private dwellings [HHCD = 11–32]

**Appendix B** Supplementary material related to publication presented in Chapter 3

**Supplementary Table 3.1.** Search strategy to identify papers indexed in Ovid MEDLINE, EMBASE and CINAHL

**Ovid MEDLINE**

| Search # | Search terms |
|---|---|
| 1 | exp Neoplasms/ |
| 2 | (cancer* or neoplasm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 3 | 1 or 2 |
| 4 | cancer survival.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 5 | (relative survival or excess mortality).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 6 | exp survival analysis/ |
| 7 | 3 and 5 |
| 8 | 3 and 6 |
| 9 | ((cancer* or tumor* or tumour*) adj3 (survival or surviving or prognosis)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 10 | 4 or 7 or 8 or 9 |
| 11 | ((socioeconomic or socio economic or social or economic or income or education* or occupation) adj5 (inequalit* or inequit* or disparit* or disadvantag* or factor* or class or difference* or status or position* or variation* or depriv* or effect* or determinant* or characteristic* or level*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 12 | 10 and 11 |
| 13 | Limit 12 to English language |

**EMBASE**

| Search # | Search terms |
|---|---|
| 1 | exp Neoplasms/ |
| 2 | (cancer* or neoplasm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 3 | 1 or 2 |
| 4 | exp cancer survival/ |
| 5 | (relative survival or excess mortality).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 6 | 3 and 4 |
| 7 | 3 and 5 |
| 8 | ((cancer* or tumor* or tumour*) adj3 (survival or surviving or prognosis)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 9 | 6 or 7 or 8 |

| | |
|---|---|
| 10 | ((socioeconomic or socio economic or social or economic or income or education* or occupation) adj5 (inequalit* or inequit* or disparit* or disadvantag* or factor* or class or difference* or status or position* or variation* or depriv* or effect* or determinant* or characteristic* or level*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 11 | 9 and 10 |
| 12 | Limit 11 to English language |

**CINAHL**

| Search # | Search terms |
|---|---|
| S1 | MH "Neoplasms+" |
| S2 | cancer* or neoplasm* |
| S3 | S1 or S2 |
| S4 | cancer survival |
| S5 | relative survival or excess mortality |
| S6 | MH "Survival Analysis+" |
| S7 | S3 and S5 |
| S8 | S3 and S6 |
| S9 | (cancer* or tutor* or tumour*) N3 (survival or surviving or prognosis) |
| S10 | S4 or S7 or S8 or S9 |
| S11 | (socioeconomic or socio economic or social or economic or income or education* or occupation) N5 (inequalit* or disparit* or disadvantag* or factor* or class or difference* or status or position* or variation* or depriv* or effect* or determinant* or characteristic* or level*) |
| S12 | S10 and S11 |
| S13 | Limit S12 to English language |

Proximity operators: **Adjn** (Adjacent to – in any order), **Nn** (Near – in any order)

**Supplementary Table 3.2.** Risk of bias of included studies using Risk of Bias In Non-Randomised Studies - of Exposures (ROBINS-E)

| Review | Risk of bias due to confounding | Risk of bias in selection of participants into the study | Risk of bias in classification of exposure(s) | Risk of bias due to inappropriate adjustment (e.g. adjusting for potential mediators) | Risk of bias due to missing data | Risk of bias in measurement of outcomes | Risk of bias in selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|---|---|
| **1.** Aarts et al, 2013 | Low | Low | Low | High | Low | Low | Low | Critical |
| **2.** Aarts et al, 2013 | Low | Low | Low | High | Mod | No information | Low | Critical |
| **3.** Aarts et al, 2011 | Low | Low | Low | High | Low | Low | Low | Critical |
| **4.** Bastiaannet et al, 2011 | Moderate | Low | Low | High | Low | Low | Low | Critical |
| **5.** Beckmann et al, 2016 | Low | Low | Low | High | Low | Low | Low | Critical |
| **6.** Berglund et al, 2010 | Low | Low | Low | High | Low | Low | Low | Critical |
| **7.** Berglund et al, 2012 | Low | Low | Low | High | Low | Low | Low | Critical |
| **8.** Bharathan et al, 2011 | Moderate | Low | Low | High | Low | Low | Low | Critical |
| **9.** Booth et al, 2010 | Moderate | Low | Low | High | Moderate | Low | Low | Critical |
| **10.** Bouchardy et al, 2006 | Low | Low | No information | High | Moderate | Low | Low | Critical |
| **11.** Braaten et al, 2009 | Low | Low | Low | High | Low | Low | Low | Critical |
| **12.** Brookfield et al, 2009 | Low | Low | Low | High | Low | No information | Low | Critical |
| **13.** Byers et al, 2008 | Low | Low | Low | High | Low | Low | Low | Critical |
| **14.** Cavalli-Björkman et al, 2011 | Moderate | Low | Low | High | Low | Low | Low | Critical |
| **15.** Chu et al, 2016 | Low | Low | Low | High | Low | Low | Low | Critical |
| **16.** Dalton et al, 2015 | Low | Low | Low | High | Low | Low | Low | Critical |
| **17.** Danzing et al, 2014 | Low | Low | Low | High | Low | Low | Low | Critical |
| **18.** Downing et al, 2007 | Low | Low | Low | High | Low | Low | Low | Critical |
| **19.** Eaker et al, 2009 | Moderate | Low | Low | High | Low | Low | Low | Critical |
| **20.** Eriksson et al, 2013 | Low | Low | Low | High | Low | Low | Low | Critical |
| **21.** Feinglass et al, 2015 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **22.** Forrest et al, 2015 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **23.** Frederiksen et al, 2012 | Low | Low | Low | High | Low | Low | Low | Critical |
| **24.** Frederiksen et al, 2009 | Low | Low | Low | High | Low | Low | Low | Critical |

| Review | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of exposure(s) | Bias due to inappropriate adjustment (adjusting for potential mediators) | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|---|---|
| **25.** Groome et al, 2006 | Low | Low | Low | High | Low | Low | Low | Critical |
| **26.** Guo et al, 2015 | Low | Low | Low | Low | Moderate | Low | Low | Moderate |
| **27.** Hines et al, 2014 | Low | Low | Low | High | Low | Low | Low | Critical |
| **28.** Ibfelt et al, 2015 | Low | Low | Low | High | Low | Low | Low | Critical |
| **29.** Ibfelt et al, 2013 | Low | Low | Low | High | Low | Low | Low | Critical |
| **30.** Jack et al, 2006 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **31.** Jeffreys et al, 2009 | Low | Low | Low | High | Low | Low | Low | Critical |
| **32.** Jembere et al, 2012 | Low | Low | Low | High | High | Low | Low | Critical |
| **33.** Johnson et al, 2014 | Low | Low | Low | High | Low | Low | Low | Critical |
| **34.** Kim et al, 2011 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **35.** Larsen et al, 2015 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **36.** Launay et al, 2012 | Moderate | Low | Low | High | Moderate | Low | Low | Critical |
| **37.** Lejeune et al, 2010 | Low | Low | Low | High | Low | Low | Low | Critical |
| **38.** Li et al, 2016 | Low | Low | Low | Low | Low | Low | Low | Low |
| **39.** Mckenzie et al, 2010 | Low | Low | Low | High | Low | Low | Low | Critical |
| **40.** O'Brien et al, 2015 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **41.** Quaglia et al, 2001 | Moderate | Low | Low | High | Moderate | Low | Low | Critical |
| **42.** Robertson et al, 2010 | Low | High | Low | High | Low | Low | Low | Critical |
| **43.** Rutherford et al, 2013 | Low | Low | Low | High | Low | Low | Low | Critical |
| **44.** Seidelin et al, 2016 | Low | Low | Low | High | High | Low | Low | Critical |
| **45.** Shafiqueet et al, 2013 | Low | Low | Low | Moderate | Moderate | Low | Low | Moderate |
| **46.** Sprague et al, 2011 | Low | Low | Low | High | Low | Low | Low | Critical |
| **47.** Stromberg et al, 2016 | Low | Low | Low | High | Low | Low | Low | Critical |
| **48.** Ueda et al, 2006 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **49.** Walsh et al, 2014 | Low | Low | Low | High | Low | Low | Low | Critical |
| **50.** Woods et al, 2006 | Moderate | Low | Low | Moderate | Low | Low | Low | Moderate |
| **51.** Yu et al, 2009 | Low | Low | Low | High | Low | Low | Low | Critical |
| **52.** Yu et al, 2008 | Low | Low | Low | High | Low | Low | Low | Critical |

**Appendix C** Supplementary material related to publication presented in Chapter 3

**Supplementary Table 4.1.** Search strategy to identify papers indexed in Ovid MEDLINE, EMBASE and CINAHL

**Ovid MEDLINE**

| Search # | Search terms |
|---|---|
| 1 | exp Neoplasms/ |
| 2 | (cancer* or neoplasm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 3 | 1 or 2 |
| 4 | cancer survival.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 5 | (relative survival or excess mortality).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 6 | exp survival analysis/ |
| 7 | 3 and 5 |
| 8 | 3 and 6 |
| 9 | ((cancer* or tumor* or tumour*) adj3 (survival or surviving or prognosis)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 10 | 4 or 7 or 8 or 9 |
| 11 | ((rural* or suburban or urban or metropolitan or remote* or location* or region* or area or geographic* or spatial or place or distance or district) adj2 (inequalit* or inequit* or disparit* or variation* or environment or residence or difference* or factor* or disadvantag*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 12 | 10 and 11 |
| 13 | Limit 12 to English language |

**EMBASE**

| Search # | Search terms |
|---|---|
| 1 | exp Neoplasms/ |
| 2 | (cancer* or neoplasm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 3 | 1 or 2 |
| 4 | exp cancer survival/ |
| 5 | (relative survival or excess mortality).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 6 | 3 and 4 |
| 7 | 3 and 5 |
| 8 | ((cancer* or tumor* or tumour*) adj3 (survival or surviving or prognosis)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 9 | 6 or 7 or 8 |

| | |
|---|---|
| 10 | ((rural* or suburban or urban or metropolitan or remote* or location* or region* or area or geographic* or spatial or place or distance or district) adj2 (inequalit* or inequit* or disparit* or variation* or environment or residence or difference* or factor* or disadvantag*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] |
| 11 | 9 and 10 |
| 12 | Limit 11 to English language |

**CINAHL**

| Search # | Search terms |
|---|---|
| S1 | MH "Neoplasms+" |
| S2 | cancer* or neoplasm* |
| S3 | S1 or S2 |
| S4 | cancer survival |
| S5 | relative survival or excess mortality |
| S6 | MH "Survival Analysis+" |
| S7 | S3 and S5 |
| S8 | S3 and S6 |
| S9 | (cancer* or tumor or* or tumour*) N3 (survival or surviving or prognosis) |
| S10 | S4 or S7 or S8 or S9 |
| S11 | (rural* or suburban or urban or metropolitan or remote* or location* or region* or area or geographic* or spatial or place or distance or district) N2 (inequalit* or inequit* or disparit* or variation* or environment or residence or difference* or factor* or disadvantag*) |
| S12 | S10 and S11 |
| S13 | Limit S12 to English language |

Proximity operators: **Adjn** (Adjacent to – in any order), **Nn** (Near – in any order)

**Supplementary Table 4.2.** Characteristics of observational studies on rural and urban residence and cancer survival in high-income countries, 1984-2016

