ETHNIC AND SOCIOECONOMIC INEQUALITIES IN BREAST CANCER SURVIVAL

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Abstract

There are likely to be many contributing factors to inequalities in cancer survival. The most commonly theorised are: differences in access to