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Anuradha et al, 2014 | Australia | The Australian state- and territory-based cancer registries<br><br>**Sample size**<br>**1,192** | Australia | 2005 | ≥18 | Ovary (including fallopian tube and peritoneum) | Accessibility/Remoteness Index of Australia (ARIA+) which is based on road distance measurements from population localities to the nearest service centres | 2 | Kaplan-Meier method, Cox proportional hazard regression | **Overall survival**<br>**Major cities (Ref.)**<br>**Regional-remote areas**<br>**Unadjusted**<br>HR=1.20 (1.00 to 1.30)<br>**Age-adjusted**<br>HR=1.20 (1.00 to 1.40)<br>**Fully adjusted**<br>HR=1.20 (1.00 to 1.40) | Age at diagnosis, co-morbidity score, stage, grade, subtype and presence of ascites |
| Baade et al, 2013 | Australia | Queensland Cancer Registry<br><br>**Sample size**<br>**22,727** | Queensland | 1997-2007 | 20-84 | Colorectum | Area-Remoteness Index of Australia (ARIA) which is based on the minimum road distance from population localities to service centres | 4 | Kaplan-Meier method, 5-year overall and cause-specific survival using discrete-time multilevel logistic regression and Markov chain Monte Carlo simulations | **Overall survival**<br>**Major city (Ref.)**<br>**Inner regional**<br>OR=0.95 (0.88 to 1.02)<br>**Outer regional**<br>OR=1.09 (1.01 to 1.18)<br>**Remote**<br>OR=1.15 (1.02 to 1.28)<br>**Cancer-specific survival**<br>**Major city (Ref.)**<br>**Inner regional**<br>OR=0.98 (0.90 to 1.06)<br>**Outer regional**<br>OR=1.15 (1.05 to 1.25)<br>**Remote**<br>OR=1.24 (1.07 to 1.42) | Age, sex, marital status, occupation, country of birth, indigenous status, area-level socio-economic disadvantage, time since diagnosis, colorectal cancer site, stage at diagnosis, tumour differentiation, surgical margins |
| Baade et al, 2011 | Australia | Australian Bureau of Statistics, Australian Cancer Database and Medicare Benefits Division | Australia | 1982-2004 | 50-79 | Prostate | the Australian Standard Geographic Classification (ASGC) - Remoteness Areas was based on subjects' usual address, categorised according to Statistical Divisions into | 2 | Relative survival (cohort method), Cox proportional hazard regression | **Overall survival**<br>**Capital cities (Ref.)**<br>**Regional-rural areas**<br>**1982-1989**<br>HR=1.01 (0.97 to 1.05) | NA |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Sample size**<br>**NA** | | | | | "capital cities" versus the rest of Australia ("regional and rural areas") | | | **1990-1999**<br>HR=1.14 (1.11 to 1.17)<br>**2000-2004**<br>HR=1.24 (1.17 to 1.31) | |
| Beckmann et al, 2016 | Australia | South Australia Central Cancer Registry linked to public/private hospitals, public/private radiotherapy services and hospital-based cancer registries<br>**Sample size**<br>**4,641** | South Australia | 2003-2008 | 50-79 | Colon and rectum | Accessibility/Remoteness Index of Australia (ARIA) | 4 | Kaplan-Meier method, Competing risk regression analysis (Fine and Gray method) | **Cancer-specific survival**<br>**Inner urban (Ref.)**<br>**Outer urban**<br>HR=0.95 (0.79 to 1.16)<br>**Rural**<br>HR=0.98 (0.82 to 1.17)<br>**Remote/very remote**<br>HR=1.12 (0.90 to 1.39)<br>**Stage A-C**<br>**Inner urban (Ref.)**<br>**Outer urban**<br>HR=0.96 (0.74 to 1.23)<br>**Rural**<br>HR=0.94 (0.75 to 1.17)<br>**Remote/very remote**<br>HR=1.35 (1.01 to 1.80)<br>**Stage D**<br>**Inner urban (Ref.)**<br>**Outer urban**<br>HR=1.00 (0.74 to 1.34)<br>**Rural**<br>HR=1.05 (0.79 to 1.41)<br>**Remote/very remote**<br>HR=0.91 (0.67 to 1.23) | Age, sex, cancer site, stage, grade, area-level socio-economic status, insurance status, co-morbidity, surgery, radiotherapy, chemotherapy, year of diagnosis |
| Bennett et al, 2007 | New Zealand | New Zealand Cancer Registry (NZCR) | New Zealand | 1998-2002 | All ages | Breast | Urban-rural residence were classified in 3 different ways based on 1) population size, 2) | 4<br>6 | Cox proportional hazards regression | **Overall survival** | Age, ethnicity, area-level |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Sample size**<br>**11,340** | | | | | comparison between a person's residential address and their workplace address, 3) distance from major cancer centre | 5 | | Urban-Rural Population Category<br>**Main urban (ref.)**<br>**Secondary urban**<br>HR=0.91 (0.80 to 1.04)<br>**Minor urban**<br>HR=1.01 (0.88 to 1.14)<br>**Rural**<br>HR=1.02 (0.90 to 1.16)<br>Urban-Rural Profile Category<br>**Main urban area (ref.)**<br>**Satellite urban**<br>HR=1.04 (0.85 to 1.28)<br>**Independent urban**<br>HR=0.99 (0.89 to 1.11)<br>**Rural with high urban influence**<br>HR=0.88 (0.65 to1.21)<br>**Rural with moderate urban influence**<br>HR=1.05 (0.82 to 1.36)<br>**Rural with low urban influence/remote**<br>HR=1.07 (0.92 to 1.25)<br>Distance from cancer centre(km)<br>**0–10 km (ref.)**<br>**11–25 km**<br>HR=0.94 (0.85 to 1.05)<br>**26–50 km**<br>HR=0.99 (0.87 to 1.12)<br>**51–100 km**<br>HR=0.86 (0.76 to 0.96)<br>**>100 km** | deprivation, stage |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | HR=1.06 (0.95 to 1.17) | |
| Bonett et al, 1984 | Australia | South Australia Cancer Registry<br><br>**Sample size**<br>**NA** | South Australia | 1977-1982 | All ages | Lung, colon, breast and cervix | Metropolitan Adelaide vs country area | 2 | Relative survival, Cox proportional hazard regression | **Overall survival**<br>**Metropolitan Adelaide (Ref.)**<br>**Country area**<br>Lung cancer<br>No difference in survival (hazard ratio not reported)<br>Colon cancer<br>HR=1.14 (0.99 to 1.32)<br>Breast cancer<br>No difference in survival (hazard ratio not reported)<br>Cervical cancer<br>HR=1.53 (1.05 to 2.23) | Age and area-level socio-economic status (colon)<br><br>Age and birthplace (cervix) |
| Brewer et al, 2009 | New Zealand | New Zealand Cancer Registry (NZCR)<br><br>**Sample size**<br>**2,260** | New Zealand | 1994-2005 | 17-93 | Cervix | Urban-rural residence was defined according to population size, based on the Statistics New Zealand classification | 3 | Cox proportional hazards regression | **Cancer-specific survival**<br>Adjusted for age and year of diagnosis<br>**Main urban (Ref.)**<br>**Secondary urban**<br>HR=1.24 (0.95 to 1.62)<br>**Rural**<br>HR=1.03 (0.70 to 1.50)<br>Adjusted for age, year of diagnosis and stage<br>**Main urban (Ref.)**<br>**Secondary urban**<br>HR=1.21 (0.93 to 1.59)<br>**Rural**<br>HR=1.19 (0.81 to 1.74)<br>Adjusted for age, year of diagnosis, stage, deprivation and ethnicity<br>**Main urban (Ref.)** | Age, year of diagnosis, ethnicity, area-level deprivation, stage at diagnosis |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Secondary urban**<br>HR=1.14 (0.87 to 1.50)<br>**Rural**<br>HR=1.11 (0.75 to 1.64)<br>Early stage<br>**Main urban (Ref.)**<br>**Secondary urban**<br>HR=1.51 (0.91 to 2.48)<br>**Rural**<br>HR=0.85 (0.39 to 1.87)<br>Late stage<br>**Main urban (Ref.)**<br>**Secondary urban**<br>HR=1.02 (0.73 to 1.42)<br>**Rural**<br>HR=1.26 (0.79 to 1.98) | |
| Chen et al, 2015 | Australia | New South Wales Central Cancer Registry (NSWCCR)<br><br>**Sample size**<br>**107,060** | New South Wales | 2000-2008 | All ages | Breast, colon, rectum, lung, ovary | Accessibility/Remoteness Index of Australia (ARIA+) | 4 | Kaplan-Meier method, Cox proportional hazards regression | **Cancer-specific survival**<br>**Large metro (Ref.)**<br>Breast cancer-localised<br>**Inner regional**<br>HR=1.08 (0.89 to 1.30)<br>**Outer regional**<br>HR=0.81 (0.57 to 1.14)<br>**Remote/very remote**<br>HR=1.34 (0.50 to 3.57)<br>Breast cancer-regionalised<br>**Inner regional**<br>HR=1.10 (0.98 to 1.25)<br>**Outer regional**<br>HR=1.22 (1.00 to 1.48)<br>**Remote/very remote**<br>HR=1.06 (0.47 to 2.36) | Sex, age at diagnosis<br>Stratified by the extent of disease (localised, regionalised, metastatic, unknown) |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Breast cancer-metastatic<br>**Inner regional**<br>HR=1.01 (0.87 to 1.18)<br>**Outer regional**<br>HR=1.30 (1.02 to 1.64)<br>**Remote/very remote**<br>HR=1.77 (0.97 to 3.20)<br>Colon cancer-localised<br>**Inner regional**<br>HR=1.06 (0.89 to 1.28)<br>**Outer regional**<br>HR=0.81 (0.57 to 1.14)<br>**Remote/very remote**<br>HR=1.34 (0.50 to 3.57)<br>Colon cancer-regionalised<br>**Inner regional**<br>HR=1.09 (0.99 to 1.19)<br>**Outer regional**<br>HR=1.03 (0.89 to 1.18)<br>**Remote/very remote**<br>HR=0.68 (0.35 to 1.30)<br>Colon cancer-metastatic<br>**Inner regional**<br>HR=1.08 (1.00 to 1.17)<br>**Outer regional**<br>HR=1.14 (1.01 to 1.29)<br>**Remote/very remote**<br>HR=1.23 (0.79 to 1.91)<br>Rectal cancer-localised<br>**Inner regional**<br>HR=0.93 (0.76 to 1.12)<br>**Outer regional**<br>HR=1.37 (1.05 to 1.78)<br>**Remote/very remote**<br>HR=0.34 (0.05 to 2.41) | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Rectal cancer-regionalised<br>**Inner regional**<br>HR=1.14 (1.00 to 1.30)<br>**Outer regional**<br>HR=1.04 (0.84 to 1.28)<br>**Remote/very remote**<br>HR=1.06 (0.44 to 2.54)<br>Rectal cancer-metastatic<br>**Inner regional**<br>HR=1.08 (0.96 to 1.22)<br>**Outer regional**<br>HR=1.02 (0.84 to 1.24)<br>**Remote/very remote**<br>HR=1.91 (0.95 to 3.84)<br>Lung cancer-localised<br>**Inner regional**<br>HR=1.07 (0.99 to 1.17)<br>**Outer regional**<br>HR=1.28 (1.13 to 1.46)<br>**Remote/very remote**<br>HR=0.80 (0.52 to 1.23)<br>Lung cancer-regionalised<br>**Inner regional**<br>HR=0.93 (0.85 to 1.02)<br>**Outer regional**<br>HR=1.07 (0.94 to 1.22)<br>**Remote/very remote**<br>HR=0.94 (0.61 to 1.44)<br>Lung cancer-metastatic<br>**Inner regional**<br>HR=1.08 (1.02 to 1.13)<br>**Outer regional**<br>HR=1.02 (0.95 to 1.11)<br>**Remote/very remote** | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | HR=0.89 (0.68 to 1.17)<br>Ovarian cancer-localised<br>**Inner regional**<br>HR=1.22 (0.75 to 2.01)<br>**Outer regional**<br>HR=2.10 (1.00 to 4.44)<br>**Remote/very remote**<br>—<br>Ovarian cancer-regionalised<br>**Inner regional**<br>HR=0.95 (0.70 to 1.29)<br>**Outer regional**<br>HR=0.96 (0.53 to 1.74)<br>**Remote/very remote**<br>HR=0.39 (0.06 to 2.82)<br>Ovarian cancer-metastatic<br>**Inner regional**<br>HR=1.12 (0.98 to 1.29)<br>**Outer regional**<br>HR=1.32 (1.06 to 1.65)<br>**Remote/very remote**<br>HR=0.86 (0.41 to 1.81) | |
| Chow et al, 2015 | United States | California Cancer Registry<br>**Sample size**<br>**123,129** | California | 1996-2008 | 18-94 | Colon | Place of residence was established based on the designation assigned to the patient's Medical Service Study Area (MSSA) by the California Office of State-wide Health Planning and Development (OSHPD) | 2 | Cox proportional hazards regression | **Cancer-specific survival**<br>**Urban (Ref.)**<br>**Rural/Frontier**<br>HR=1.04 (1.01 to 1.07) | Stage, surgery, grade, age, lymphadenectomy, sex, race, marital status, insurance status, and year of diagnosis |
| Coory et al, 2006 | Australia | Queensland Cancer Registry (QCR)<br>**Sample size** | Queensland | 1996-2001 | All ages | Melanoma | Rurality was defined based on Local Government Areas (LGA) | 3 | Cox proportional hazards regression | **Cancer-specific survival**<br>**Crude hazard ratios**<br>**Urban (Ref.)**<br>**Regional** | Age, sex, thickness, level of invasion, subsite |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **12,827** | | | | | | | | HR=1.04 (0.86 to 1.26)<br>**Rural**<br>HR=1.28 (1.07 to 1.52)<br>**Adjusted hazard ratios**<br>**Urban (Ref.)**<br>**Regional**<br>HR=1.05 (0.86 to 1.27)<br>**Rural**<br>HR=1.20 (1.02 to 1.43) | |
| Crowell et al, 2007 | United States | Surveillance, Epidemiology, and End Results (SEER) registries<br>**New Mexico Sample size: 872**<br>**SEER Sample size: 20,278** | New Mexico | 1988-1997 | All ages | Non-small cell lung | Rural-Urban residence based on patient's county of residence at time of diagnosis, applying 1993 USDA Rural-Urban Continuum codes (RUCC) | 2 | Kaplan-Meier method, Cox proportional hazards regression | **Overall survival**<br>**Urban (Ref.)**<br>**Rural**<br>HR=1.12 (0.95 to 1.31)<br>Stage IB<br>**Urban (Ref.)**<br>**Rural**<br>HR=1.27 (1.03 to 1.51)<br>HR=1.26 (1.01 to 1.56) | Age at diagnosis, sex, stage at diagnosis<br>Additional adjustment for surgery |
| Dasgupta et al, 2012 | Australia | Queensland Cancer Registry (QCR)<br>**Sample size 18,568** | Queensland | 1997-2006 | 30-79 | Breast | Accessibility/Remoteness Index of Australia (ARIA+) | 4 | Discrete-time multilevel logistic regression and Markov chain Monte Carlo simulation | **Cancer-specific survival**<br>**Major city (Ref.)**<br>**Inner regional**<br>OR=1.07 (0.93 to 1.24)<br>**Outer regional**<br>OR=1.15 (1.01 to 1.35)<br>**Remote/very remote**<br>OR=1.26 (0.95 to 1.69)<br>**Major city (Ref.)**<br>**Inner regional**<br>OR=1.01 (0.90 to 1.12)<br>**Outer regional** | Age, indigenous status, occupation, time (years after diagnosis), marital status, cancer stage<br>Additional adjustment for area-level socio-economic status |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | OR=1.11 (0.96 to 1.25)<br>**Remote/very remote/**<br>OR=1.18 (0.99 to 1.53) | |
| Eggleston et al, 2006 | United States | Texas Cancer Registry<br><br>**Sample size**<br>**7,237** | Texas | 1995-2001 | ≥18 | Cervix | Rural residence was defined using Zip code-level from the US census 2000 and categorised based on distribution of the Texas population | 5 | Kaplan-Meier method, Cox proportional hazards regression | **Cancer-specific survival**<br>**Urban (Ref.)**<br>**Mid-Urban**<br>HR=0.90 (0.80 to 1.10)<br>**Rural**<br>HR=1.10 (0.90 to 1.30)<br>**Mid-Rural**<br>HR=1.20 (1.00 to 1.40)<br>**Very Rural**<br>HR=1.00 (0.80 to 1.20)<br>Early stage<br>**Urban (Ref.)**<br>**Mid-Urban**<br>HR=0.90 (0.60 to 1.20)<br>**Rural**<br>HR=1.20 (0.80 to 1.80)<br>**Mid-Rural**<br>HR=1.20 (0.90 to 1.70)<br>**Very Rural**<br>HR=0.80 (0.50 to 1.30)<br>Late stage<br>**Urban (Ref.)**<br>**Mid-Urban**<br>HR=0.90 (0.80 to 1.10)<br>**Rural**<br>HR=1.00 (0.80 to 1.30)<br>**Mid-Rural**<br>HR=1.20 (1.00 to 1.50)<br>**Very Rural**<br>HR=1.10 (0.80 to 1.30) | Age, race/ethnicity, area-level socio-economic status, stage at diagnosis<br><br>Age, race/ethnicity, area-level socio-economic status, |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fitzgerald | United States | Surveillance, Epidemiology, and End Results (SEER) registries<br><br>**Sample size**<br>**176,011** | United States | 1992-2002 | ≥40 | Colorectum | Rural-urban continuum was defined based on the county population | 5 | Cox proportional hazards regression | **Overall survival**<br>**Large metropolitan**<br>HR=1.04 (1.02 to 1.05)<br>**Metropolitan (Ref.)**<br>**Urban**<br>HR=1.03 (1.00 to 1.06)<br>**Small urban**<br>HR=1.02 (0.99 to 1.05)<br>**Rural**<br>HR=1.08 (1.02 to 1.14) | Age, race, sex, area-level socio-economic status |
| Gorey et al, 2008 | Canada | Ontario Cancer Registry (OCR)<br><br>**Sample size**<br>**29,934** | Ontario | 1986-1988<br>1995-1997 | ≥25 | Breast | Based on population size and distance to treatment centres | 11 | Maximum likelihood logistic regression | **Overall survival**<br>1986-1988, 1995-1997<br>**City of Toronto (Ref.)**<br>**Other greater metropolitan Toronto**<br>OR=0.91 (0.80 to 1.03)<br>OR=0.96 (0.85 to 1.08)<br>**Large cities**<br>OR=0.87 (0.76 to 0.99)<br>OR=0.89 (0.78 to 1.02)<br>**Mid-sized cities**<br>OR=0.84 (0.74 to 0.97)<br>OR=0.92 (0.81 to 1.05)<br>**Small cities**<br>OR=0.95 (0.81 to 1.13)<br>OR=0.93 (0.80 to 1.09)<br>**Very small cities**<br>OR=1.12 (0.93 to 1.35)<br>OR=0.94 (0.79 to 1.12)<br>**Towns and villages**<br>OR=0.79 (0.66 to 0.93)<br>OR=0.86 (0.75 to 0.99)<br>**Rural**<br>OR=0.86 (0.73 to 1.01) | Age |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | OR=0.80 (0.68 to 0.96)<br>**Remote**<br>OR=0.88 (0.70 to 1.10)<br>OR=0.84 (0.70 to 1.00)<br>**Very remote**<br>OR=1.19 (0.76 to1.86)<br>OR=0.99 (0.66 to 1.49)<br>**Extremely remote**<br>OR=0.70 (0.44 to 1.11)<br>OR=1.48 (0.89 to 2.45) | |
| Hallet et al, 2015 | Canada | Ontario Cancer Registry (OCR) linked with the Canadian Institute of Health Information Discharge Abstract Database and the Registered Persons Database (RPDB)<br>**Sample size**<br>**6,271** | Ontario | 1994-2011 | ≥19 | Neuroendocrine | Based on population size | 2 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Urban (Ref.)**<br>**Rural**<br>HR=1.16 (1.04 to 1.30) | Age, sex, area-level median income, primary tumour location, metastatic status |
| Hall et al, 2005 | Australia | The Western Australian Data Linkage System (Western Australian Cancer Registry linked to hospital data)<br>**Sample size**<br>**14,587** | Western Australia | 1982-2001 | All ages | Colorectum | Accessibility/Remoteness Index of Australia (ARIA) | 5 | Cox proportional hazards regression | **Overall survival**<br>1982-2001, 1991-2001<br>**Very accessible (Ref.)**<br>**Accessible**<br>HR=0.91 (0.78 to 1.05)<br>HR=0.85 (0.71 to 1.02)<br>**Moderate accessible**<br>HR=1.16 (0.97 to 1.37)<br>HR=1.10 (0.90 to 1.34)<br>**Remote** | Age, sex, calendar period, Charlson weighted co-morbidity index, indigenous status, marital status, admission type, surgical status, histology of cancer |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | HR=1.20 (0.87 to 1.67)<br>HR=1.19 (0.85 to 1.66)<br>**Very remote**<br>HR=0.98 (0.67 to 1.45)<br>HR=1.05 (0.71 to 1.54) | **1991-2001 cohort**<br>Additional adjustment for areal-level socio-economic status, location of hospital, insurance classification and hospital status |
| Hines et al, 2014 | United States | Georgia Comprehensive Cancer Registry (GCCR)<br><br>**Sample size**<br>**30,100** | Georgia | 2000-2007 | 45-85 | Colorectum | Census tract geographic residency statues obtained from Rural-Urban Commuting Area (RUCA) primary codes from the US Department of Agriculture | 3 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>All stages – Unadjusted<br>**Urban (Ref.)**<br>**Suburban**<br>HR=1.01 (0.97 to 1.06)<br>**Rural**<br>HR=1.13 (1.07 to 1.20)<br>All stages – Adjusted for age, gender, race, disease stage, geography and tumour grade<br>**Urban (Ref.)**<br>**Suburban**<br>HR=1.04 (0.99 to 1.09)<br>**Rural**<br>HR=1.14 (1.07 to 1.22)<br>All stages – Additional adjustment for treatment<br>**Urban (Ref.)**<br>**Suburban**<br>HR=1.03 (0.98 to 1.08)<br>**Rural** | Age, gender, race, disease stage, tumour grade,<br>Geography, treatment (surgery,<br>chemotherapy, or radiation), and area-level socio-economic status |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | HR=1.10 (1.04 to 1.18)<br>All stages – Fully adjusted (additional adjustment for socio-economic status)<br>**Urban (Ref.)**<br>**Suburban**<br>HR=0.98 (0.93 to 1.03)<br>**Rural**<br>HR=1.00 (0.93 to 1.07)<br>Fully adjusted, localised and regional stages<br>**Urban (Ref.)**<br>**Suburban**<br>HR=1.00 (0.92 to 1.08)<br>**Rural**<br>HR=0.95 (0.85 to 1.05)<br>Fully adjusted, regional + lymph node positive and distant stages<br>**Urban (Ref.)**<br>**Suburban**<br>HR=0.97 (0.91 to 1.04)<br>**Rural**<br>HR=1.02 (0.94 to 1.12) | |
| Johnson et al, 2014 | United States | Georgia Comprehensive Cancer Registry (GCCR)<br>**Sample size**<br>**32,711** | Georgia | 2000-2009 | 50-85 | Lung | Rural-Urban Commuting Area (RUCA) primary codes | 3 | Cox proportional hazards regression | **Overall survival**<br>Adjusted for age, gender, race, tumour grade and tumour stage<br>**Urban (Ref.)**<br>**Suburban**<br>HR=1.04 (1.01 to 1.07)<br>**Rural**<br>HR=1.07 (1.03 to 1.11) | Age, sex, race, tumour grade, tumour stage, treatment (surgery, chemotherapy, radiation) |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Additional adjustment for treatment<br>**Urban (Ref.)**<br>**Suburban**<br>HR=1.01 (0.98 to 1.04)<br>**Rural**<br>HR=1.00 (0.97 to 1.04)<br>Fully adjusted (Additional adjustment for socio-economic status)<br>**Urban (Ref.)**<br>**Suburban**<br>HR=0.98 (0.94 to 1.01)<br>**Rural**<br>HR=0.96 (0.92 to 1.00)<br>Fully adjusted, Stage 1, II<br>**Urban (Ref.)**<br>**Suburban**<br>HR=0.91 (0.84 to 0.98)<br>**Rural**<br>HR=0.90 (0.82 to 0.99)<br>Fully adjusted, Stage III<br>**Urban (Ref.)**<br>**Suburban**<br>HR=0.98 (0.91 to 1.06)<br>**Rural**<br>HR=0.97 (0.89 to 1.07) | Additional adjustment for area-level socio-economic status |
| Jong et al, 2004 | Australia | New South Wales Central Cancer Registry<br>**Sample size**<br>**132,516** | New South Wales | 1992-1996 | < 90 | All malignancies (20 cancer types) | Accessibility/Remoteness Index of Australia (ARIA) | 4 | Relative survival, relative excess risk using generalised linear model | **Cancer-specific survival**<br>All cancers combined - not adjusted for stage<br>**Highly Accessible (Ref.)**<br>**Accessible**<br>EMRR=0.99 (0.96 to 1.02) | Age, sex, years since diagnosis and stage at diagnosis |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Moderately accessible**<br>EMRR=1.04 (0.98 to 1.11)<br>**Remote/very remote**<br>EMRR=1.35 (1.20 to 1.51)<br>All cancers combined - adjusted for stage<br>**Highly Accessible (Ref.)**<br>**Accessible**<br>EMRR=1.02 (0.99 to 1.04)<br>**Moderately accessible**<br>EMRR=1.02 (0.96 to 1.09)<br>**Remote/very remote**<br>EMRR=1.25 (1.11 to 1.41)<br>**Head and neck cancer**<br>**Highly Accessible (Ref.)**<br>**Accessible**<br>Not adjusted for stage<br>EMRR=0.81 (0.70 to 0.94)<br>Adjusted for stage<br>EMRR=0.85 (0.74 to 0.99)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=1.02 (0.76 to 1.37)<br>Adjusted for stage<br>EMRR=0.97 (0.72 to 1.31)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=1.41 (0.93 to 2.13)<br>Adjusted for stage<br>EMRR=1.43 (0.95 to 2.16)<br>**Colon cancer**<br>**Highly Accessible (Ref.)** | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Accessible**<br>Not adjusted for stage<br>EMRR=1.09 (1.00 to 1.19)<br>Adjusted for stage<br>EMRR=1.15 (1.05 to 1.25)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=1.12 (0.90 to 1.39)<br>Adjusted for stage<br>EMRR=1.30 (1.04 to 1.63)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=0.89 (0.52 to 1.50)<br>Adjusted for stage<br>EMRR=1.01 (0.61 to 1.68)<br>**Rectal cancer**<br>**Highly Accessible (Ref.)**<br>**Accessible**<br>Not adjusted for stage<br>EMRR=0.98 (0.86 to 1.12)<br>Adjusted for stage<br>EMRR=1.07 (0.94 to 1.21)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=1.25 (0.94 to 1.65)<br>Adjusted for stage<br>EMRR=1.22 (0.92 to 1.62)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=1.78 (1.06 to 2.97)<br>Adjusted for stage<br>EMRR=2.32 (1.38 to 3.89)<br>**Liver cancer**<br>**Highly Accessible (Ref.)** | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Accessible**<br>Not adjusted for stage<br>EMRR=1.22 (0.95 to 1.58)<br>Adjusted for stage<br>EMRR=1.22 (0.94 to 1.58)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=1.24 (0.61 to 2.54)<br>Adjusted for stage<br>EMRR=1.35 (0.66 to 2.78)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=0.79 (0.32 to 1.94)<br>Adjusted for stage<br>EMRR=0.78 (0.31 to 1.96)<br>**Pancreatic Pancreas cancer**<br>**Highly Accessible (Ref.)**<br>**Accessible**<br>Not adjusted for stage<br>EMRR=1.04 (0.91 to 1.18)<br>Adjusted for stage<br>EMRR=1.08 (0.95 to 1.23)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=0.87 (0.65 to 1.15)<br>Adjusted for stage<br>EMRR=0.91 (0.68 to 1.21)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=1.28 (0.75 to 2.18)<br>Adjusted for stage<br>EMRR=1.41 (0.82 to 2.41)<br>**Lung cancer** | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Highly Accessible (Ref.)** | |
| | | | | | | | | | | **Accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.07 (1.01 to 1.13) | |
| | | | | | | | | | | Adjusted for stage<br>EMRR=1.07 (1.01 to 1.13) | |
| | | | | | | | | | | **Moderately accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.19 (1.04 to 1.35) | |
| | | | | | | | | | | Adjusted for stage<br>EMRR=1.21 (1.07 to 1.38) | |
| | | | | | | | | | | **Remote/very remote** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.07 (0.84 to 1.36) | |
| | | | | | | | | | | Adjusted for stage<br>EMRR=1.03 (0.80 to 1.31) | |
| | | | | | | | | | | **Melanoma of the skin** | |
| | | | | | | | | | | **Highly Accessible (Ref.)** | |
| | | | | | | | | | | **Accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=0.68 (0.56 to 0.83) | |
| | | | | | | | | | | Adjusted for stage<br>EMRR=0.71 (0.60 to 0.85) | |
| | | | | | | | | | | **Moderately accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.03 (0.70 to 1.52) | |
| | | | | | | | | | | Adjusted for stage<br>EMRR=0.92 (0.64 to 1.34) | |
| | | | | | | | | | | **Remote/very remote** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=0.67 (0.22 to 2.07) | |
| | | | | | | | | | | Adjusted for stage | |
| | | | | | | | | | | EMRR=1.04 (0.42 to 2.58) | |
| | | | | | | | | | | **Breast cancer** | |
| | | | | | | | | | | **Highly Accessible (Ref.)** | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Accessible**<br>Not adjusted for stage<br>EMRR=1.10 (0.96 to 1. 27)<br>Adjusted for stage<br>EMRR=1.11 (0.98 to 1.26)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=0.91 (0.64 to 1.29)<br>Adjusted for stage<br>EMRR=0.89 (0.65 to 1.24)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=1.21 (0.60 to 243)<br>Adjusted for stage<br>EMRR=1.47 (0.78 to 2.78)<br>**Cervical cancer**<br>**Highly Accessible (Ref.)**<br>**Accessible**<br>Not adjusted for stage<br>EMRR=1.70 (1.32 to 2.20)<br>Adjusted for stage<br>EMRR=1.73 (1.33 to 2.25)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=0.73 (0.35 to 1.51)<br>Adjusted for stage<br>EMRR=0.83 (0.39 to 1.74)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=3.22 (1.54 to 6.75)<br>Adjusted for stage<br>EMRR=2.25 (1.06 to 4.77)<br>**Uterine cancer** | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Highly Accessible (Ref.)** | |
| | | | | | | | | | | **Accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=0.98 (0.69 to 1.38)<br>Adjusted for stage<br>EMRR=0.98 (0.70 to 1.39) | |
| | | | | | | | | | | **Moderately accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.23 (0.61 to 2.50)<br>Adjusted for stage<br>EMRR=1.43 (0.73 to 2.78) | |
| | | | | | | | | | | **Remote/very remote** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.94 (0.64 to 5.86) | |
| | | | | | | | | | | Adjusted for stage | |
| | | | | | | | | | | EMRR=2.17 (0.72 to 6.52) | |
| | | | | | | | | | | **Ovarian cancer** | |
| | | | | | | | | | | **Highly Accessible (Ref.)** | |
| | | | | | | | | | | **Accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.10 (0.92 to 1.31)<br>Adjusted for stage<br>EMRR=1.11 (0.92 to 1.331) | |
| | | | | | | | | | | **Moderately accessible** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=0.82 (0.51 to 1.30)<br>Adjusted for stage<br>EMRR=0.84 (0.53 to 1.33) | |
| | | | | | | | | | | **Remote/very remote** | |
| | | | | | | | | | | Not adjusted for stage<br>EMRR=1.61 (0.70 to 3.73) | |
| | | | | | | | | | | Adjusted for stage | |
| | | | | | | | | | | EMRR=1.34 (0.57 to 3.14) | |
| | | | | | | | | | | **Prostate cancer** | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Highly Accessible (Ref.)**<br>**Accessible**<br>Not adjusted for stage<br>EMRR=1.18 (1.01 to 1.38)<br>Adjusted for stage<br>EMRR=1.16 (1.01, 1.33)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=1.44 (1.04 to 1.99)<br>Adjusted for stage<br>EMRR=1.16 (0.86 to 1.56)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=3.38 (2.21 to 5.16)<br>Adjusted for stage<br>EMRR=2.53 (1.60 to 4.01)<br>**Non-Hodgkin lymphoma**<br>**Highly Accessible (Ref.)**<br>**Accessible**<br>Not adjusted for stage<br>EMRR=0.93 (0.81 to 1.06)<br>**Moderately accessible**<br>Not adjusted for stage<br>EMRR=1.16 (0.84 to 159)<br>**Remote/very remote**<br>Not adjusted for stage<br>EMRR=0.99 (0.53 to 1.85) | |
| Klein et al, 2011 | United States | Surveillance, Epidemiology, and End Results (SEER) registries<br>**Sample size** | United States | 1988-2006 | All ages | Male breast | Based on population size | 2 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Metropolitan counties**<br>**Non-metropolitan counties**<br>HR=1.19 (1.01, 1.40) | Age, race, marital status, area-level of education and median family income, stage at diagnosis |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **4,222** | | | | | | | | | |
| Kneuertz et al, 2014 | United States | Texas Cancer Registry (TCR)<br>**Sample size**<br>**1,089** | Texas | 2000-2008 | All ages | Liver (Intrahepatic cholangiocarcinoma) | Based on population density | 2 | Cox proportional hazards regression (univariate analysis) | **Overall survival**<br>**Urban (Ref.)**<br>**Rural**<br>HR=1.15 (0.99, 1.34) | _ |
| Krzyżak et al, 2010 | Poland | Voivodship Cancer Registry (Bialystok)<br>**Sample size**<br>**659** | Podlaskie Voivodship | 2001-2002 | ≥15 | Breast | Rural-urban residence was defined based on the address of patients according to the National Official Register of Territorial Division of the Country (TERYT) | 2 | Relative survival (Hakulinen method), excess mortality rate | **Cancer-specific survival**<br>**Urban (Ref.)**<br>**Rural**<br>EMRR=1.37 (1.01 to 1.86) | Age at diagnosis, stage at diagnosis |
| Lee et al, 2014 | Canada | British Columbia Cancer Registry<br>**Sample size**<br>**1,440** | British Columbia | 2003-2008 | 18-80 | Diffuse Large B-Cell Lymphoma (DLBCL) | The Statistics Canada Postal Code Conversion File was used to link each patient's postal codes to 2006 census geographic area data (rural-urban areas were defined based on population size and density) | 4 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Large urban (Ref.)**<br>**Medium urban**<br>HR=1.4 (1.0 to 1.9)<br>**Small urban**<br>HR=1.4 (1.0 to 2.0)<br>**Rural**<br>HR=1.0 (0.7 to 1.4)<br>**Cancer-specific survival**<br>**Large urban (Ref.)**<br>**Medium urban**<br>HR=1.4 (1.0 to 1.9)<br>**Small urban**<br>HR=1.3 (0.9 to 2.0)<br>**Rural**<br>HR=0.9 (0.6 to 1.3) | Age, stage, LDH (lactate dehydrogenase), ECOG (Eastern Cooperative Oncology Group) performance status, curative chemotherapy, radiotherapy, histology |
| Markossian et al, 2012 | United States | Surveillance, Epidemiology, | Georgia | 1992-2007 | ≥15 | Breast | Rural-urban continuum code classification (RUCC) | 2 | Cox proportional hazards regression | **Cancer-specific survival**<br>**Urban (Ref.)** | Race, age, area-level socio-economic status, |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | and End Results (SEER)<br><br>**Sample size**<br>**23,500** | | | | | | | | **Rural**<br>HR=1.04 (0.85 to 1.26) | tumour stage, tumour grade, hormone receptor status, treatment (surgery/radiation) |
| Markossian et al, 2016 | United States | South-eastern safety-net academic medical centre<br><br>**Sample size**<br>**245** | Georgia | 2009-2012 | All ages | Pancreas | Rural-Urban Commuting Area codes (RUCA) | 3 | Cox proportional hazards regression | **2-year overall survival**<br>**Urban (Ref.)**<br>**Large rural**<br>Unadjusted<br>HR=1.38 (0.91 to 2.09)<br>Adjusted<br>HR=2.63 (1.45 to 4.76)<br>**Small rural or isolated**<br>Unadjusted<br>HR=1.85 (1.02 to 3.33)<br>Adjusted<br>HR=1.74 (0.84 to 3.60) | Age, race, sex, marital status, employment, primary payer, primary care provider affiliation, area-level socio-economic status, co-morbidity, tumour characteristics, initial treatment |
| Martinez et al, 2012 | United States | Surveillance, Epidemiology, and End Results (SEER)<br><br>**Sample size**<br>**1,507** | Sacramento and 13 surrounding counties | 2000-2006 | All ages | Breast | Rural-urban continuum code classification (RUCC) | 2 | Cox proportional hazards regression | **Overall survival**<br>**Urban (Ref.)**<br>**Non-urban**<br>HR=0.97 (0.77 to 1.21)<br>**Cancer-specific survival**<br>**Urban (Ref.)**<br>**Non-urban**<br>HR=0.95 (0.73 to 1.23) | Age, race/ethnicity, tumour size, tumour grade, hormone (oestrogen, progesterone) receptor status, number of metastatic nodes, radiation |
| Martin et al, 2015 | Australia | Royal Perth Hospital Cancer Registry, regional cancer centres, electronic patient | Western Australia | 2007-2011 | All ages | Melanoma, colorectum, breast, lung, upper gastrointestinal | Based on residential postcode | 2 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Cancer-specific survival**<br>**(Three year)**<br>**Metropolitan Perth (Ref.)**<br>**Regional**<br>HR=1.10 (1.01 to 1.29) | Eastern Cooperative Group Performance Status ≥ 2, male sex |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | records and medical case notes<br><br>**Sample size**<br>**1,581** | | | | tract, pancreas and prostate | | | | | |
| Mitchell et al, 2006 | Australia | Western Australia Cancer Registry<br><br>**Sample size**<br>**899** | Western Australia | 1999 | 22-92 | Breast | Area of residence classified as urban or rural based on the postcode of the woman's usual residence | 2 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Urban (Ref.)**<br>**Rural**<br>Adjusted for age<br>HR=1.84 (1.28 to 2.64)<br>Adjusted for age and tumour characteristics<br>HR=1.62 (1.10 to 2.38)<br>Adjusted for age and treatment<br>HR=1.46 (0.99 to 2.14)<br>Adjusted for age, tumour characteristics and treatment<br>HR=1.36 (0.90 to 2.04)<br>Adjusted for age, tumour characteristics and treatment, not adjusted for high-caseload surgeon<br>HR=1.57 (1.05 to 2.33)<br>Adjusted for all variables<br>HR=1.38 (0.91 to 2.08) | Age, tumour size, lymph node status, histological grade, vascular invasion, treatment (breast-conserving surgery, radiotherapy, chemotherapy, hormonal therapy, high-caseload surgeon), mode of detection (diagnostic mammogram, breast ultrasound, fine needle aspiration, core biopsy, open biopsy with and without frozen section) |
| Modesitt et al, 2006 | United States | Kentucky Cancer Registry<br><br>**Sample size**<br>**3,562** | Kentucky | 1995-2002 | All ages | Endometrium | Rural-urban continuum code (RUCC) | 2 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Urban (Ref.)**<br>**Rural**<br>HR=0.98 (0.86 to 1.12)<br>**Cancer-specific survival** | Age, race, smoking status, insurance status, stage, grade, nodal status |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Urban (Ref.)**<br>**Rural**<br>HR=0.77 (0.63 to 0.94) | |
| Nennecke et al, 2014 | Germany | German population-based cancer registries including 11 federal states<br><br>**Sample size**<br>**817,182** | Germany | 1997-2006 | ≥15 | All malignancies (15 cancer types) | Urban-rural classification was defined according to the district types of settlement structure and based on both population density and the characteristics of the supraordinate regions | 4 | Age-standardised relative survival (period analysis), excess mortality using Poisson regression | **Cancer-specific survival**<br>**Colorectal cancer (Females)**<br>**City core (Ref.)**<br>**Densely populated outer**<br>EMRR=1.01 (0.97 to 1.05)<br>**Rural outer conurbation**<br>EMRR=0.99 (0.98 to 1.00)<br>**Rural**<br>EMRR=0.94 (0.90 to 0.99)<br>**Pancreatic Pancreas cancer (Males)**<br>**City core (Ref.)**<br>**Densely populated outer**<br>EMRR=1.08 (1.02 to 1.15)<br>**Rural outer conurbation**<br>EMRR=1.00 (0.99 to 1.02)<br>**Rural**<br>EMRR=0.96 (0.90 to 1.02)<br>**Female breast cancer**<br>**City core (Ref.)**<br>**Densely populated outer**<br>EMRR=1.05 (0.99 to 1.11)<br>**Rural outer conurbation**<br>EMRR=1.21 (1.08 to 1.36)<br>**Rural**<br>EMRR=1.19 (1.07 to 1.32) | Age, T-stage, year of follow-up |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Prostate cancer**<br>**City core (Ref.)**<br>**Densely populated outer**<br>EMRR=1.06 (0.97 to 1.16)<br>**Rural outer conurbation**<br>EMRR=1.23 (1.09 to 1.39)<br>**Rural**<br>EMRR=1.10 (1.00 to 1.21)<br>**Bladder cancer (Males)**<br>**City core (Ref.)**<br>**Densely populated outer**<br>EMRR=0.98 (0.91 to 1.06)<br>**Rural outer conurbation**<br>EMRR=0.92 (0.84 to 1.01)<br>**Rural**<br>EMRR=1.07 (0.99 to 1.15)<br>**Melanoma (Males)**<br>**City core (Ref.)**<br>**Densely populated outer**<br>EMRR=1.12 (0.94 to 1.33)<br>**Rural outer conurbation**<br>EMRR=1.18 (0.98 to 1.43)<br>**Rural**<br>EMRR=1.24 1.03 to 1.49) | |
| O'Malley et al, 2003 | United States | Women diagnosed with ovarian cancer and received surgical treatment (identified through | Northern California | 1994-1996 | 23-97 | Ovary | Region of residence | 3 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Cancer-specific survival**<br>**San Francisco Bay area (Ref.)**<br>**Sacramento**<br>HR=2.1 (1.7 to 2.6)<br>**Rural Northern California**<br>HR=2.6 (2.0 to 3.3) | Age, race/ ethnicity, area-level socio-economic status, stage, grade, histology, co-morbidity, chemotherapy |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | California Cancer Registry (CCR) and Surveillance Epidemiology and End Results (SEER) Program)<br><br>**Sample size**<br>**1,051** | | | | | | | | | use, treatment provider |
| Panchal et al, 2016 | United States | Stage-III colon cancer patients who received colon cancer–specific surgery between 2004 and 2009 (identified from SEER-Medicare database)<br><br>**Sample size**<br>**8,275** | United States<br>16 states | 2004-2009 | ≥ 66 | Colon (stage III) | Rural-urban continuum codes (RUCC) | 5 | Logistic regression, cox proportional hazards regression | **Cancer-specific survival**<br>**Big metro (Ref.)**<br>**Metro**<br>Unadjusted<br>HR=1.16 (0.95 to 1.42)<br>Adjusted<br>HR=1.27 (0.90 to 1.80)<br>**Urban**<br>Unadjusted<br>HR=0.78 (0.49 to 1.23)<br>Adjusted<br>HR=0.89 (0.44 to 1.84)<br>**Less urban**<br>Unadjusted<br>HR=1.02 (0.74 to 1.41)<br>Adjusted<br>HR=1.37 (0.56 to 3.32)<br>**Rural**<br>Unadjusted<br>HR=1.10 (0.58 to 2.08)<br>Adjusted<br>HR=1.96 (0.55 to 6.95) | Age, race, sex, marital status, area-level median household income, co-morbidity, tumour grade, node involvement, tumour size, radiation, oxaliplatin chemotherapy |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Papa et al, 2014 | Australia | Victorian Radical Prostatectomy Register<br><br>**Sample size**<br>**1,984** | Victoria | 1995-2000 | All ages | Prostate | Australian Standard Geographic Classification (ASGC) | 3 | Cox proportional hazards regression, competing risk regression (Fine and Grey method) | **Overall survival**<br>**Major metropolitan (Ref.)**<br>**Inner regional**<br>HR=1.09 (0.75 to 1.57)<br>**Outer regional/Remote**<br>HR=1.34 (0.70 to 2.57)<br>**Cancer-specific survival**<br>**Major metropolitan (Ref.)**<br>**Inner regional**<br>HR=1.64 (0.83 to 3.23)<br>**Outer regional/Remote**<br>HR=4.09 (1.56 to 10.7) | Area-level socio-economic status, private or public hospital treatment, age at surgery, PSA level at radical prostatectomy, Gleason score, tumour stage, biochemical recurrence |
| Pozet et al, 2008 | France | Doubs Cancer Registry<br><br>**Sample size**<br>**802** | Eastern France (Doubs, Haute-Saone, and Territoire de Belfort) | 2000-2001 | 15-92 | Lung | Each area of residence was assigned a degree of rurality which was calculated using socio-demographic and farming parameters from the 1999 French INSEE census | 3 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Semi-urban (Ref.)**<br>**Urban**<br>HR=1.18 (0.91 to 1.53)<br>**Rural**<br>HR=1.42 (1.06 to 1.90) | Age, smoking status, WHO performance status, stage, reference treatment |
| Raju et al, 2015 | Canada | Ontario Cancer Registry linked to administrative datasets at the Institute for Clinical Evaluation Science and the Canadian Institute for Health Information's Discharge Abstract Database<br><br>**Sample size**<br>**9,224** | Ontario | 2004-2011 | All ages | Pancreas | Geographic area of residence was defined by geocoding postcodes into dissemination areas | 2 | Relative survival, Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Non-Rural (Ref.)**<br>**Rural residence**<br>HR=1.08 (1.01 to 1.15) | Age, sex, area-level median family income, site of cancer, comorbidity, year of diagnosis |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Robsahm et al, 2005 | Norway | Database of all Norwegians with individual socio-demographic information linked to Cancer Registry of Norway<br><br>**Sample size**<br>**5,042** | Norway | 1964-1992 | 30-62 | Breast | Rural-urban areas were classified according to the main income resources for the municipality in 1968 | 2 | Cox proportional hazards regression | **Cancer-specific survival**<br>**Urban (Ref.)**<br>**Rural**<br>[1] HR=0.79 (0.66 to 0.94)<br><br>**Urban (Ref.)**<br>**Rural**<br>[2] HR=0.83 (0.69 to 0.98) | [1]Age, calendar time, birth cohort<br><br>[2]Additional adjustment for age at first childbirth, individual-level of education, individual-level of occupational physical activity |
| Rolland-Portal et al, 1997 | France | Registry of haematopoietic malignancies<br><br>**Sample size**<br>**451** | Côte-d'Or | 1980-1991 | ≥ 20 | Non-Hodgkin's lymphoma | NA | 3 | Kaplan-Meier method (crude overall survival), relative survival, cox proportional hazards regression, excess mortality rate ratio | **Overall survival**<br>**Dijon/urban (Ref.)**<br>**Small towns**<br>HR=0.96 (0.72 to 1.27)<br>**Rural**<br>HR=1.63 (1.15 to 2.30)<br>**Relative survival**<br>**Dijon/urban (Ref.)**<br>**Small towns**<br>EMRR=1.03 (0.69 to 1.54)<br>**Rural**<br>EMRR=2.20 (1.41 to 3.42) | Sex, age at diagnosis, histological grade classification, place of hospitalisation, period of diagnosis |
| Rybojad et al, 2013 | Poland | Patients from the Department of Thoracic Surgery of the Medical University<br><br>**Sample size**<br>**125** | Lublin | 2006-2007 | NA | Lung | Residence (urban-rural) was determined based on the address of patients (urban population was defined as areas with a population exceeding 10,000 inhabitants. Less inhabited areas were considered as rural) | 2 | NA | **Overall survival**<br>**Urban areas (Ref.)**<br>**Rural areas**<br>OR=1.27 (0.63 to 2.58) | - |
| Sankaranar-ayanan et al, 2014 | United States | Nebraska Cancer Registry | Nebraska | 1998-2003 | ≥19 | Colon and rectum | County of residence was defined using the county-based Office Management | 3 | Kaplan-Meier method (crude overall survival), cox | **Overall survival**<br>**Colon cancer** | Age, race/ethnicity, marital status, |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Sample size**<br>**6,547** | | | | | and Budget (OMB) classification of geographical access | | proportional hazards regression | Adjusted for demographics<br>**Rural (Ref.)**<br>**Micropolitan**<br>HR=0.83 (0.73 to 0.93)<br>**Urban**<br>HR=1.11 (1.00 to 1.23)<br>Adjusted for demographics + stage<br>**Rural (Ref.)**<br>**Micropolitan**<br>HR=0.97 (0.86 to 1.10)<br>**Urban**<br>HR=1.13 (1.02 to 1.26)<br>Adjusted for demographics + stage + treatment<br>**Rural (Ref.)**<br>**Micropolitan**<br>HR=1.01 (0.89 to 1.14)<br>**Urban**<br>HR=1.15 (1.04 to 1.28) | cancer stage, treatment (surgery, radiation, chemotherapy) |
| | | | | | | | | | | **Rectal cancer**<br>Adjusted for demographics<br>**Rural (Ref.)**<br>**Micropolitan**<br>HR=0.89 (0.71 to 1.12)<br>**Urban**<br>HR=1.25 (1.00 to 1.55)<br>Adjusted for demographics + stage<br>**Rural (Ref.)**<br>**Micropolitan**<br>HR=1.11 (0.88 to 1.40)<br>**Urban**<br>HR=1.13 (0.91 to 1.41) | Age, insurance payer, cancer stage, treatment (surgery, radiation, chemotherapy) |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Adjusted for demographics + stage + treatment<br>**Rural (Ref.)**<br>**Micropolitan**<br>HR=1.16 (0.92 to 1.47)<br>**Urban**<br>HR=1.16 (0.93 to 1.44)<br>**Overall survival**<br>Hazard ratios were calculated using urban as reference category<br>**Colon cancer**<br>Adjusted for demographics<br>**Urban (Ref.)**<br>**Rural**<br>HR=0.90 (0.81 to 1.00)<br>Adjusted for demographics + stage<br>**Urban (Ref.)**<br>**Rural**<br>HR=0.88 (0.79 to 0.98)<br>Adjusted for demographics + stage + treatment<br>**Urban (Ref.)**<br>**Rural**<br>HR=0.87 (0.78 to 0.96)<br>**Rectal cancer**<br>Adjusted for demographics<br>**Urban (Ref.)**<br>**Rural**<br>HR=0.80 (0.64 to 0.99)<br>Adjusted for demographics + stage | |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **Urban (Ref.)**<br>**Rural**<br>HR=0.89 (0.71 to 1.10)<br>Adjusted for demographics + stage + treatment<br>**Urban (Ref.)**<br>**Rural**<br>HR=0.86 (0.69 to 1.08) | |
| Singla et al, 2014 | Australia | South Australian Clinical Registry for Metastatic Colorectal Cancer<br>**Sample size**<br>**1,981** | South Australia | 2006 | All ages | Colorectum | Australian Standard Geographic Classification (ASGC) – Remoteness Structure | 4 | Cox proportional hazards regression | **Overall survival**<br>**Major city (Ref.)**<br>**Inner regional**<br>HR=0.65 (0.32 to 1.32)<br>**Outer regional**<br>HR=1.50 (0.78 to 2.90)<br>**Remote**<br>HR=1.43 (0.48 to 4.29) | Sex, age, grade, histology, primary site, areal-level socio-economic status, metastases characteristics, tumour characteristics, treatment factors (chemotherapy, surgery) |
| Wang et al, 2013 | United States | Surveillance, Epidemiology, and End Results (SEER) registries<br>**Sample size**<br>**29,527** | United States | 2004-2009 | All ages | Gastroesophagus (Squamous Cell Carcinoma of Oesophagus, Adenocarcinoma of Oesophagus, Adenocarcinoma of the Gastric Cardia) | Rural-Urban Communication Code (RUCC) | 3 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Cancer-specific survival**<br>squamous cell carcinoma of the oesophagus<br>**Metropolitan (Ref.)**<br>**Urban**<br>HR=1.02 (0.91 to 1.14)<br>**Rural**<br>HR=1.10 (0.91 to 1.33)<br>Adenocarcinoma of the oesophagus<br>**Metropolitan (Ref.)**<br>**Urban**<br>HR=1.02 (0.93 to 1.12)<br>**Rural**<br>HR=1.05 (0.93 to 1.20) | Sex, age, race, region, marital status, surgery, radiotherapy, and stage at diagnosis |

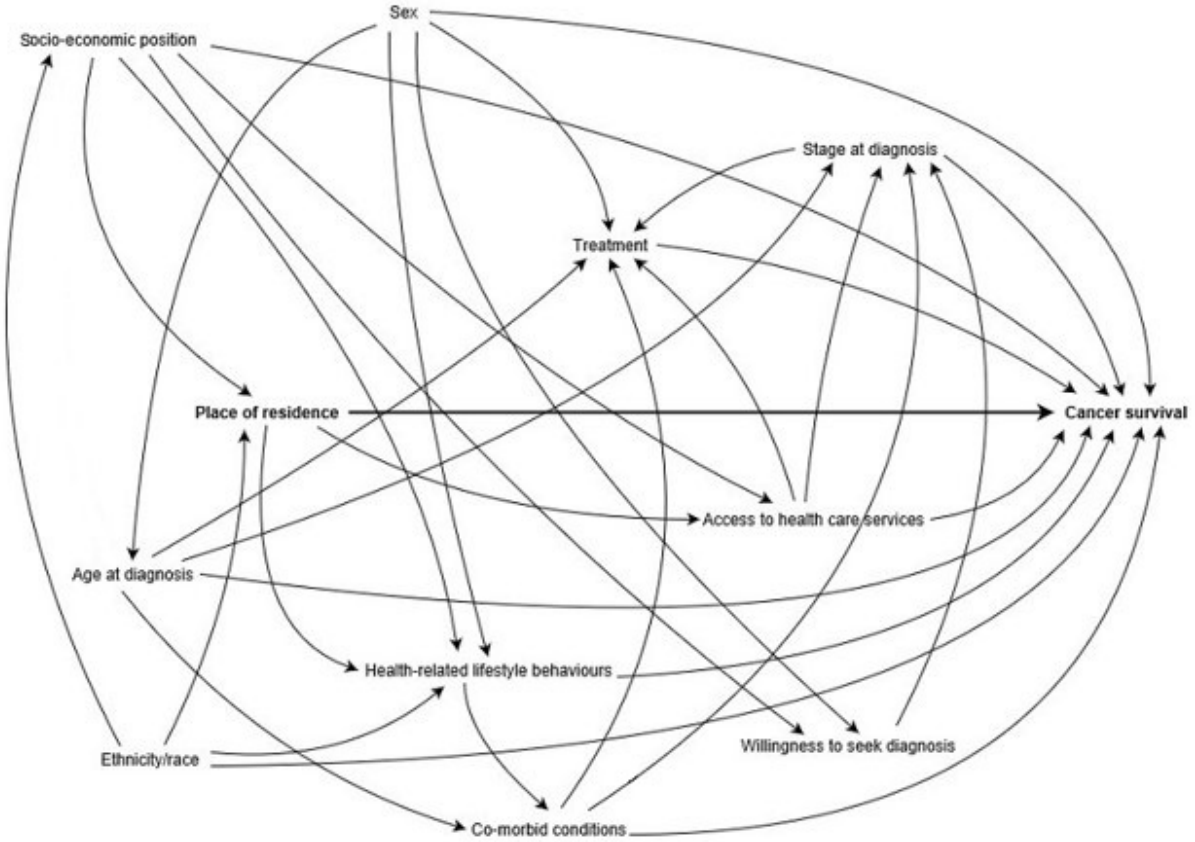
| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Adenocarcinoma of the gastric cardia<br>**Metropolitan (Ref.)**<br>**Urban**<br>HR=1.32 (1.16 to 1.53)<br>**Rural**<br>HR=1.07 (0.87 to 1.33) | |
| Wong et al, 2016 | Australia | Oncology services across the Barwon South Western region in Victoria<br>**Sample size**<br>**1,778** | South Western Victoria | 2009 | All ages | Gastrointestinal, urinary, breast, lung, melanoma, lymphoma, Gynaecological | Australian Standard Geographical Classification–Remoteness area (ASGC-RA) | 3 | Kaplan-Meier method (crude overall survival), Cox proportional hazards regression | **Overall survival**<br>**Major cities (Ref.)**<br>**Inner regional areas**<br>NA<br>**Outer regional areas**<br>HR=0.86 (0.77, 0.97) | Age, sex, area-level socio-economic status |
| Yu et al, 2015 | Australia | New South Wales Central Cancer Registry<br>**Sample size**<br>**63,757** | New South Wales | 1987-2007 | 18-84 | Breast | Australian Standard Geographic Classification–Remoteness Structure (ASGC-RA) | 3 | Relative survival (period analysis), Relative excess risk using Poisson regression | **Cancer-specific survival**<br>Localised stage<br>**Major cities (Ref.)**<br>Inner Regional<br>EMRR=0.83 (0.68, 1.01)<br>Rural<br>EMRR=0.78 (0.57, 1.08)<br>Non-localised stage<br>**Major cities (Ref.)**<br>Inner Regional<br>EMRR=1.00 (0.92, 1.09)<br>Rural<br>EMRR=1.25 (1.11, 1.41) | Age at diagnosis, at-risk period, area-level socio-economic status<br>Stratified by disease stage at diagnosis |
| Yu et al, 2014 | Australia | New South Wales Central Cancer Registry<br>**Sample size**<br>**68,686** | New South Wales | 1982-2007 | 18-84 | Prostate | Australian Standard Geographic Classification–Remoteness Area (ASGC-RA) | 3 | Relative survival (period analysis), Relative excess risk using Poisson regression | **Cancer-specific survival**<br>Unadjusted<br>**Major cities (Ref.)**<br>Inner Regional<br>EMRR=1.36 (1.25, 1.47)<br>Rural<br>EMRR=1.66 (1.49, 1.86) | Age at diagnosis, spread of disease at diagnosis, prostate cancer incidence rate, at-risk period, years of follow-up, and area-level socio-economic status |

| Paper | Country of study | Data sources or Settings / Sample size | Population included | Years of diagnosis | Age range | Anatomic site of cancer(s) | Measures of area of residence | No. of groups | Analyses | Results (95% CI) | Covariate adjusted for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Adjusted for age and at-risk period<br>**Major cities (Ref.)**<br>Inner Regional<br>EMRR=1.31 (1.22, 1.41)<br>Rural<br>EMRR=1.61 (1.46, 1.77)<br>Additional adjustment for spread of disease, incident rate and socio-economic status<br>**Major cities (Ref.)**<br>Inner Regional<br>EMRR=1.18 (1.10, 1.27)<br>Rural<br>EMRR=1.32 (1.19, 1.46) | . |

**Supplementary Table 4.3.** Risk of bias of included studies using Risk of Bias In Non-Randomised Studies-of Exposures (ROBINS-E)

| Review | Risk of bias due to confounding | Risk of bias in selection of participants into the study | Risk of bias in measurement of exposure(s) | Risk of bias due to inappropriate adjustment (e.g. adjusting for potential mediators) | Risk of bias due to missing data | Risk of bias in measurement of outcomes | Risk of bias in selection of the reported result | Overall bias* |
|---|---|---|---|---|---|---|---|---|
| **1.** Anuradha et al, 2014 | Moderate | Low | Low | High | High | Low | Low | Critical |
| **2.** Baade et al, 2013 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **3.** Baade et al, 2011 | Moderate | Low | Low | Low | No information | Low | Low | Moderate |
| **4.** Beckmann et al, 2016 | Low | Low | Low | High | Low | Low | Low | Critical |
| **5.** Bennett et al, 2007 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **6.** Bonett et al, 1984 | Moderate | Low | Low | Low | No information | Low | Low | Moderate |
| **7.** Brewer et al, 2009 | Low | Low | Low | High | Low | Low | Low | Critical |
| **8.** Chen et al, 2015 | Moderate | Low | Low | Moderate | Moderate | Low | Moderate | Serious |
| **9.** Chow et al, 2015 | Low | Low | Low | High | Moderate | Low | Low | Critical |
| **10.** Coory et al, 2006 | Moderate | Low | Low | High | Low | Low | Low | Critical |
| **11.** Crowell et al, 2007 | Moderate | Low | Low | High | Low | Low | Low | Serious |
| **12.** Dasgupta et al, 2012 | Low | Low | Low | High | Low | No information | Low | Critical |
| **13.** Eggleston et al, 2006 | Low | Low | Low | High | Moderate | No information | Low | Critical |
| **14.** Fitzgerald et al, 2014 | Low | Low | Low | Low | Low | No information | Low | Low |
| **15.** Gorey et al, 2008 | Moderate | Low | Low | Low | Low | No information | Low | Moderate |
| **16.** Hallet et al, 2015 | Low | Low | Low | High | Low | Low | Low | Critical |
| **17.** Hall et al, 2005 | Low | Low | Low | High | High | Low | Low | Critical |
| **18.** Hines et al, 2014 | Moderate | Low | Low | High | Moderate | No information | Low | Critical |
| **19.** Jong et al, 2004 | Moderate | Low | Low | High | High | Low | Low | Critical |
| **20.** Klein et al, 2011 | Low | Low | No information | High | Low | Low | Low | Critical |
| **21.** Kneuertz et al, 2014 | High | Low | Low | Low | High | No information | Low | Critical |
| **22.** Krzyżak et al, 2010 | Moderate | Low | Low | High | Low | Low | Low | Critical |

| Review | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of exposure(s) | Bias due to inappropriate adjustment (adjusting for potential mediators) | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall bias* |
|---|---|---|---|---|---|---|---|---|
| **23.** Lee et al, 2014 | Moderate | Low | Low | High | Moderate | Low | Low | Critical |
| **24.** Markossian et al, 2012 | Low | Low | Low | High | High | Low | Low | Critical |
| **25.** Markossian et al, 2016 | Low | High | Low | High | High | Low | Low | Critical |
| **26.** Martinez et al, 2012 | Moderate | Low | Low | High | Moderate | No information | Low | Critical |
| **27.** Martin et al, 2015 | Moderate | High | Low | Low | Low | No information | Low | Critical |
| **28.** Mitchell et al, 2006 | Moderate | Low | Low | High | High | Low | Low | Critical |
| **29.** Modesitt et al, 2006 | Low | Low | Low | High | High | No information | Low | Critical |
| **30.** Mohamadi Johnson et al, 2014 | Low | Low | Low | High | High | No information | Low | Critical |
| **31.** Nennecke et al, 2014 | Moderate | Low | Low | High | High | No information | Moderate | Critical |
| **32.** O'Malley et al, 2003 | Low | High | Low | High | Moderate | Low | Low | Critical |
| **33.** Panchal et al, 2016 | Low | High | Low | High | Low | No information | Low | Critical |
| **34.** Papa et al, 2014 | Low | High | Low | High | Low | Low | Low | Critical |
| **35.** Pozet et al, 2008 | Moderate | Low | Low | High | High | Low | Low | Critical |
| **36.** Raju et al, 2015 | Low | Low | Low | High | Low | Low | Low | Critical |
| **37.** Robsahm et al, 2005 | Low | Low | Low | Moderate | Low | No information | Low | Moderate |
| **38.** Rolland-Portal et al, 1997 | Moderate | Low | No information | High | Moderate | Low | Low | Critical |
| **39.** Rybojad et al, 2013 | High | High | Low | Low | Low | Low | Low | Critical |
| **40.** Sankaranarayanan et al, 2014 | Moderate | Low | Low | High | Low | Low | Low | Critical |
| **41.** Singla et al, 2013 | Low | Low | Low | High | No information | No information | Low | Critical |
| **42.** Wang et al, 2013 | Moderate | Low | Low | High | Moderate | No information | Low | Critical |
| **43.** Wong et al, 2016 | Low | High | Low | Low | Low | Low | Low | Critical |
| **44.** Yu et al, 2015 | Moderate | Low | Low | Moderate | Low | Low | Low | Moderate |
| **45.** Yu et al, 2014 | Moderate | Low | Low | High | High | Low | Low | Critical |




**Supplementary Figure 4.1.** Directed acyclic graph (DAG) showing assumed causal association between place of residence and cancer survival

**Appendix D** Supplementary material related to publication presented in Chapter 7

**Supplementary Table 7.1.** Excess mortality rate ratios (EMRRs) for men compared with women, by age at diagnosis

| | Age at diagnosis (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 15-44 | 45-54 | 55-64 | 65-74 | 75+ | p-trend* | p-departure from linearity* |
| Cancer site | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | | |
| Head and neck | 1.12 (0.88, 1.42) | 1.42 (1.20, 1.68) | 1.27 (1.13, 1.43) | 1.25 (1.11, 1.40) | 0.94 (0.83, 1.07) | 0.001 | 0.02 |
| Esophagus | 1.70 (1.11, 2.60) | 1.59 (1.26, 2.02) | 1.27 (1.12, 1.45) | 1.20 (1.09, 1.33) | 0.95 (0.88, 1.04) | <0.001 | 0.6 |
| Colorectum | 0.97 (0.87, 1.09) | 1.14 (1.07, 1.23) | 1.11 (1.06, 1.17) | 1.05 (1.00, 1.09) | 0.96 (0.92, 1.01) | 0.001 | 0.005 |
| Pancreas | 1.59 (1.24, 2.04) | 1.11 (0.97, 1.26) | 1.19 (1.10, 1.30) | 1.07 (1.01, 1.14) | 0.98 (0.92, 1.03) | <0.001 | 0.2 |
| Lung, bronchus and trachea | 1.25 (1.09, 1.43) | 1.23 (1.15, 1.31) | 1.17 (1.12, 1.22) | 1.10 (1.07, 1.14) | 0.99 (0.96, 1.03) | <0.001 | 0.3 |
| Bone and cartilages | 1.59 (1.14, 2.22) | 1.21 (0.56, 2.60) | 1.76 (0.84, 3.69) | 1.25 (0.74, 2.12) | 1.24 (0.77, 1.99) | 0.4 | 0.9 |
| Melanoma | 2.18 (1.86, 2.55) | 2.42 (1.99, 2.92) | 1.92 (1.63, 2.27) | 1.82 (1.49, 2.23) | 1.65 (1.33, 2.05) | 0.008 | 0.5 |
| Mesothelioma | 3.32 (1.60, 6.88) | 1.03 (0.74, 1.44) | 1.09 (0.86, 1.37) | 1.07 (0.88, 1.30) | 1.09 (0.92, 1.30) | 0.3 | 0.04 |
| Kidney | 1.59 (1.20, 2.12) | 1.29 (1.05, 1.57) | 1.41 (1.22, 1.64) | 1.09 (0.96, 1.24) | 1.03 (0.92,1.15) | <0.001 | 0.3 |
| Bladder | 0.95 (0.57, 1.60) | 0.77 (0.58, 1.03) | 0.81 (0.67, 0.96) | 0.77 (0.68, 0.87) | 0.69 (0.63, 0.75) | 0.06 | 0.8 |
| Renal pelvis, ureter, other/unspecified | 1.43 (0.37, 5.44) | 0.83 (0.47, 1.45) | 0.69 (0.50, 0.95) | 0.78 (0.62, 0.99) | 0.79 (0.64, 0.96) | 1.0 | 0.5 |
| Thyroid | 5.23 (2.14, 12.8) | 3.43 (1.79, 6.57) | 2.65 (1.72, 4.09) | 1.33 (0.93, 1.90) | 0.71 (0.48, 1.05) | <0.001 | 0.9 |
| Non-Hodgkin Lymphoma | 1.47 (1.25, 1.73) | 1.37 (1.18, 1.60) | 1.37 (1.23, 1.54) | 1.09 (0.99, 1.19) | 0.95 (0.88, 1.02) | <0.001 | 0.3 |

CI, confidence interval; ***** likelihood ratio test (p <0.05 was considered statistically significant)

**Supplementary Table 7.2.** Excess mortality rate ratios (EMRRs) for men compared with women, by time since diagnosis

| | Time since diagnosis (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | p-trend* | p-departure from linearity* |
| **Cancer site** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | | |
| Head and neck | 1.17 (1.08, 1.28) | 1.17 (1.04, 1.32) | 1.19 (0.99, 1.72) | 1.36 (1.08, 1.72) | 1.38 (1.03, 1.84) | 0.2 | 0.9 |
| Esophagus | 1.08 (1.01, 1.15) | 1.23 (1.08, 1.40) | 1.29 (1.02, 1.62) | 1.18 (0.80, 1.74) | 2.30 (1.20, 4.37) | 0.002 | 0.4 |
| Colorectum | 0.99 (0.96, 1.03) | 1.05 (0.99, 1.10) | 1.15 (1.08, 1.24) | 1.13 (1.03, 1.25) | 1.22 (1.08, 1.39) | <0.001 | 0.6 |
| Pancreas | 1.08 (1.04, 1.12) | 1.04 (0.94, 1.15) | 0.90 (0.74, 1.12) | 1.33 (0.91, 1.95) | 0.69 (0.41, 1.78) | 0.1 | 0.2 |
| Lung, bronchus and trachea | 1.09 (1.07, 1.12) | 1.11 (1.06, 1.16) | 1.06 (0.97, 1.15) | 1.10 (0.97, 1.25) | 1.01 (0.85, 1.20) | 0.3 | 0.6 |
| Bone and cartilages | 1.42 (1.02, 1.96) | 1.27 (0.86, 1.86) | 1.99 (1.04, 3.79) | 1.24 (0.62, 2.50) | 2.11 (0.70, 6.34) | 0.6 | 0.7 |
| Melanoma | 2.05 (1.78, 2.35) | 2.05 (1.75, 2.41) | 2.00 (1.64, 2.43) | 2.05 (1.62, 2.58) | 1.78 (1.32, 2.39) | 0.5 | 0.9 |
| Mesothelioma | 1.04 (0.92, 1.19) | 1.14 (0.92, 1.43) | 2.04 (1.33, 3.15) | 1.19 (0.67, 2.09) | 0.96 (0.46, 1.98) | 0.2 | 0.08 |
| Kidney | 1.12 (1.03, 1.22) | 1.18 (0.99, 1.41) | 1.58 (1.25, 2.00) | 1.48 (1.08, 2.04) | 1.17 (0.82, 1.68) | 0.02 | 0.2 |
| Bladder | 0.65 (0.60, 0.71) | 0.72 (0.63, 0.83) | 1.22 (0.96, 1.54) | 0.98 (0.73, 1.31) | 0.85 (0.56, 1.29) | <0.001 | 0.03 |
| Renal pelvis, ureter, other/unspecified | 0.79 (0.67, 0.94) | 0.63 (0.47, 0.83) | 0.97 (0.67, 1.41) | 0.82 (0.47, 1.42) | 0.61 (0.26, 1.44) | 0.9 | 0.2 |
| Thyroid | 1.33 (1.06, 1.66) | 1.79 (1.04, 3.08) | 14.91 (0.52, 427.5) | 2.22 (0.73, 6.77) | 2.87 (0.91, 9.05) | 0.05 | 0.7 |
| Non-Hodgkin Lymphoma | 1.11 (1.05, 1.18) | 1.18 (1.06, 1.32) | 1.17 (1.00, 1.38) | 1.15 (0.95, 1.39) | 1.11 (0.89, 1.38) | 0.7 | 0.8 |

CI, confidence interval; ***** likelihood ratio test (p <0.05 was considered statistically significant)

**Supplementary Table 7.3.** Excess mortality rate ratios (EMRRs) for men compared with women, by year of diagnosis

| | Year of diagnosis | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1982-1986 | 1987-1991 | 1992-1996 | 1997-2001 | 2002-2006 | 2007-2011 | 2012-2015 | p-trend* | p-departure from linearity* |
| **Cancer site** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | | |
| Head and neck | 1.03 (0.88, 1.19) | 1.14 (0.98, 1.32) | 1.24 (1.06, 1.44) | 1.27 (1.08, 1.49) | 1.19 (1.01, 1.39) | 1.12 (0.96, 1.32) | 1.63 (1.29, 2.07) | 0.1 | 0.02 |
| Esophagus | 1.25 (1.07, 1.46) | 1.10 (0.96, 1.26) | 1.10 (0.96, 1.26) | 1.20 (1.04, 1.38) | 1.09 (0.95, 1.26) | 1.03 (0.90, 1.18) | 1.15 (0.97, 1.37) | 0.2 | 0.3 |
| Colorectum | 1.08 (1.01, 1.15) | 1.10 (1.03, 1.16) | 1.01 (0.95, 1.07) | 1.02 (0.96, 1.09) | 1.03 (0.97, 1.10) | 1.00 (0.94, 1.07) | 1.00 (0.91, 1.09) | 0.002 | 0.2 |
| Pancreas | 1.26 (1.13, 1.40) | 1.09 (0.98, 1.21) | 1.03 (0.93, 1.13) | 0.99 (0.91, 1.09) | 1.11 (1.01, 1.21) | 1.02 (0.94, 1.11) | 1.03 (0.93, 1.13) | 0.001 | 0.001 |
| Lung, bronchus and trachea | 1.05 (0.99, 1.11) | 1.03 (0.98, 1.09) | 1.02 (0.97, 1.07) | 1.10 (1.05, 1.16) | 1.10 (1.05, 1.15) | 1.15 (1.09, 1.20) | 1.21 (1.15, 1.28) | <0.001 | <0.001 |
| Bone and cartilages | 1.48 (0.87, 2.53) | 1.51 (0.90, 2.54) | 1.34 (0.83, 2.15) | 1.34 (0.72, 2.49) | 1.50 (0.77, 2.91) | 1.09 (0.65, 1.84) | 3.63 (1.26, 10.49) | 0.6 | 0.6 |
| Melanoma | 1.92 (1.60, 2.32) | 2.20 (1.78, 2.72) | 2.18 (1.71, 2.77) | 2.02 (1.62, 2.52) | 1.92 (1.56, 2.37) | 2.33 (1.88, 2.90) | 1.50 (1.13, 1.99) | 0.9 | <0.001 |
| Mesothelioma | 1.35 (0.75, 2.43) | 1.06 (0.71, 1.58) | 0.86 (0.64, 1.15) | 1.09 (0.84, 1.40) | 1.24 (0.97, 1.57) | 1.17 (0.94, 1.46) | 1.16 (0.87, 1.53) | 0.4 | 0.4 |
| Kidney | 1.17 (0.96, 1.43) | 1.28 (1.08, 1.52) | 1.12 (0.95, 1.32) | 1.39 (1.17, 1.64) | 1.10 (0.93, 1.31) | 1.09 (0.92, 1.30) | 1.04 (0.83, 1.31) | 0.1 | 0.07 |
| Bladder | 0.86 (0.72, 1.02) | 0.76 (0.64, 0.91) | 0.73 (0.62, 0.87) | 0.65 (0.55, 0.78) | 0.72 (0.61, 0.85) | 0.71 (0.61, 0.82) | 0.70 (0.58, 0.86) | 0.05 | <0.001 |
| Renal pelvis, ureter, other/unspecified | 0.66 (0.45, 0.96) | 0.63 (0.41, 0.96) | 0.83 (0.59, 1.18) | 0.90 (0.65, 1.25) | 1.03 (0.76, 1.42) | 0.73 (0.53, 1.00) | 0.57 (0.40, 0.82) | 0.9 | 0.2 |
| Thyroid | 1.22 (0.78, 1.91) | 1.03 (0.64, 1.67) | 1.49 (0.82, 2.70) | 1.69 (0.99, 2.89) | 1.71 (1.01, 2.89) | 1.33 (0.79, 2.34) | 2.32 (1.29, 4.18) | 0.04 | 1.0 |
| Non-Hodgkin Lymphoma | 1.09 (0.97, 1.24) | 1.16 (1.03, 1.31) | 1.10 (0.99, 1.23) | 1.20 (1.07, 1.34) | 1.06 (0.94, 1.19) | 1.17 (1.03, 1.34) | 1.12 (0.94, 1.34) | 0.7 | <0.001 |

CI, confidence interval; ***** likelihood ratio test (p <0.05 was considered statistically significant)

**Supplementary Table 7.4.** Lung cancer five-year age-standardized net survival and excess mortality rate ratios (EMRRs) for men compared with women, by histological type

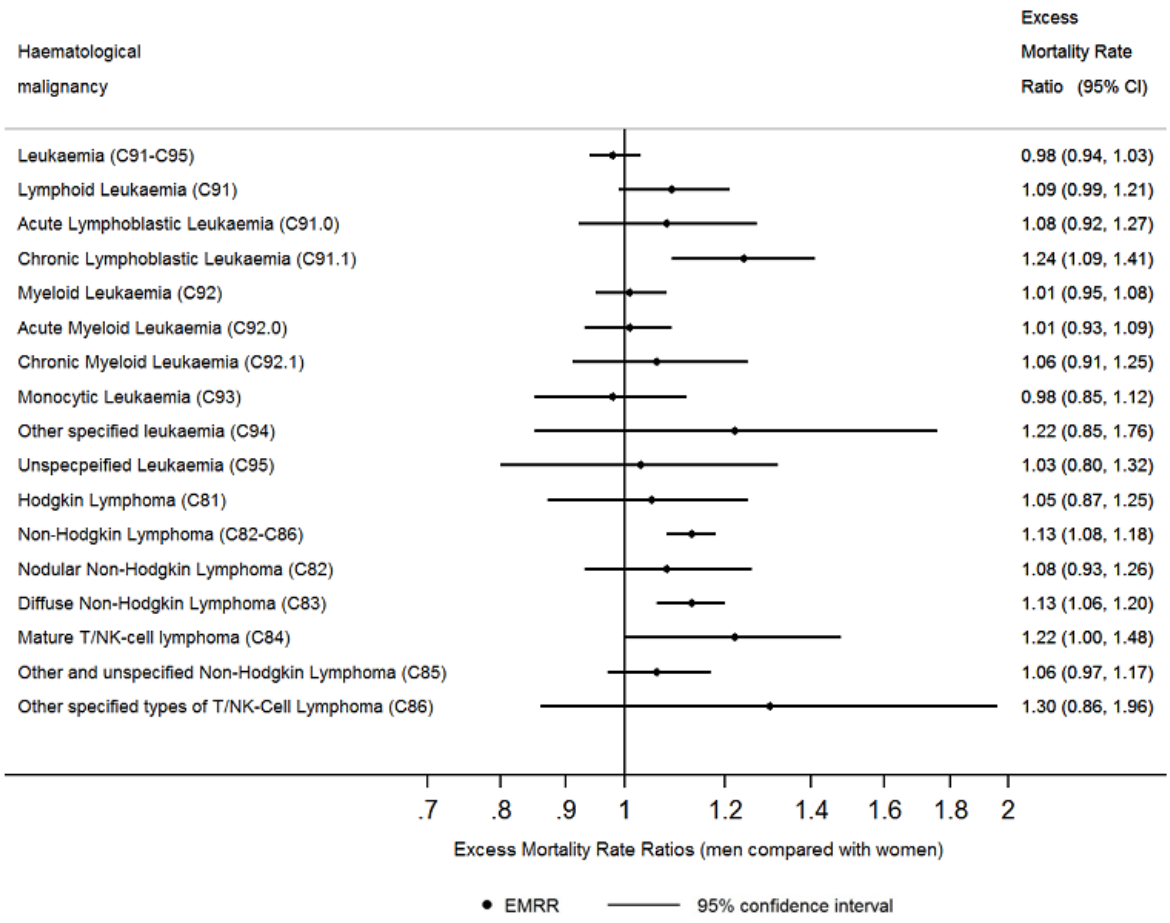
| Histological classification | Men | Women | Men vs Women | |
|---|---|---|---|---|
| | Net survival (95% CI) | Net survival (95% CI) | EMRR (95% CI) | p-value (LR test) |
| Squamous cell carcinoma | 15.8 (15.0, 16.7) | 15.7 (14.2, 17.2) | 0.94 (0.89, 0.98) | 0.007 |
| Adenocarcinoma | 15.1 (14.3, 16.0) | 20.4 (19.3, 21.6) | 1.23 (1.18, 1.27) | <0.001 |
| Large cell carcinoma | 7.9 (7.1, 8.7) | 9.2 (8.1, 10.5) | 1.03 (0.98, 1.08) | 0.3 |
| Small cell carcinoma | 4.2 (3.6, 4.9) | 6.4 (5.5, 7.4) | 1.12 (1.07, 1.18) | <0.001 |

CI, confidence interval; LR, likelihood ratio (p <0.05 was considered statistically significant)

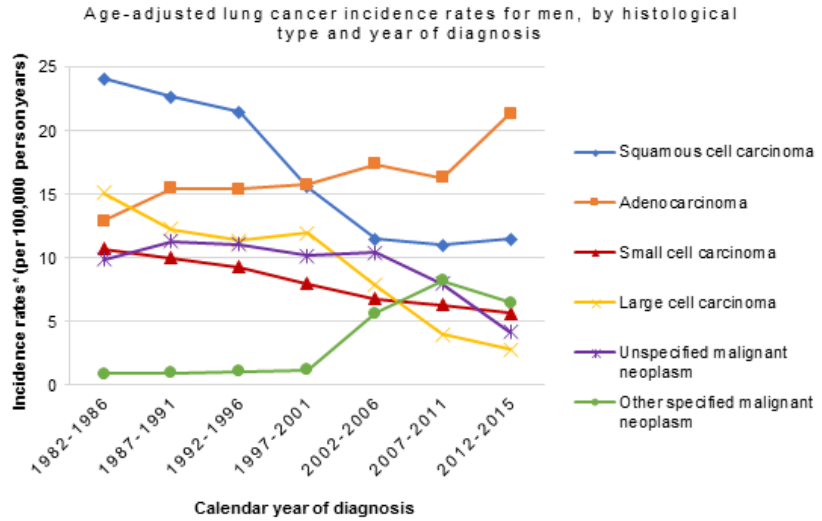
**Supplementary Table 7.5.** Lung cancer excess mortality rate ratios (EMRRs) for men compared with women, by histological type and period of diagnosis

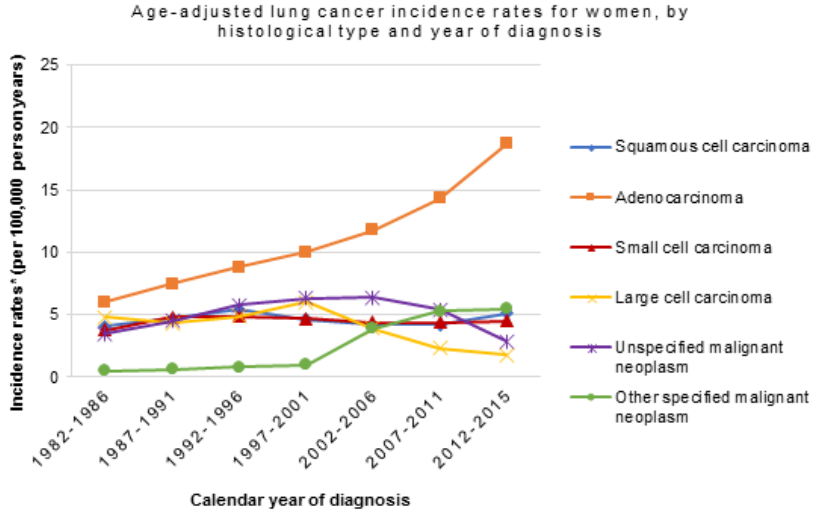
| Histological classification | 1982-1986 | 1987-1991 | 1992-1996 | 1997-2001 | 2002-2006 | 2007-2011 | 2012-2015 | p-trend* | p-departure from linearity* |
|---|---|---|---|---|---|---|---|---|---|
| | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | | |
| Squamous cell carcinoma | 1.01 (0.89, 1.16) | 0.84 (0.75, 0.94) | 0.91 (0.82, 1.02) | 0.92 (0.82, 1.04) | 0.97 (0.85, 1.10) | 1.01 (0.89, 1.15) | 0.94 (0.82, 1.09) | 0.4 | 0.002 |
| Adenocarcinoma | 1.13 (1.00, 1.27) | 1.26 (1.14, 1.40) | 1.21 (1.10, 1.34) | 1.28 (1.17, 1.41) | 1.20 (1.11, 1.31) | 1.20 (1.11, 1.30) | 1.28 (1.17, 1.40) | 0.6 | 0.06 |
| Large cell carcinoma | 1.03 (0.91, 1.16) | 1.07 (0.94, 1.21) | 0.92 (0.82, 1.03) | 1.10 (0.98, 1.22) | 1.07 (0.93, 1.22) | 1.02 (0.85, 1.21) | 0.95 (0.76, 1.18) | 0.7 | <0.001 |
| Small cell carcinoma | 1.11 (0.96, 1.27) | 1.01 (0.90, 1.15) | 1.07 (0.95, 1.21) | 1.12 (0.99, 1.26) | 1.18 (1.03, 1.34) | 1.17 (1.04, 1.33) | 1.22 (1.05, 1.42) | 0.09 | 0.9 |

CI, confidence interval; ***** likelihood ratio test (p <0.05 was considered statistically significant)




**Supplementary Figure 7.1.** Excess mortality rate ratios (EMRRs) within five years post diagnosis for men compared with women, 1982-2015




*The incidence rates are age-adjusted to the Victorian population according to year of diagnosis

**Supplementary Figure 7.2.** Age-adjusted lung cancer incidence rates (per 100,000 person-years) for men and women by histological type and year of diagnosis.

**Appendix E** Supplementary material related to publication presented in Chapter 8

**S 8.1 Table.** Number of cases and deaths by area-level socio-economic disadvantage in Victoria, Australia, 2001-2015

| ICD-10 | Cancer site | Q1 (Least disadvantaged) | | Q2 | | Q3 | | Q4 | | Q5 (Most disadvantaged) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Cases* | *Deaths* | *Cases* | *Deaths* | *Cases* | *Deaths* | *Cases* | *Deaths* | *Cases* | *Deaths* |
| C00-14, C30-32 | Head and neck | 1,719 | 552 | 1,923 | 640 | 2,142 | 802 | 2,398 | 984 | 3,034 | 1,370 |
| C15 | Oesophagus | 606 | 459 | 675 | 496 | 717 | 579 | 903 | 743 | 1,060 | 866 |
| C16 | Stomach | 1,034 | 719 | 1,214 | 857 | 1,311 | 946 | 1,471 | 1,088 | 1,798 | 1,353 |
| C17 | Small intestine | 227 | 92 | 249 | 122 | 224 | 103 | 223 | 85 | 282 | 133 |
| C18-20 | Colorectum | 7,697 | 3,243 | 8,023 | 3,493 | 8,708 | 3,928 | 9,588 | 4,602 | 10,487 | 5,269 |
| C21 | Anus and anal canal | 215 | 66 | 190 | 77 | 203 | 81 | 232 | 95 | 243 | 119 |
| C22 | Liver | 653 | 502 | 783 | 609 | 805 | 619 | 937 | 746 | 1371 | 1,079 |
| C23-24 | Gallbladder and biliary tract | 349 | 258 | 362 | 283 | 451 | 352 | 428 | 339 | 604 | 481 |
| C25 | Pancreas | 1,365 | 1,182 | 1,384 | 1,198 | 1,454 | 1,277 | 1,641 | 1,459 | 1,900 | 1,699 |
| C33-34 | Lung, bronchus and trachea | 3,851 | 3,127 | 4,518 | 3,646 | 5,335 | 4,395 | 6,577 | 5,493 | 8,701 | 7,307 |
| C43 | Melanoma | 6,800 | 1,130 | 5,862 | 1,128 | 5,802 | 1,220 | 5,553 | 1,346 | 4,650 | 1,268 |
| C45 | Mesothelioma | 299 | 262 | 301 | 270 | 365 | 329 | 359 | 328 | 392 | 362 |
| C47-49 | Connective and soft tissue | 411 | 128 | 424 | 174 | 375 | 145 | 378 | 171 | 365 | 181 |
| C50 | Female breast | 10,510 | 1,671 | 9,612 | 1,666 | 9,326 | 1,867 | 9,104 | 2,018 | 8,991 | 2,176 |
| C53 | Cervix | 394 | 87 | 439 | 109 | 444 | 124 | 505 | 154 | 587 | 184 |
| C54-55 | Uterus | 1,311 | 278 | 1,373 | 293 | 1,416 | 307 | 1,480 | 333 | 1,708 | 433 |
| C56 | Ovary | 816 | 475 | 813 | 463 | 866 | 521 | 896 | 577 | 916 | 581 |
| C51-52, C57 | Vulva, vagina, other/ unspecified | 267 | 120 | 259 | 99 | 299 | 121 | 314 | 147 | 389 | 157 |

| ICD-10 | Cancer site | Q1 (Least disadvantaged) | | Q2 | | Q3 | | Q4 | | Q5 (Most disadvantaged) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Cases* | *Deaths* | *Cases* | *Deaths* | *Cases* | *Deaths* | *Cases* | *Deaths* | *Cases* | *Deaths* |
| C61 | Prostate | 12,722 | 2,366 | 11,519 | 2,596 | 11,150 | 2,787 | 11,059 | 3,221 | 10,797 | 3,439 |
| C64 | Kidney | 1,403 | 454 | 1,492 | 494 | 1,572 | 519 | 1,783 | 634 | 1,996 | 849 |
| C67 | Bladder | 1,075 | 582 | 1,146 | 609 | 1,277 | 701 | 1,463 | 838 | 1,722 | 1,014 |
| C65-66, C68 | Renal pelvis, ureter, other/unspecified | 167 | 94 | 207 | 113 | 205 | 120 | 258 | 176 | 292 | 184 |
| C70-72 | Brain and central nervous system | 1,053 | 731 | 1,073 | 786 | 1,070 | 772 | 1,046 | 815 | 1,034 | 783 |
| C73 | Thyroid | 1,154 | 65 | 1,119 | 100 | 1,058 | 100 | 1,003 | 121 | 1,058 | 116 |
| C80 | Unknown primary | 959 | 806 | 1,131 | 970 | 1,337 | 1,169 | 1,584 | 1,414 | 1,994 | 1,780 |
| C81 | Hodgkin Lymphoma | 421 | 47 | 407 | 53 | 424 | 56 | 387 | 68 | 402 | 84 |
| C82-86 | Non-Hodgkin Lymphoma | 3,012 | 966 | 2,771 | 905 | 2,805 | 1,058 | 2,881 | 1,108 | 3,026 | 1,276 |
| C90 | Multiple Myeloma | 972 | 506 | 925 | 500 | 976 | 552 | 1,041 | 615 | 1,107 | 690 |
| C91-95 | Leukaemia | 1,595 | 719 | 1,636 | 804 | 1,680 | 848 | 1,789 | 985 | 1,920 | 1,071 |

**S 8.2 Table.** Five-year age-standardised net survival by area-level socio-economic disadvantage in Victoria, Australia, 2001-2015

| | | Q1 (Least disadvantaged) | Q2 | Q3 | Q4 | Q5 (Most Disadvantaged) |
|---|---|---|---|---|---|---|
| **ICD-10** | **Cancer site** | **Net survival % (95% CI)** | **Net survival % (95% CI)** | **Net survival % (95% CI)** | **Net survival % (95% CI)** | **Net survival % (95% CI)** |
| C00-C14, C30-C32 | Head and Neck | 77.6 (74.7 – 80.2) | 78.0 (75.1 – 80.6) | 74.5 (71.8 – 77.0) | 70.6 (68.0 – 73.0) | 65.9 (63.6 – 68.1) |
| C15 | Oesophagus | 25.1 (21.2 – 29.3) | 27.9 (23.9 – 32.0) | 18.8 (15.5 – 22.3) | 17.0 (14.1 – 20.1) | 17.4 (14.7 – 20.2) |
| C16 | Stomach | 32.7 (29.1 – 36.3) | 31.1 (28.0 – 34.2) | 28.0 (25.0 – 31.0) | 26.0 (23.3 – 28.7) | 27.2 (24.8 – 29.8) |
| C17 | Small intestine | 64.5 (55.7 – 72.0) | 56.8 (49.1 – 63.8) | 59.8 (51.4 – 67.2) | 66.7 (57.6 – 74.3) | 63.7 (56.1 – 70.3) |
| C18-20 | Colorectum | 71.5 (70.0 – 72.9) | 68.3 (66.8 – 69.7) | 67.0 (65.6 – 68.3) | 65.5 (64.1 – 66.8) | 62.9 (61.7 – 64.2) |
| C21 | Anal and anal canal | 74.5 (65.5 – 81.5) | 71.1 (61.2 – 79.0) | 67.9 (59.4 – 75.1) | 69.3 (60.1 – 76.8) | 61.5 (53.5 – 68.5) |
| C22 | Liver | 19.7 (16.3 – 23.3) | 18.6 (15.4 – 21.9) | 16.8 (13.8 – 20.0) | 15.4 (12.6 – 18.5) | 16.8 (14.5 – 19.4) |
| C23-C24 | Gallbladder and biliary tract | 22.5 (17.4 – 28.0) | NA | 24.8 (20.2 – 29.7) | 18.5 (14.3 – 23.2) | 19.8 (16.0 – 23.8) |
| C25 | Pancreas | 8.7 (7.0 – 10.6) | 9.6 (7.7 – 11.7) | 7.7 (6.1 – 9.5) | 6.5 (5.2 – 8.1) | 8.7 (7.2 – 10.4) |
| C33-C34 | Lung, bronchus, and trachea | 17.7 (16.3 – 19.2) | 17.4 (16.1 – 18.7) | 16.8 (15.6 – 18.0) | 15.3 (14.2 – 16.4) | 14.2 (13.3 – 15.1) |
| C43 | Melanoma | 93.2 (91.8 – 94.4) | 92.0 (90.6 – 93.3) | 90.6 (89.1 – 91.9) | 89.3 (87.8 – 90.6) | 88.4 (86.7 – 89.9) |
| C45 | Mesothelioma | 7.9 (4.8 – 12.1) | 7.5 (4.4 – 11.5) | NA | 4.8 (2.7 – 7.8) | NA |
| C47-C49 | Connective and soft tissue | 74.2 (67.8 – 79.5) | 65.9 (59.5 – 71.5) | 67.4 (60.4 – 73.5) | 63.4 (57.0 – 69.2) | 58.6 (51.8 – 64.8) |
| C50 | Female Breast | 92.6 (91.6 – 93.5) | 90.4 (89.4 – 91.4) | 89.6 (88.6 – 90.6) | 89.1 (88.0 – 90.1) | 87.7 (86.7 – 88.7) |
| C53 | Cervix | 77.2 (72.4 – 81.3) | 76.1 (71.4 – 80.2) | 74.9 (70.0 – 79.1) | 72.4 (67.8 – 76.5) | 74.3 (70.2 – 78.0) |
| C54-C55 | Uterus | 87.1 (84.1 – 89.5) | 86.2 (83.4 – 88.6) | 85.4 (82.4 – 87.9) | 85.2 (82.4 – 87.6) | 84.0 (81.5 – 86.3) |

| | | Q1 (Least disadvantaged) | Q2 | Q3 | Q4 | Q5 (Most Disadvantaged) |
|---|---|---|---|---|---|---|
| **ICD-10** | **Cancer site** | **Net survival % (95% CI)** | **Net survival % (95% CI)** | **Net survival % (95% CI)** | **Net survival % (95% CI)** | **Net survival % (95% CI)** |
| C56 | Ovary | 44.1 (40.4 – 47.7) | 42.5 (38.8 – 46.1) | 41.7 (38.0 – 45.3) | 38.9 (35.3 – 42.1) | 40.7 (37.2 – 44.2) |
| C51-C52-C57 | Vulva, vagina, other/unspecified | 61.6 (53.3 – 68.9) | 73.9 (64.6 – 81.1) | 65.8 (578.4 – 72.9) | 60.2 (53.0 – 66.7) | 63.9 (56.8 – 70.2) |
| C61 | Prostate | 94.1 (93.1 – 94.9) | 93.3 (92.3 – 94.2) | 92.3 (91.2 – 93.2) | 91.4 (90.3 – 92.3) | 90.2 (89.1 – 91.2) |
| C64 | Kidney | 74.7 (71.6 – 77.5) | 72.9 (69.9 – 75.7) | 74.7 (71.6 – 77.4) | 73.6 (70.9 – 76.1) | 68.0 (65.4 – 70.4) |
| C67 | Bladder | 57.8 (53.7 – 61.8) | 54.7 (50.5 – 58.8) | 54.0 (50.0 – 57.8) | 52.1 (48.2 – 55.8) | 49.0 (45.5 – 52.4) |
| C65-C66-C68 | Renal pelvis, ureter, other/unspecified urinary organs | 51.1 (41.6 – 59.8) | 44.5 (35.5 – 53.1) | 39.8 (32.1 – 47.4) | 39.8 (32.1 – 47.4) | 37.8 (30.7 – 44.9) |
| C70-C72 | Brain and CNS | 26.0 (23.5 – 28.6) | 24.0 (21.5 – 26.5) | 24.6 (22.1 – 27.1) | 22.4 (19.9 – 25.0) | 23.7 (21.2 – 26.3) |
| C73 | Thyroid | 96.6 (94.1 – 98.0) | 94.9 (92.6 – 96.4) | 94.8 (92.2 – 96.5) | 94.0 (91.5 – 95.7) | 93.9 (91.3 – 95.7) |
| C80 | Unknown primary | 16.9 (14.3 – 19.6) | 16.8 (14.4 – 19.4) | 13.3 (11.2 – 15.5) | 13.4 (11.4 – 15.5) | 12.6 (10.9 – 14.4) |
| C81 | Hodgkin Lymphoma | 89.7 (85.8 – 92.6) | 89.4 (85.9 – 92.0) | 88.5 (84.4 – 91.6) | 88.6 (85.0 – 91.5) | 86.2 (82.5 – 89.1) |
| C82-85 | Non-Hodgkin Lymphoma | 77.8 (75.6 – 79.8) | 75.8 (73.5 – 78.0) | 72.7 (70.4 – 74.7) | 71.5 (69.3 – 73.7) | 69.0 (66.8 – 71.1) |
| C90 | Multiple Myeloma | 50.8 (46.5 – 55.0) | 46.8 (42.8 – 50.7) | 50.0 (45.9 – 53.9) | 45.6 (41.8 – 49.4) | 47.3 (43.4 – 51.2) |
| C91-C95 | Leukaemia | 53.8 (50.6 – 56.8) | 52.7 (49.6 – 55.6) | 54.1 (51.0 – 57.0) | 53.0 (50.1 – 55.8) | 52.4 (49.6 – 55.1) |

CI, confidence interval; NA, not available (age-standardised net survival cannot be estimated)

**S 8.3 Table.** Five-year excess mortality rate ratios (EMRRs), by year of diagnosis, per quintile increase in socio-economic disadvantage (SEIFA)

| | | Year of diagnosis | | | | |
|---|---|---|---|---|---|---|
| **ICD-10** | **Cancer site** | **2001-2005 EMRR (95% CI)** | **2006-2010 EMRR (95% CI)** | **2011-2015 EMRR (95% CI)** | **P-trend^** | **P-departure from linearity^** |
| C00-14, C30-32 | Head and neck | 1.10 (1.04, 1.15) | 1.17 (1.11, 1.23) | 1.19 (1.12, 1.26) | 0.03 | 0.3 |
| C15 | Oesophagus | 1.09 (1.04, 1.14) | 1.10 (1.05, 1.15) | 1.02 (0.97, 1.07) | 0.06 | 0.3 |
| C16 | Stomach | 1.05 (1.01, 1.09) | 1.07 (1.03, 1.11) | 1.02 (0.98, 1.06) | 0.4 | 0.3 |
| C18-20 | Colorectum | 1.07 (1.05, 1.09) | 1.10 (1.07, 1.12) | 1.07 (1.04, 1.10) | 0.6 | 0.003 |
| C21 | Anus and anal canal | 1.23 (1.05, 1.45) | 1.15 (1.00, 1.33) | 1.00 (0.86, 1.17) | 0.1 | 0.9 |
| C22 | Liver | 1.03 (0.99, 1.08) | 1.03 (0.99, 1.07) | 1.04 (1.00, 1.09) | 0.8 | 0.9 |
| C23-24 | Gallbladder and biliary tract | 1.06 (1.00, 1.13) | 1.04 (0.98, 1.10) | 1.04 (0.97, 1.11) | 0.7 | 1.0 |
| C25 | Pancreas | 1.04 (1.01, 1.08) | 1.04 (1.01, 1.07) | 1.08 (1.05, 1.11) | 0.1 | 0.03 |
| C33-34 | Lung, bronchus, and trachea | 1.04 (1.02, 1.06) | 1.04 (1.03, 1.06) | 1.05 (1.03, 1.07) | 0.3 | 0.4 |
| C43 | Melanoma | 1.16 (1.09, 1.25) | 1.20 (1.13, 1.27) | 1.19 (1.10, 1.29) | 0.6 | 0.2 |
| C47-49 | Connective and soft tissue | 1.08 (0.97, 1.21) | 1.10 (0.99, 1.22) | 1.10 (0.98, 1.23) | 0.9 | 0.7 |
| C50 | Female breast | 1.13 (1.08, 1.18) | 1.12 (1.07, 1.17) | 1.20 (1.12, 1.27) | 0.3 | 0.6 |
| C56 | Ovary | 1.10 (1.05, 1.15) | 1.05 (1.00, 1.10) | 1.04 (0.98, 1.11) | 0.2 | 0.08 |
| C61 | Prostate | 1.13 (1.07, 1.18) | 1.19 (1.11, 1.27) | 1.09 (0.98, 1.20) | 0.1 | 0.001 |
| C64 | Kidney | 1.07 (1.01, 1.13) | 1.07 (1.01, 1.13) | 1.05 (0.98, 1.12) | 0.7 | 1.0 |
| C67 | Bladder | 1.07 (1.02, 1.13) | 1.08 (1.03, 1.14) | 1.05 (0.99, 1.12) | 0.7 | 0.6 |
| C70-72 | Brain and central nervous system | 1.03 (0.99, 1.07) | 1.05 (1.02, 1.10) | 1.09 (1.04, 1.14) | 0.08 | 0.7 |
| C80 | Unknown primary | 1.06 (1.02, 1.09) | 1.09 (1.05, 1.12) | 1.09 (1.05, 1.13) | 0.1 | 0.05 |
| C82-86 | Non-Hodgkin lymphoma | 1.13 (1.08, 1.18) | 1.12 (1.07, 1.17) | 1.05 (1.00, 1.11) | 0.07 | 0.1 |
| C90 | Multiple myeloma | 1.01 (0.96, 1.07) | 1.05 (1.00, 1.11) | 1.08 (1.01, 1.15) | 0.2 | 0.1 |
| C91-95 | Leukaemia | 1.05 (1.00, 1.09) | 1.02 (0.98, 1.06) | 1.03 (0.98, 1.08) | 0.7 | 0.7 |

CI, confidence interval; ^ likelihood ratio test; SEIFA, Socio-Economic Indexes for Areas

**S 8.4 Table.** Five-year excess mortality rate ratios (EMRRs), by time since diagnosis, per quintile increase in socio-economic disadvantage (SEIFA)

| | | Time since diagnosis (years) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | P-trend^ | P-departure from linearity^ |
| ICD-10 | Cancer site | EMRR (95% CI) | EMRR (95% CI) | EMRR (95% CI) | EMRR (95% CI) | EMRR (95% CI) | | |
| C00-14, C30-32 | Head and neck | 1.12 (1.07, 1.17) | 1.17 (1.10, 1.24) | 1.12 (1.02, 1.22) | 1.23 (1.09, 1.40) | 1.28 (1.11, 1.48) | 0.07 | 0.6 |
| C15 | Oesophagus | 1.06 (1.03, 1.10) | 1.10 (1.04, 1.17) | 1.10 (0.99, 1.22) | 1.12 (0.94, 1.34) | 1.11 (0.86, 1.43) | 0.2 | 1.0 |
| C16 | Stomach | 1.05 (1.02, 1.08) | 1.04 (0.99, 1.09) | 1.01 (0.93, 1.10) | 1.10 (0.95, 1.26) | 1.06 (0.89, 1.27) | 0.9 | 0.8 |
| C18-20 | Colorectum | 1.09 (1.07, 1.11) | 1.06 (1.03, 1.09) | 1.07 (1.03, 1.11) | 1.08 (1.03, 1.14) | 1.06 (0.99, 1.13) | 0.2 | 0.6 |
| C21 | Anus and anal canal | 1.16 (1.01, 1.34) | 1.10 (0.94, 1.29) | 1.22 (0.98, 1.50) | 1.17 (0.90, 1.50) | 0.18 (0.02, 1.41) | 0.5 | 0.1 |
| C22 | Liver | 1.05 (1.02, 1.08) | 1.01 (0.95, 1.07) | 0.95 (0.87, 1.04) | 1.02 (0.89, 1.16) | 1.14 (0.97, 1.34) | 0.4 | 0.1 |
| C23-24 | Gallbladder and biliary tract | 1.07 (1.02, 1.11) | 0.99 (0.92, 1.08) | 1.12 (0.98, 1.28) | 0.93 (0.76, 1.12) | 0.98 (0.68, 1.41) | 0.3 | 0.3 |
| C25 | Pancreas | 1.07 (1.05, 1.09) | 1.01 (0.97, 1.06) | 0.93 (0.85, 1.01) | 1.00 (0.85, 1.18) | 0.84 (0.67, 1.06) | <0.001 | 0.6 |
| C33-34 | Lung, bronchus, and trachea | 1.05 (1.04, 1.06) | 1.03 (1.00, 1.05) | 1.01 (0.97, 1.05) | 1.06 (1.00, 1.12) | 0.97 (0.89, 1.06) | 0.02 | 0.4 |
| C43 | Melanoma | 1.24 (1.16, 1.33) | 1.16 (1.07, 1.25) | 1.16 (1.06, 1.27) | 1.17 (1.04, 1.30) | 1.08 (0.93, 1.25) | 0.09 | 0.8 |
| C47-49 | Connective and soft tissue | 1.09 (1.00, 1.19) | 1.04 (0.91, 1.18) | 1.09 (0.90, 1.31) | 1.24 (0.95, 1.62) | 1.34 (1.00, 1.78) | 0.2 | 0.6 |
| C50 | Female breast | 1.21 (1.14, 1.28) | 1.14 (1.08, 1.21) | 1.10 (1.04, 1.16) | 1.11 (1.04, 1.18) | 1.11 (1.03, 1.19) | 0.03 | 0.6 |
| C56 | Ovary | 1.13 (1.08, 1.18) | 1.06 (0.99, 1.13) | 1.04 (0.96, 1.13) | 0.95 (0.86, 1.04) | 0.97 (0.85, 1.10) | <0.001 | 0.8 |
| C61 | Prostate | 1.16 (1.10, 1.22) | 1.09 (1.01, 1.17) | 1.29 (1.17, 1.43) | 1.07 (0.96, 1.18) | 1.07 (0.95, 1.20) | 0.4 | 0.01 |
| C64 | Kidney | 1.07 (1.03, 1.12) | 1.05 (0.96, 1.15) | 1.08 (0.98, 1.20) | 1.04 (0.90, 1.21) | 1.05 (0.88, 1.25) | 0.8 | 1.0 |
| C67 | Bladder | 1.06 (1.02, 1.10) | 1.10 (1.03, 1.17) | 1.03 (0.94, 1.14) | 1.06 (0.93, 1.21) | 1.17 (0.98, 1.40) | 0.6 | 0.5 |
| C70-72 | Brain and central nervous system | 1.09 (1.06, 1.13) | 1.00 (0.95, 1.05) | 0.96 (0.87, 1.05) | 0.95 (0.83, 1.09) | 1.06 (0.89, 1.28) | <0.001 | 0.1 |
| C80 | Unknown primary | 1.08 (1.06, 1.10) | 1.01 (0.94, 1.08) | 1.02 (0.89, 1.17) | 1.10 (0.91, 1.32) | 1.04 (0.82, 1.33) | 0.3 | 0.4 |

| | | 1 | 2 | 3 | 4 | 5 | P-trend^ | P-departure from linearity^ |
|---|---|---|---|---|---|---|---|---|
| **ICD-10** | **Cancer site** | **EMRR (95% CI)** | **EMRR (95% CI)** | **EMRR (95% CI)** | **EMRR (95% CI)** | **EMRR (95% CI)** | | |
| C82-86 | Non-Hodgkin lymphoma | 1.11 (1.08, 1.15) | 1.06 (0.99, 1.13) | 1.15 (1.05, 1.27) | 1.06 (0.94, 1.19) | 1.20 (1.04, 1.38) | 0.8 | 0.2 |
| C90 | Multiple myeloma | 1.08 (1.03, 1.13) | 1.02 (0.95, 1.09) | 1.03 (0.95, 1.11) | 1.01 (0.91, 1.11) | 0.99 (0.88, 1.11) | 0.08 | 0.9 |
| C91-95 | Leukaemia | 1.05 (1.02, 1.08) | 1.03 (0.97, 1.09) | 0.96 (0.88, 1.04) | 1.07 (0.96, 1.18) | 0.89 (0.78, 1.01) | 0.02 | 0.2 |

CI, confidence interval; ^ likelihood ratio test; SEIFA, Socio-Economic Indexes for Areas

**S 8.5 Table.** Five-year excess mortality rate ratios (EMRRs), by age at diagnosis, per quintile increase in socio-economic disadvantage (SEIFA)

| | | Age at diagnosis (years) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 15-44 | 45-54 | 55-64 | 65-74 | 75+ | P-trend^ | P-departure from linearity^ |
| ICD-10 | Cancer site | EMRR (95% CI) | EMRR (95% CI) | EMRR (95% CI) | EMRR (95% CI) | EMRR (95% CI) | | |
| C00-14, C30-32 | Head and neck | 1.19 (1.03, 1.37) | 1.19 (1.09, 1.29) | 1.19 (1.12, 1.26) | 1.13 (1.06, 1.20) | 1.09 (1.03, 1.16) | 0.05 | 0.9 |
| C15 | Oesophagus | 1.05 (0.88, 1.26) | 1.12 (1.02, 1.22) | 1.09 (1.03, 1.16) | 1.09 (1.04, 1.15) | 1.05 (1.01, 1.09) | 0.08 | 0.9 |
| C16 | Stomach | 1.06 (0.96, 1.16) | 1.05 (0.98, 1.13) | 1.01 (0.96, 1.07) | 1.05 (1.00, 1.09) | 1.06 (1.02, 1.10) | 0.4 | 0.7 |
| C18-20 | Colorectum | 1.12 (1.05, 1.19) | 1.09 (1.05, 1.14) | 1.08 (1.04, 1.11) | 1.09 (1.06, 1.12) | 1.07 (1.05, 1.10) | 0.2 | 0.9 |
| C21 | Anus and anal canal | 1.75 (1.13, 2.72) | 1.02 (0.84, 1.23) | 1.13 (0.94, 1.35) | 1.24 (1.01, 1.51) | 1.04 (0.88, 1.22) | 0.4 | 0.1 |
| C22 | Liver | 1.08 (0.94, 1.24) | 1.03 (0.96, 1.10) | 1.08 (1.03, 1.14) | 0.99 (0.95, 1.04) | 1.04 (1.00, 1.08) | 0.3 | 0.2 |
| C23-24 | Gallbladder and biliary tract | 0.91 (0.71, 1.18) | 1.09 (0.95, 1.24) | 1.02 (0.94, 1.11) | 1.04 (0.97, 1.11) | 1.07 (1.01, 1.13) | 0.4 | 0.7 |
| C25 | Pancreas | 1.02 (0.91, 1.14) | 1.06 (0.99, 1.12) | 1.05 (1.01, 1.09) | 1.06 (1.03, 1.09) | 1.05 (1.03, 1.08) | 0.7 | 1.0 |
| C33-34 | Lung, bronchus, and trachea | 1.13 (1.04, 1.21) | 1.05 (1.01, 1.08) | 1.05 (1.02, 1.07) | 1.05 (1.03, 1.07) | 1.03 (1.02, 1.05) | 0.05 | 0.3 |
| C43 | Melanoma | 1.26 (1.14, 1.39) | 1.17 (1.07, 1.29) | 1.17 (1.08, 1.27) | 1.23 (1.12, 1.35) | 1.12 (1.04, 1.21) | 0.2 | 0.5 |
| C47-49 | Connective and soft tissue | 1.23 (1.06, 1.41) | 1.27 (1.05, 1.54) | 1.05 (0.90, 1.24) | 1.01 (0.89, 1.16) | 1.04 (0.93, 1.17) | 0.03 | 0.6 |
| C50 | Female breast | 1.06 (1.00, 1.13) | 1.15 (1.09, 1.22) | 1.17 (1.10, 1.24) | 1.18 (1.09, 1.26) | 1.12 (1.05, 1.19) | 0.3 | 0.1 |
| C56 | Ovary | 1.12 (0.99, 1.27) | 1.05 (0.96, 1.15) | 1.05 (0.98, 1.12) | 1.07 (1.01, 1.13) | 1.08 (1.02, 1.13) | 0.8 | 0.8 |
| C61 | Prostate | 1.00 (0.57, 1.77) | 1.46 (1.18, 1.80) | 1.20 (1.07, 1.36) | 1.37 (1.21, 1.54) | 1.09 (1.05, 1.14) | <0.001 | 0.01 |
| C64 | Kidney | 1.01 (0.87, 1.17) | 1.09 (0.99, 1.20) | 1.12 (1.04, 1.20) | 1.07 (0.99, 1.15) | 1.04 (0.98, 1.10) | 0.5 | 0.5 |
| C67 | Bladder | 1.19 (0.90, 1.58) | 1.22 (1.05, 1.40) | 1.15 (1.06, 1.25) | 1.08 (1.02, 1.15) | 1.04 (1.00, 1.08) | 0.004 | 0.9 |
| C70-72 | Brain and central nervous system | 1.02 (0.95, 1.10) | 1.07 (1.01, 1.14) | 1.00 (0.96, 1.05) | 1.10 (1.05, 1.15) | 1.07 (1.02, 1.12) | 0.2 | 0.1 |
| C80 | Unknown primary | 1.14 (1.00, 1.29) | 1.14 (1.06, 1.23) | 1.10 (1.04, 1.16) | 1.11 (1.07, 1.15) | 1.04 (1.02, 1.07) | 0.005 | 0.6 |

| | 15-44 | 45-54 | 55-64 | 65-74 | 75+ | P-trend^ | P-departure from linearity^ | 15-44 |
|---|---|---|---|---|---|---|---|---|
| **ICD-10** | **Cancer site** | **EMRR (95% CI)** | **EMRR (95% CI)** | **EMRR (95% CI)** | **EMRR (95% CI)** | **EMRR (95% CI)** | | |
| C82-86 | Non-Hodgkin lymphoma | 1.08 (0.97, 1.20) | 1.07 (0.98, 1.18) | 1.12 (1.05, 1.20) | 1.16 (1.10, 1.22) | 1.08 (1.04, 1.12) | 0.9 | 0.3 |
| C90 | Multiple myeloma | 0.97 (0.75, 1.27) | 1.09 (0.96, 1.25) | 1.08 (1.00, 1.17) | 1.01 (0.95, 1.07) | 1.05 (1.00, 1.10) | 0.7 | 0.6 |
| C91-95 | Leukaemia | 1.08 (0.98, 1.18) | 1.08 (0.99, 1.19) | 1.00 (0.94, 1.07) | 1.06 (1.01, 1.11) | 1.01 (0.98, 1.05) | 0.2 | 0.4 |

CI, confidence interval; ^ likelihood ratio test; SEIFA, Socio-Economic Indexes for Areas

**S 8.6 Table.** Fiver-year excess mortality rate ratios (EMRRs), by sex, per quintile increase in socio-economic disadvantage (SEIFA)

| | | Sex | | |
|---|---|---|---|---|
| | | Men | Women | P-trend^ |
| ICD-10 | Cancer site | EMRR (95% CI) | EMRR (95% CI) | |
| C00-14, C30-32 | Head and neck | 1.16 (1.12, 1.20) | 1.10 (1.03, 1.17) | 0.2 |
| C15 | Oesophagus | 1.07 (1.04, 1.11) | 1.07 (1.02, 1.13) | 0.8 |
| C16 | Stomach | 1.04 (1.01, 1.07) | 1.06 (1.02, 1.10) | 0.5 |
| C18-20 | Colorectum | 1.10 (1.08, 1.12) | 1.06 (1.04, 1.08) | 0.006 |
| C21 | Anus and anal canal | 1.18 (1.04, 1.34) | 1.08 (0.96, 1.22) | 0.3 |
| C22 | Liver | 1.03 (1.00, 1.06) | 1.04 (1.00, 1.09) | 0.8 |
| C23-24 | Gallbladder and biliary tract | 1.07 (1.02, 1.13) | 1.03 (0.98, 1.08) | 0.3 |
| C25 | Pancreas | 1.06 (1.03, 1.08) | 1.05 (1.03, 1.08) | 0.9 |
| C33-34 | Lung, bronchus, and trachea | 1.04 (1.03, 1.06) | 1.04 (1.03, 1.06) | 0.9 |
| C43 | Melanoma | 1.18 (1.13, 1.24) | 1.19 (1.11, 1.28) | 0.8 |
| C47-49 | Connective and soft tissue | 1.15 (1.06, 1.25) | 1.02 (0.93, 1.12) | 0.1 |
| C64 | Kidney | 1.08 (1.04, 1.13) | 1.04 (0.98, 1.10) | 0.4 |
| C67 | Bladder | 1.07 (1.03, 1.11) | 1.07 (1.02, 1.13) | 0.8 |
| C70-72 | Brain and central nervous system | 1.03 (1.00, 1.06) | 1.09 (1.05, 1.13) | 0.008 |
| C80 | Unknown primary | 1.09 (1.06, 1.11) | 1.06 (1.04, 1.09) | 0.3 |
| C82-86 | Non-Hodgkin lymphoma | 1.11 (1.07, 1.15) | 1.10 (1.06, 1.15) | 0.9 |
| C90 | Multiple myeloma | 1.04 (1.00, 1.09) | 1.04 (1.00, 1.10) | 0.8 |
| C91-95 | Leukaemia | 1.04 (1.00, 1.07) | 1.03 (0.99, 1.07) | 0.7 |

CI, confidence interval; ^ likelihood ratio test; SEIFA, Socio-Economic Indexes for Areas

**S 8.7 Table.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis, including and excluding cases living outside major cities, per quintile increase in socio-economic disadvantage (SEIFA), 2001-2015

| ICD-10 | Cancer site | EMRR (95% CI) $ | P-value ^ | EMRR (95% CI) * | P-value ^ |
|---|---|---|---|---|---|
| C00-14, C30-32 | Head and neck | 1.15 (1.11 to 1.18) | <0.001 | 1.13 (1.08 to 1.17) | <0.001 |
| C15 | Oesophagus | 1.07 (1.04 to 1.10) | <0.001 | 1.06 (1.03 to 1.10) | 0.001 |
| C16 | Stomach | 1.05 (1.02 to 1.07) | <0.001 | 1.02 (1.00 to 1.05) | 0.09 |
| C17 | Small intestine | 1.00 (0.93 to 1.07) | 1.0 | 1.00 (0.92 to 1.09) | 1.0 |
| C18-20 | Colorectum | 1.08 (1.07 to 1.10) | <0.001 | 1.08 (1.06 to 1.10) | <0.001 |
| C21 | Anus and anal canal | 1.13 (1.04 to 1.23) | 0.006 | 1.15 (1.03 to 1.27) | 0.01 |
| C22 | Liver | 1.04 (1.01 to 1.06) | 0.004 | 1.03 (1.00 to 1.06) | 0.07 |
| C23-24 | Gallbladder and biliary tract | 1.05 (1.01 to 1.09) | 0.008 | 1.05 (1.01 to 1.09) | 0.02 |
| C25 | Pancreas | 1.05 (1.04 to 1.07) | <0.001 | 1.04 (1.02 to 1.06) | <0.001 |
| C33-34 | Lung, bronchus and trachea | 1.04 (1.03 to 1.05) | <0.001 | 1.04 (1.03 to 1.05) | <0.001 |
| C43 | Melanoma | 1.18 (1.14 to 1.23) | <0.001 | 1.22 (1.16 to 1.28) | <0.001 |
| C45 | Mesothelioma | 1.03 (1.00 to 1.07) | 0.07 | 1.06 (1.01 to 1.11) | 0.02 |
| C47-49 | Connective and soft tissue | 1.10 (1.03 to 1.17) | 0.004 | 1.07 (0.99 to 1.16) | 0.09 |
| C50 | Female breast | 1.14 (1.10 to 1.17) | <0.001 | 1.15 (1.12 to 1.19) | <0.001 |
| C53 | Cervix | 1.03 (0.97 to 1.10) | 0.4 | 1.04 (0.97 to 1.12) | 0.3 |
| C54-55 | Uterus | 1.04 (0.99 to 1.10) | 0.1 | 1.02 (0.96 to 1.09) | 0.5 |
| C56 | Ovary | 1.07 (1.04 to 1.10) | <0.001 | 1.05 (1.01 to 1.09) | 0.009 |
| C51-52, C57 | Vulva, vagina, other/unspecified | 1.03 (0.96 to 1.11) | 0.4 | 1.06 (0.97 to 1.16) | 0.2 |
| C61 | Prostate | 1.14 (1.10 to 1.18) | <0.001 | 1.10 (1.05 to 1.15) | <0.001 |
| C64 | Kidney | 1.07 (1.03 to 1.10) | <0.001 | 1.03 (0.99 to 1.07) | 0.2 |
| C67 | Bladder | 1.07 (1.04 to 1.10) | <0.001 | 1.07 (1.03 to 1.10) | 0.001 |
| C65-66, C68 | Renal pelvis, ureter, other/unspecified | 1.07 (1.00 to 1.14) | 0.05 | 1.08 (1.00 to 1.17) | 0.05 |
| C70-72 | Brain and central nervous system | 1.05 (1.03 to 1.08) | <0.001 | 1.03 (1.00 to 1.06) | 0.03 |
| C73 | Thyroid | 1.06 (0.95 to 1.17) | 0.3 | 1.05 (0.92 to 1.18) | 0.5 |
| C80 | Unknown primary | 1.07 (1.05 to 1.09) | <0.001 | 1.09 (1.06 to 1.11) | <0.001 |
| C81 | Hodgkin Lymphoma | 1.07 (0.96 to 1.19) | 0.2 | 1.07 (0.94 to 1.21) | 0.3 |
| C82-86 | Non-Hodgkin Lymphoma | 1.10 (1.07 to 1.13) | <0.001 | 1.10 (1.07 to 1.14) | <0.001 |
| C90 | Multiple Myeloma | 1.04 (1.01 to 1.08) | 0.01 | 1.03 (0.99 to 1.07) | 0.1 |
| C91-95 | Leukaemia | 1.03 (1.01 to 1.07) | 0.01 | 1.04 (1.01 to 1.07) | 0.02 |

CI, confidence interval; ^ likelihood ratio test; $ EMRRS were estimated including all cases; *EMRRs were estimated excluding cases living outside major cities

**Appendix F** Supplementary material related to publication presented in Chapter 9

**Supplementary Table 9.1.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis, by socio-economic disadvantage, for cancer cases residing outside major cities compared with those residing in major cities, 2001-2015

| Area-level socio-economic disadvantage (SEIFA quintiles) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Q1 (Most disadvantaged) | Q2 | Q3 | Q4 | Q5 (Least disadvantaged) | Change in EMRR per SEIFA quintile | p-trend^ | p-departure from linearity^ |
| Cancer site | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | EMRR (95%CI) | | |
| Head and neck | 0.96 (0.83, 1.11) | 0.87 (0.73, 1.05) | 0.83 (0.67, 1.03) | 0.73 (0.55, 0.97) | 0.67 (0.43, 1.04) | 0.90 (0.84, 0.97) | 0.008 | 1.0 |
| Oesophagus | 1.17 (1.01, 1.35) | 1.15 (0.98, 1.34) | 1.16 (0.96, 1.38) | 1.19 (0.95, 1.49) | 1.12 (0.83, 1.51) | 1.01 (0.95, 1.07) | 0.9 | 0.3 |
| Stomach | 1.23 (1.09, 1.39) | 1.25 (1.10, 1.43) | 1.20 (1.04, 1.39) | 0.96 (0.79, 1.15) | 1.07 (0.83, 1.37) | 0.95 (0.90, 1.00) | 0.04 | 0.7 |
| Small intestine | 1.06 (0.68, 1.64) | 1.08 (0.62, 1.89) | 1.19 (0.72, 1.98) | 0.56 (0.32, 0.98) | 1.71 (0.65, 4.52) | 0.99 (0.83, 1.20) | 1.0 | 0.02 |
| Colorectum | 0.99 (0.92, 1.07) | 1.02 (0.93, 1.10) | 0.94 (0.86, 1.04) | 1.10 (0.99, 1.23) | 0.93 (0.78, 1.10) | 1.01 (0.97, 1.04) | 0.7 | 0.2 |
| Anus and anal canal | 1.08 (0.67, 1.76) | 1.15 (0.66, 1.98) | 0.95 (0.51, 1.77) | 0.96 (0.41, 2.24) | 1.19 (0.43, 3.30) | 1.08 (0.88, 1.33) | 0.5 | 1.0 |
| Liver | 1.12 (0.98, 1.28) | 1.32 (1.12, 1.54) | 1.39 (1.15, 1.66) | 1.18 (0.95, 1.47) | 1.01 (0.74, 1.39) | 1.00 (0.95, 1.07) | 0.9 | 0.2 |
| Gallbladder and biliary tract | 1.02 (0.83, 1.24) | 1.10 (0.86, 1.39) | 1.14 (0.89, 1.45) | 1.18 (0.85, 1.64) | 1.17 (0.67, 2.07) | 1.04 (0.95, 1.14) | 0.4 | 0.9 |
| Pancreas | 1.20 (1.09, 1.33) | 1.06 (0.96, 1.18) | 1.06 (0.94, 1.20) | 1.19 (1.03, 1.37) | 1.14 (0.94, 1.39) | 0.98 (0.94, 1.03) | 0.4 | 0.3 |
| Lung, bronchus and trachea | 1.05 (1.00, 1.10) | 1.03 (0.98, 1.09) | 1.02 (0.95, 1.09) | 1.12 (1.03, 1.22) | 1.04 (0.92, 1.17) | 1.00 (0.98, 1.03) | 0.8 | 0.5 |
| Melanoma | 0.73 (0.57, 0.93) | 0.74 (0.59, 0.93) | 0.69 (0.51, 0.91) | 0.91 (0.65, 1.27) | 0.68 (0.40, 1.17) | 1.02 (0.92, 1.12) | 0.8 | 0.7 |
| Mesothelioma | 0.85 (0.68, 1.06) | 0.94 (0.75, 1.19) | 1.08 (0.84, 1.38) | 0.86 (0.63, 1.18) | 1.36 (0.90, 2.04) | 1.06 (0.97, 1.15) | 0.2 | 0.6 |
| Connective and soft tissue | 1.41 (0.95, 2.08) | 1.12 (0.75, 1.67) | 1.57 (1.02, 2.44) | 1.15 (0.75, 1.79) | 1.21 (0.59, 2.47) | 1.00 (0.86, 1.16) | 1.0 | 0.6 |
| Female breast | 0.88 (0.75, 1.03) | 0.82 (0.69, 0.97) | 0.98 (0.82, 1.17) | 0.95 (0.76, 1.19) | 0.98 (0.71, 1.36) | 1.05 (0.99, 1.12) | 0.1 | 0.3 |
| Cervix | 1.33 (0.94, 1.90) | 0.64 (0.42, 0.98) | 1.12 (0.72, 1.73) | 1.73 (1.07, 2.80) | 1.78 (0.91, 3.49) | 1.09 (0.94, 1.27) | 0.2 | 0.03 |

| | Q1 (Most disadvantaged) | Q2 | Q3 | Q4 | Q5 (Least disadvantaged) | Change in EMRR per SEIFA quintile | p-trend^ | p-departure from linearity^ |
|---|---|---|---|---|---|---|---|---|
| **Cancer site** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | **EMRR (95%CI)** | | |
| Uterus | 1.03 (0.76, 1.38) | 1.16 (0.83, 1.61) | 0.91 (0.61, 1.34) | 0.94 (0.60, 1.45) | 0.55 (0.24, 1.22) | 0.91 (0.80, 1.04) | 0.2 | 0.9 |
| Ovary | 1.14 (0.95, 1.37) | 1.14 (0.95, 1.36) | 1.15 (0.93, 1.41) | 1.20 (0.94, 1.53) | 0.77 (0.52, 1.14) | 0.97 (0.90, 1.04) | 0.4 | 0.4 |
| Vulva, vagina, other/unspecified | 0.92 (0.61, 1.39) | 1.01 (0.66, 1.55) | 0.96 (0.55, 1.65) | 1.19 (0.61, 2.32) | 1.79 (0.93, 3.47) | 1.11 (0.93, 1.32) | 0.3 | 0.6 |
| Prostate | 1.28 (1.06, 1.54) | 0.93 (0.75, 1.16) | 0.81 (0.60, 1.08) | 1.30 (0.90, 1.86) | 1.05 (0.54, 2.06) | 0.97 (0.88, 1.08) | 0.6 | 0.05 |
| Testis | 0.57 (0.15, 2.17) | 0.47 (0.06, 3.42) | 2.70 (0.87, 8.39) | 7.85 (1.47, 41.9) | 1.50 (0.27, 8.34) | 1.44 (0.88, 2.37) | 0.2 | 0.4 |
| Kidney | 1.43 (1.19, 1.71) | 0.90 (0.73, 1.12) | 1.07 (0.84, 1.37) | 0.99 (0.75, 1.31) | 1.10 (0.73, 1.66) | 0.91 (0.83, 0.99) | 0.02 | 0.1 |
| Bladder | 1.02 (0.87, 1.20) | 0.94 (0.77, 1.13) | 1.01 (0.81, 1.26) | 1.01 (0.77, 1.34) | 0.96 (0.64, 1.43) | 0.99 (0.92, 1.07) | 0.8 | 1.0 |
| Renal pelvis, ureter, other | 0.80 (0.55, 1.18) | 1.29 (0.90, 1.87) | 0.99 (0.62, 1.57) | 1.04 (0.57, 1.90) | 2.30 (0.90, 5.83) | 1.09 (0.92, 1.29) | 0.3 | 0.5 |
| Brain and central nervous system | 1.13 (0.97, 1.30) | 1.07 (0.92, 1.23) | 1.09 (0.94, 1.28) | 0.90 (0.76,1.08) | 0.81 (0.64, 1.03) | 0.94 (0.89, 0.99) | 0.02 | 0.9 |
| Thyroid | 1.66 (0.91, 3.01) | 0.61 (0.32, 1.17) | 2.02 (1.09, 3.76) | 0.74 (0.30, 1.83) | 1.48 (0.47, 4.66) | 1.06 (0.83, 1.35) | 0.7 | 0.05 |
| Unknown primary | 0.85 (0.77, 0.94) | 1.02 (0.91, 1.13) | 0.86 (0.75, 0.97) | 0.95 (0.81, 1.11) | 1.00 (0.78, 1.26) | 1.02 (0.97, 1.07) | 0.4 | 0.3 |
| Hodgkin lymphoma | 1.15 (0.66, 2.0) | 0.72 (0.37, 1.40) | 1.02 (0.49, 2.12) | 0.90 (0.38, 2.14) | 0.67 (0.20, 2.24) | 0.93 (0.72, 1.20) | 0.6 | 1.0 |
| Non-Hodgkin lymphoma | 0.98 (0.84, 1.13) | 0.97 (0.82, 1.15) | 0.89 (0.74, 1.07) | 0.94 (0.75, 1.19) | 0.81 (0.58, 1.13) | 0.97 (0.91, 1.04) | 0.4 | 1.0 |
| Multiple myeloma | 1.06 (0.87, 1.29) | 1.07 (0.88, 1.31) | 0.88 (0.70, 1.11) | 1.03 (0.80, 1.33) | 0.95 (0.65, 1.37) | 0.99 (0.91, 1.06) | 0.7 | 0.7 |
| Leukaemia | 1.02 (0.88, 1.18) | 1.01 (0.86, 1.18) | 0.91 (0.77, 1.08) | 1.17 (0.96, 1.42) | 1.24 (0.94, 1.63) | 1.04 (0.98, 1.10) | 0.3 | 0.7 |

CI, confidence interval; ^ likelihood ratio test; SEIFA, Socio-Economic Indexes for Areas

**Supplementary Table 9.2.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis, by sex, for cancer cases residing outside major cities compared with those residing in major cities, 2001-2015

| | Sex, adjusted for area-level socio-economic disadvantage | | |
|---|---|---|---|
| | Men | Women | P-value^ |
| Cancer site | EMRR (95%CI) | EMRR (95%CI) | |
| Head and neck | 0.89 (0.80, 0.99) | 0.81 (0.67, 0.98) | 0.2 |
| Oesophagus | 1.21 (1.10, 1.34) | 1.06 (0.92, 1.23) | 0.1 |
| Stomach | 1.14 (1.05, 1.24) | 1.22 (1.09, 1.37) | 0.2 |
| Small intestine | 0.73 (0.51, 1.04) | 1.23 (0.87, 1.73) | 0.1 |
| Colorectum | 0.98 (0.92, 1.03) | 1.03 (0.97, 1.10) | 0.9 |
| Anus and anal canal | 0.92 (0.62, 1.38) | 1.21 (0.83, 1.77) | 0.5 |
| Liver | 1.26 (1.15, 1.39) | 1.09 (0.93, 1.26) | 0.08 |
| Gallbladder and biliary tract | 0.99 (0.82, 1.19) | 1.16 (1.00, 1.36) | 0.3 |
| Pancreas | 1.09 (1.01, 1.18) | 1.16 (1.07, 1.25) | 0.3 |
| Lung, bronchus and trachea | 1.06 (1.02, 1.10) | 1.03 (0.98, 1.08) | 0.2 |
| Melanoma | 0.83 (0.71, 0.96) | 0.56 (0.44, 0.72) | 0.006 |
| Mesothelioma | 0.95 (0.84, 1.08) | 1.00 (0.75, 1.32) | 1.0 |
| Connective and soft tissue | 1.30 (1.00, 1.69) | 1.14 (0.85, 1.54) | 0.4 |
| Kidney | 1.10 (0.96, 1.25) | 1.17 (0.98, 1.40) | 0.6 |
| Bladder | 0.96 (0.85, 1.08) | 1.06 (0.90, 1.26) | 0.4 |
| Renal pelvis, ureter, other | 1.29 (0.96, 1.73) | 0.86 (0.64, 1.15) | 0.04 |
| Brain and central nervous system | 1.03 (0.93, 1.13) | 1.02 (0.91, 1.14) | 0.6 |
| Thyroid | 1.02 (0.62, 1.66) | 1.08 (0.70, 1.67) | 0.6 |
| Unknown primary | 0.90 (0.83, 0.98) | 0.93 (0.86,1.01) | 0.7 |
| Hodgkin lymphoma | 0.82 (0.53, 1.27) | 1.02 (0.63, 1.65) | 0.7 |
| Non-Hodgkin lymphoma | 0.92 (0.82, 1.03) | 0.97 (0.85, 1.10) | 0.7 |
| Multiple myeloma | 1.04 (0.90, 1.19) | 0.98 (0.84, 1.14) | 0.6 |
| Leukaemia | 1.08 (0.98, 1.20) | 0.94 (0.83, 1.06) | 0.05 |

CI, confidence interval; ^ likelihood ratio test

**Supplementary Table 9.3.** Excess mortality rate ratios (EMRRs) within 5 years of diagnosis, using life tables by remoteness of residence and derived life tables by remoteness of residence and SEIFA, for cancer cases residing outside major cities compared with those residing in major cities, 2001-2015

| ICD-10 | Cancer site | EMRR (95% CI) [$] | p-value ^ | EMRR (95% CI) * | p-value ^ |
|---|---|---|---|---|---|
| C00-14, C30-32 | Head and neck | 0.96 (0.88 to 1.05) | 0.4 | 0.95 (0.87 to 1.04) | 0.3 |
| C15 | Oesophagus | 1.22 (1.13 to 1.31) | <0.001 | 1.21 (1.12 to 1.31) | <0.001 |
| C16 | Stomach | 1.20 (1.12 to 1.28) | <0.001 | 1.19 (1.12 to 1.27) | <0.001 |
| C17 | Small intestine | 0.98 (0.78 to 1.24) | 0.9 | 0.98 (0.78 to 1.24) | 0.9 |
| C18-20 | Colorectum | 1.07 (1.03 to 1.12) | 0.001 | 1.06 (1.02 to 1.10) | 0.005 |
| C21 | Anus and anal canal | 1.16 (0.89 to 1.50) | 0.3 | 1.14 (0.88 to 1.48) | 0.3 |
| C22 | Liver | 1.23 (1.14 to 1.33) | <0.001 | 1.23 (1.14 to 1.33) | <0.001 |
| C23-24 | Gallbladder and biliary tract | 1.13 (1.01 to 1.27) | 0.03 | 1.13 (1.01 to 1.27) | 0.03 |
| C25 | Pancreas | 1.16 (1.10 to 1.23) | <0.001 | 1.16 (1.10 to 1.22) | <0.001 |
| C33-34 | Lung, bronchus and trachea | 1.08 (1.05 to 1.11) | <0.001 | 1.07 (1.04 to 1.10) | <0.001 |
| C43 | Melanoma | 0.93 (0.82 to 1.05) | 0.3 | 0.90 (0.80 to 1.01) | 0.09 |
| C45 | Mesothelioma | 1.00 (0.90 to 1.12) | 1.0 | 0.99 (0.89 to 1.11) | 0.9 |
| C47-49 | Connective and soft tissue | 1.32 (1.10 to 1.59) | 0.003 | 1.30 (1.09 to 1.57) | 0.004 |
| C50 | Female breast | 1.03 (0.95 to 1.12) | 0.5 | 1.01 (0.93 to 1.09) | 0.9 |
| C53 | Cervix | 1.16 (0.95 to 1.41) | 0.1 | 1.16 (0.96 to 1.40) | 0.1 |
| C54-55 | Uterus | 0.99 (0.84 to 1.17) | 0.9 | 0.98 (0.83 to 1.15) | 0.8 |
| C56 | Ovary | 1.17 (1.07 to 1.28) | 0.001 | 1.17 (1.06 to 1.28) | 0.001 |
| C51-52, C57 | Vulva, vagina, other/unspecified | 1.09 (0.87 to 1.35) | 0.5 | 1.07 (0.86 to 1.32) | 0.6 |
| C61 | Prostate | 1.27 (1.12 to 1.43) | <0.001 | 1.14 (1.03 to 1.26) | 0.01 |

| ICD-10 | Cancer site | EMRR (95% CI) $ | p-value ^ | EMRR (95% CI) * | p-value ^ |
|---|---|---|---|---|---|
| C62 | Testis | 1.33 (0.65 to 2.71) | 0.4 | 1.46 (0.75 to 2.83) | 0.3 |
| C64 | Kidney | 1.16 (1.05 to 1.28) | 0.004 | 1.14 (1.03 to 1.26) | 0.01 |
| C67 | Bladder | 1.06 (0.96 to 1.16) | 0.2 | 1.05 (0.96 to 1.14) | 0.2 |
| C65-66, C68 | Renal pelvis, ureter, other/unspecified | 1.10 (0.91 to 1.34) | 0.3 | 1.10 (0.91 to 1.34) | 0.3 |
| C70-72 | Brain and central nervous system | 1.07 (1.00 to 1.15) | 0.05 | 1.07 (1.00 to 1.15) | 0.06 |
| C73 | Thyroid | 1.21 (0.88 to 1.65) | 0.2 | 1.17 (0.86 to 1.59) | 0.3 |
| C80 | Unknown primary | 0.97 (0.92 to 1.03) | 0.3 | 0.97 (0.92 to 1.02) | 0.2 |
| C81 | Hodgkin Lymphoma | 0.90 (0.66 to 1.24) | 0.5 | 0.91 (0.66 to 1.24) | 0.5 |
| C82-86 | Non-Hodgkin Lymphoma | 1.03 (0.95 to 1.12) | 0.4 | 1.03 (0.95 to 1.11) | 0.5 |
| C90 | Multiple Myeloma | 1.05 (0.95 to 1.16) | 0.3 | 1.04 (0.95 to 1.15) | 0.3 |
| C91-95 | Leukaemia | 1.05 (0.97 to 1.14) | 0.2 | 1.04 (0.97 to 1.13) | 0.3 |

CI, confidence interval; ^ likelihood ratio test; $ EMRRs were estimated using life tables by remoteness of residence; *EMRRs were estimated using derived life tables by remoteness of residence and SEIFA

**Supplementary 9.4.** Derived life tables by area of residence and area-level socio-economic disadvantage

New life tables were generated from two separate life tables, stratified by SEIFA and area of residence. We estimated the probability of death in the next year ($q_x$) by SEIFA and area of residence for each particular age ($x$) and by sex and calendar year. The Victorian population in each cell of a derived life table by SEIFA quintile and area of residence was calculated from ABS 2011 census population data by SA1 with 10 entries in each table for each age, sex and year. These population counts were used as weights to formulate 5 SEIFA equations and 2 residential area equations for the probability of death by SEIFA and area of residence. In addition, we formulated equations expressing the requirement that the risk ratio for SEIFA quintiles and residential area categories be consistent across the 10 entries in the probability of death table. The equations could not be all satisfied, so least squares optimisation was applied to determine the $q_x$ for each of the 10 cells in the table, satisfying all equations only approximately.

For each age, sex and year, let

$q_{ij}$ = death rate for remoteness category $i$ and SEIFA category $j$

$s_j$ = death rate for SEIFA category $j$

$r_i$ = death rate for remoteness category $i$, 1=city, 2=rural

$\mathrm{p}_{1j}$ = population in city with SEIFA category $j$

$\mathrm{p}_{2j}$ = population in rural areas with SEIFA category $j$

$\mathrm{u}_j = \mathrm{p}_{1j} + \mathrm{p}_{2j}$ = population with SEIFA category $j$

$$\mathrm{z}_1 = \sum_{\mathrm{j}=1}^{\mathrm{j}=5} \mathrm{p}_{1j} = \text{population in city}$$

$$\mathrm{z}_2 = \sum_{\mathrm{j}=1}^{\mathrm{j}=5} \mathrm{p}_{2j} = \text{population in rural areas}$$

Define the relevant weights based on the population data:

$$\mathrm{w}_{1j} = \frac{\mathrm{p}_{1j}}{\mathrm{u}_j}$$

$$\mathrm{w}_{2j} = \frac{\mathrm{p}_{2j}}{\mathrm{u}_j}$$

$$\mathrm{v}_{1j} = \frac{\mathrm{p}_{1j}}{\mathrm{z}_1}$$

$$\mathrm{v}_{2j} = \frac{\mathrm{p}_{2j}}{\mathrm{z}_2}$$

The SEIFA category equations are:

$$\begin{aligned} w_{11}\, q_{11} + w_{21}\, q_{21} &= s_1 \\ w_{12}\, q_{12} + w_{22}\, q_{22} &= s_2 \\ w_{13}\, q_{13} + w_{23}\, q_{23} &= s_3 \\ w_{14}\, q_{14} + w_{24}\, q_{24} &= s_4 \\ w_{15}\, q_{15} + w_{25}\, q_{25} &= s_5 \end{aligned} \tag{1}$$

The rural/city equations are:

$$\begin{aligned} v_{11}\, q_{11} + v_{12}\, q_{12} + v_{13}\, q_{13} + v_{14}\, q_{14} + v_{15}\, q_{15} &= r_1 \\ v_{21}\, q_{21} + v_{22}\, q_{22} + v_{23}\, q_{23} + v_{24}\, q_{24} + v_{25}\, q_{25} &= r_2 \end{aligned} \tag{2}$$

These equations are not full rank because we expect the total number of deaths to be the same for both life tables:

$$u_1\, s_1 + u_2\, s_2 + u_3\, s_3 + u_4\, s_4 + u_5\, s_5 = z_1\, r_1 + z_2\, r_2$$

and the weights add to one:

$$w_{1j} + w_{2j} = 1$$

$$v_{11} + v_{12} + v_{13} + v_{14} + v_{15} = 1$$

$$v_{21} + v_{22} + v_{23} + v_{24} + v_{25} = 1$$

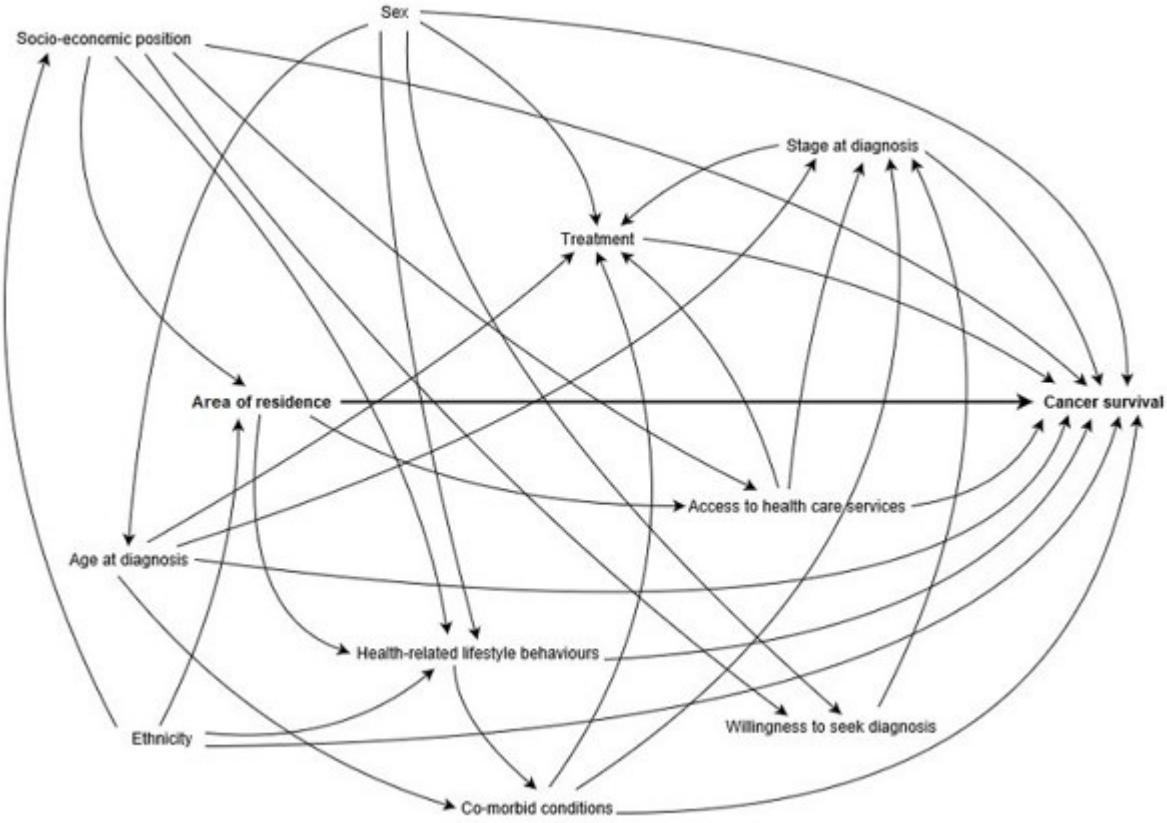
There are 10 parameters (the $q_{ij}$ s) and seven equations so the system of equations is not fully determined. Also, the life tables are not perfectly compatible with respect to the total number of deaths. Therefore, we add the following equations to make the system over determined and express that we would like the risk ratios to be as consistent as possible:

$$\frac{r_1}{r_2} = \frac{q_{11}}{q_{21}} = \frac{q_{12}}{q_{22}} = \frac{q_{13}}{q_{23}} = \frac{q_{14}}{q_{24}} = \frac{q_{15}}{q_{25}} \tag{3}$$

and

$$\frac{s_j}{s_k} = \frac{q_{1j}}{q_{1k}} = \frac{q_{2j}}{q_{2k}},\ j \neq k \tag{4}$$

This system of equations (1 to 4 above) can be solved approximately by least squares optimisation with the objective function a weighted sum of the squares of residuals for each equation. The Mata function **optimise** within Stata version 14 was used to perform the optimisation.




**Supplementary Figure 9.1.** Directed acyclic graph (DAG) showing assumed causal association between area of residence and cancer survival

**Appendix G** Supplementary material related to publication presented in Chapter 10

**Supplementary Table 10.1.** Odds ratios of associations between area-level socio-economic disadvantage and colon cancer-specific survival in Victoria, Australia, 2008-2011

| | 1-year survival from stage III colon cancer | | | 5-year survival from stage III colon cancer | | |
|---|---|---|---|---|---|---|
| | **All cases (n=553)** | **Men (n=296)** | **Women (n=257)** | **All cases (n=553)** | **Men (n=296)** | **Women (n=257)** |
| **Socio-economic index for area (SEIFA)** | Odds ratio (95% CI) | | | Odds ratio (95% CI) | | |
| Least disadvantaged | 1 (Reference) | | | 1 (Reference) | | |
| Most disadvantaged | 0.73 (0.31, 1.70) * | 0.80 (0.26, 2.48) $ | 0.65 (0.18, 2.31) $ | 1.68 (1.13, 2.50) * | 2.57 (1.42, 4.63) $ | 1.13 (0.65, 1.97) $ |

Analyses were restricted to individuals residing in the least and most disadvantaged areas

*Adjusted for sex and age; $ Adjusted for age

**Supplementary Table 10.2.** Odds ratios of associations between area-level socio-economic disadvantage and mediators, Victoria, Australia, 2008-2011

| Stage III colon cancer | All cases (n=553) | Men (n=296) | Women (n=257) |
|---|---|---|---|
| | Odds ratio (95% CI) [&] | | |
| At least one co-morbidity (Yes) | 1.54 (0.75, 3.16) * | 2.19 (0.89, 5.40) ^ | 0.73 (0.21, 2.52) ^ |
| Substage (3C) | 1.03 (0.66, 1.63) * | 0.73 (0.39, 1.36) ^ | 1.55 (0.78, 3.05) ^ |
| Surgery within 4 weeks of diagnosis (No) | 2.33 (1.41, 3.85) * | 2.59 (1.31, 5.12) ^ | 2.04 (0.96, 4.31) ^ |
| Chemotherapy within 8 weeks of surgery (No) | 2.15 (1.50, 3.07) * | 2.74 (1.66, 4.53) ^ | 1.64 (0.98, 2.75) ^ |
| | **All cases (n=542)** | **Men (n=291)** | **Women (n=251)** |
| Substage (3C) [$] | 1.00 (0.63, 1.59) * | 0.79 (0.42, 1.48) ^ | 1.34 (0.67, 2.68) ^ |
| Emergency presentation (Yes) [$] | 1.52 (0.97, 2.37) * | 1.36 (0.73, 2.51) ^ | 1.70 (0.89, 3.23) ^ |
| Hospital type (Public) [$] | 5.87 (4.02, 8.56) * | 5.54 (3.31, 9.27) ^ | 6.24 (3.56, 10.91) ^ |
| Surgical volume of hospital, median number of colon surgeries per year (<32) [$] | 1.45 (0.78, 2.69) * | 1.50 (0.60, 3.73) ^ | 1.44 (0.62, 3.37) ^ |
| Number of nodes taken at surgery (<12) [$] | 0.74 (0.39, 1.41) * | 0.90 (0.38, 2.09) ^ | 0.57 (0.21, 1.55) ^ |

Analyses were restricted to individuals residing in the least and most disadvantaged areas

*Adjusted for sex and age; ^Adjusted for age

[$] Restricted to cases who received surgery within 6 months of diagnosis

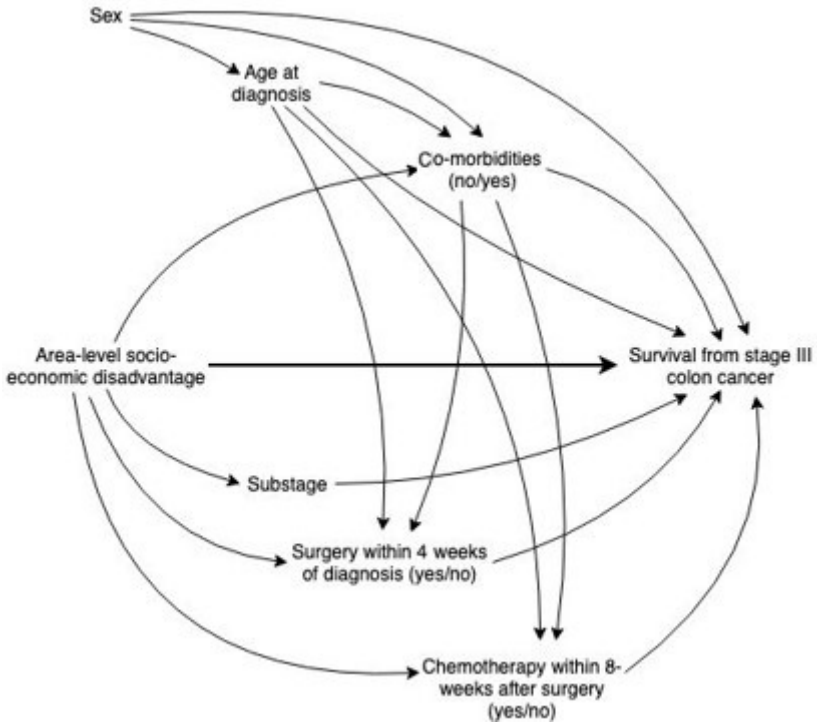
[&] Odds ratios (95% confidence interval) from logistic regression for most disadvantaged versus least disadvantaged (reference)

**Supplementary Table 10.3.** Odds ratios of associations between mediators and 1- and 5-year (stage III) colon cancer-specific survival in Victoria, Australia, 2008-2011

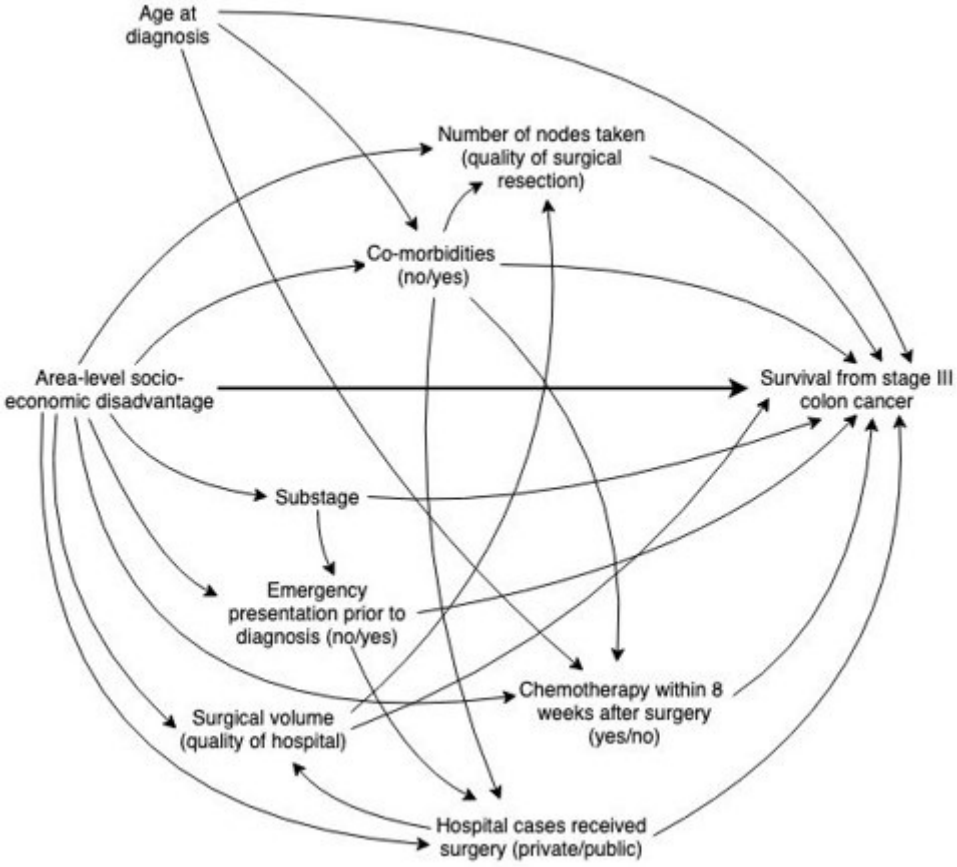
| | 1-year survival from stage III colon cancer | | | 5-year survival from stage III colon cancer | | |
|---|---|---|---|---|---|---|
| **Stage III colon cancer** | **All cases (n=553)** | **Men (n=296)** | **Women (n=257)** | **All cases (n=553)** | **Men (n=296)** | **Women (n=257)** |
| Mediators | Odds ratio (95% CI) | | | Odds ratio (95% CI) | | |
| **At least one co-morbidity** | | | | | | |
| No | 1 (Reference) | | | 1 (Reference) | | |
| Yes | 3.25 (1.10, 9.59) * | 4.09 (1.14, 14.68) # | 1.85 (0.20, 16.73) # | 1.60 (0.80, 3.20) * | 1.63 (0.71, 3.77) # | 1.57 (0.46, 5.42) # |
| **Received surgery within 4 weeks of diagnosis** | | | | | | |
| Yes | 1 (Reference) | | | 1 (Reference) | | |
| No | 0.67 (0.19, 2.31) * | 1.33 (0.35, 5.06) # | - | 0.89 (0.53, 1.49) * | 0.99 (0.49, 1.99) # | 0.78 (0.36, 1.67) # |
| **Received chemotherapy within 8 weeks after surgery** | | | | | | |
| Yes | 1 (Reference) | | | 1 (Reference) | | |
| No | 2.25 (0.88, 5.77) * | 3.81 (0.98, 14.83) # | 1.21 (0.31, 4.68) # | 1.75 (1.18, 2.61) * | 1.73 (0.99, 3.02) # | 1.78 (1.01, 3.14) # |
| **Sub-stage** $ | | | | | | |
| 3A/3B | 1 (Reference) | | | 1 (Reference) | | |
| 3C | 1.52 (0.54, 4.24) * | 1.05 (0.22, 4.95) # | 2.17 (0.53, 8.84) # | 2.57 (1.59, 4.14) * | 1.83 (0.93, 3.61) # | 3.65 (1.82, 7.31) # |
| **Emergency presentation** $ | | | | | | |
| No | 1 (Reference) | | | 1 (Reference) | | |
| Yes | 2.90 (1.20, 7.00) * | 4.63 (1.43, 15.0) # | 1.61 (0.40, 6.50) # | 2.94 (1.88, 4.60) * | 3.24 (1.73, 6.07) # | 2.71 (1.43, 5.14) # |
| **Hospital type** $ | | | | | | |
| Private | 1 (Reference) | | | 1 (Reference) | | |
| Public | 1.19 (0.49, 2.89) * | 3.44 (0.74, 16.06) # | 0.46 (0.12, 1.67) # | 1.71 (1.14, 2.57) * | 2.86 (1.54, 5.32) # | 1.10 (0.63, 1.92) # |
| **Surgical volume of hospital** $ | | | | | | |
| ≥32 | 1 (Reference) | | | 1 (Reference) | | |
| <32 | 1.00 (0.23, 4.45) * | 1.18 (0.14, 9.62) # | 0.84 (0.10, 6.99) # | 0.94 (0.48, 1.85) * | 0.96 (0.34, 2.71) # | 0.91 (0.38, 2.21) # |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Number of nodes taken at surgery** [$] | | | | | | |
| ≥12 | 1 (Reference) | | | 1 (Reference) | | |
| <12 | 1.13 (0.25, 5.08) * | - | 3.10 (0.59, 16.26) [#] | 1.02 (0.49, 2.12) * | 0.64 (0.21, 1.95) [#] | 1.61 (0.58, 4.49) [#] |
| Missing | 1.32 (0.17, 10.57) * | 2.05 (0.24, 17.66) [#] | - | 5.98 (2.17, 16.50) * | 5.63 (1.58, 20.04) [#] | 6.60 (1.23, 35.60) [#] |

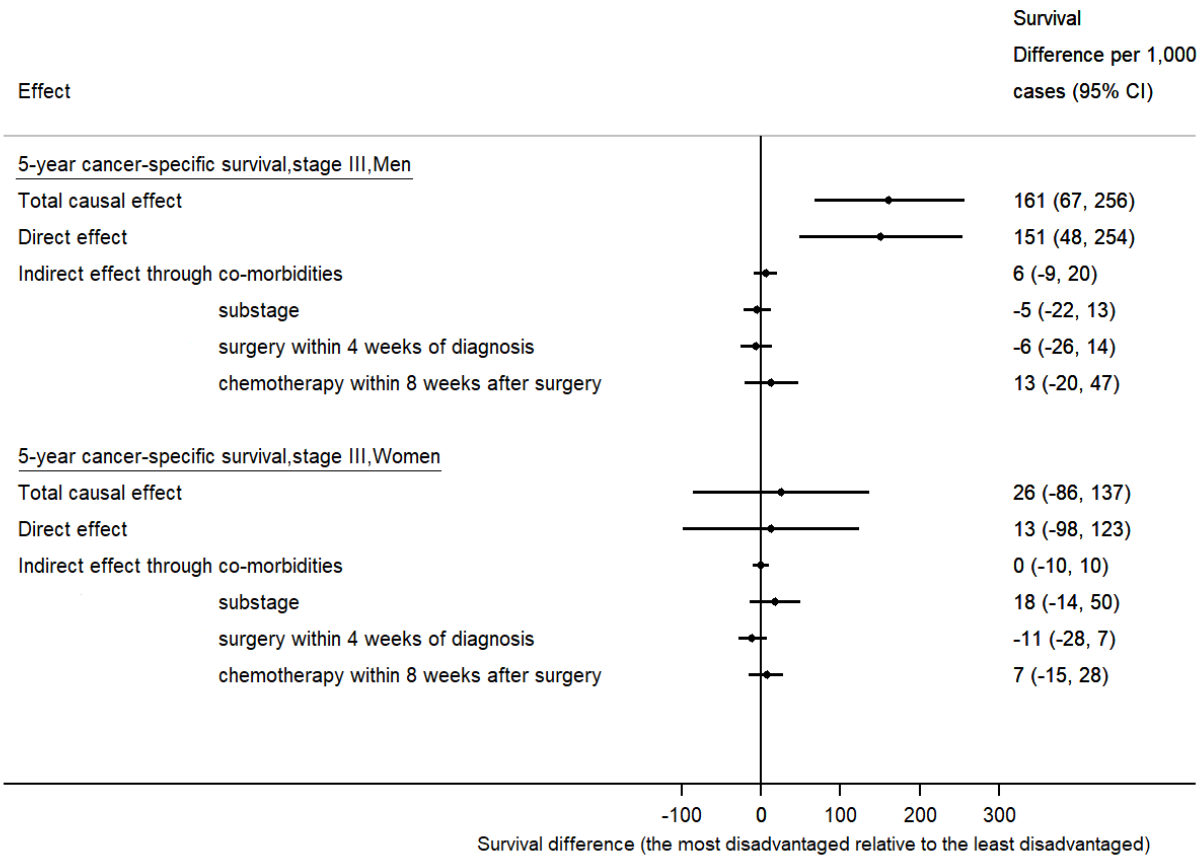
*Adjusted for sex and age; [#] Adjusted for age; [$] Restricted to cases who received surgery within 6 months of diagnosis




**Supplementary Figure 10.1A.** Directed acyclic graph (DAG) showing the assumed causal structure underlying the effect of area-level socio-economic disadvantage on survival from stage III colon cancer

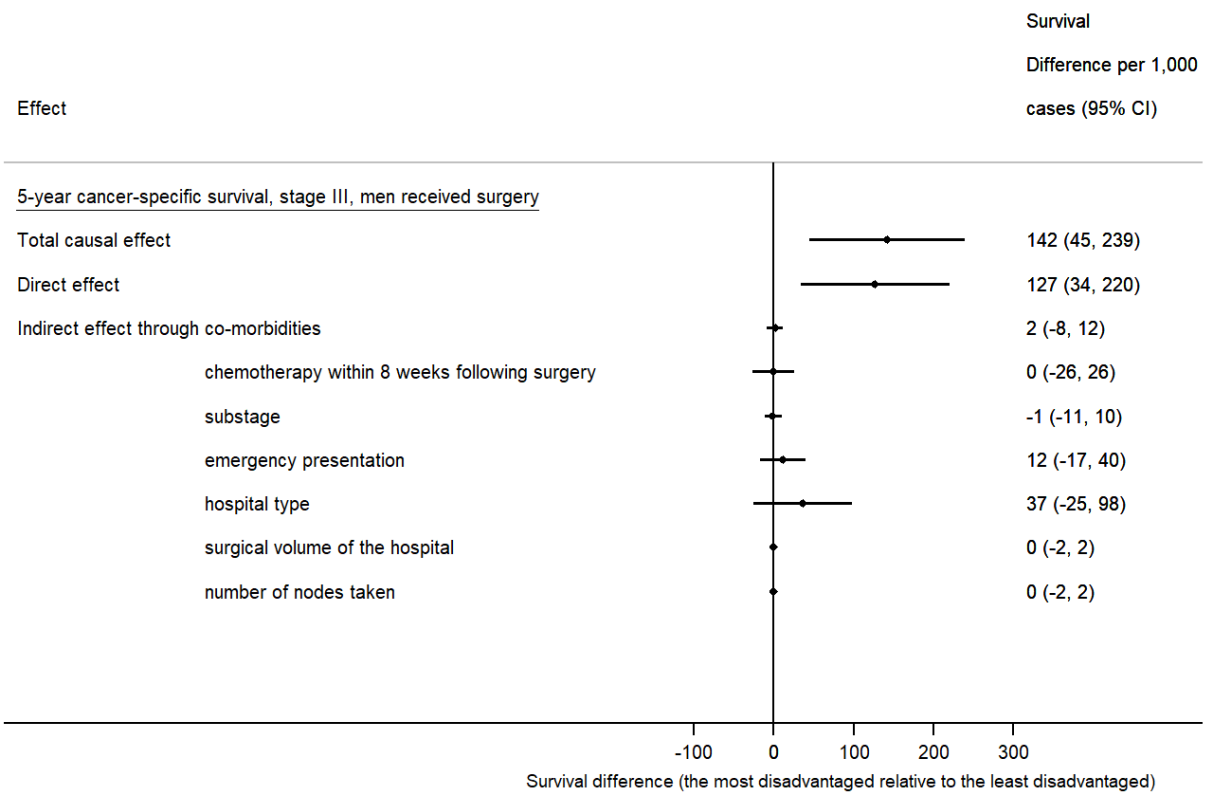



**Supplementary Figure 10.1B.** Directed acyclic graph (DAG) showing the assumed causal structure underlying the effect of area-level socio-economic disadvantage on survival from stage III colon cancer for cases who received surgery within 6 months following diagnosis

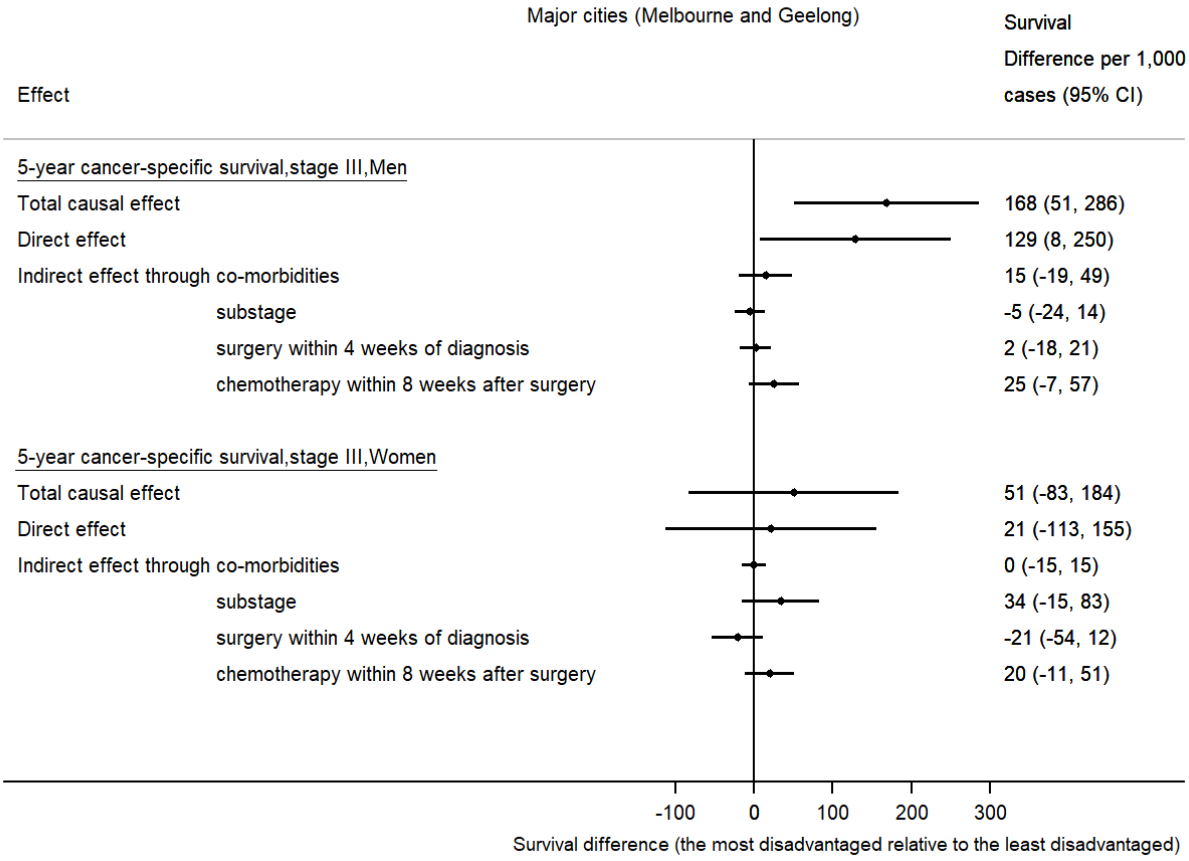



**Supplementary Figure 10.2.** Results of interventional mediation analysis with co-morbidities, substage, receiving surgery within 4 weeks of diagnosis and intravenous chemotherapy within 8 weeks after surgery as mediators of interest, and area-level socio-economic disadvantage and death from colon cancer within 5 years following diagnosis, Victoria, Australia, 2008-2011

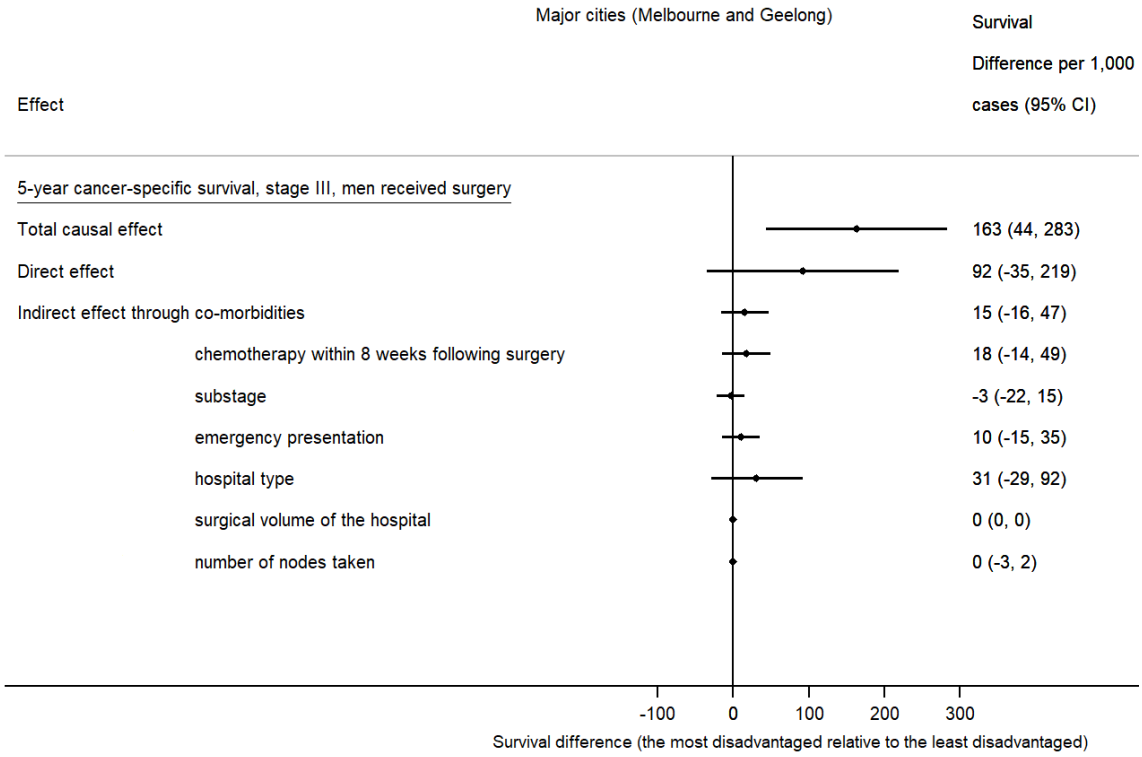
Mediation analyses were conducted by including an interaction term between disadvantage and substage as well as disadvantage and chemotherapy




**Supplementary Figure 10.3.** Results of interventional mediation analysis with co-morbidities, receiving chemotherapy within 6 months after diagnosis, hospital type, surgical volume of the hospital, number of nodes taken during surgery, waiting time to receive surgery as mediators of interest, and area-level socio-economic disadvantage and death from colon cancer within 5 years of diagnosis, Victoria, Australia, 2008-2011
Analyses were restricted to men receiving surgery within 6 months of diagnosis. Mediation analyses were conducted by including an interaction term between disadvantage and chemotherapy, disadvantage and substage, disadvantage and emergency presentation as well as disadvantage and hospital type




**Supplementary Figure 10.4.** Results of interventional mediation analysis with co-morbidities, substage, receiving surgery within 4 weeks following diagnosis and intravenous chemotherapy within 8 weeks following surgery as mediators of interest, and area-level socio-economic disadvantage and death from colon cancer within 5 years following diagnosis, Victorian major cities, Australia, 2008-2011




**Supplementary Figure 10.5.** Results of interventional mediation analysis with co-morbidities, receiving chemotherapy within 8 weeks following diagnosis, substage, hospital type, surgical volume of the hospital, number of nodes taken during surgery, waiting time to receive surgery as mediators of interest, and area-level socio-economic disadvantage and death from colon cancer within 5 years following diagnosis, Victorian major cities, Australia, 2008-2011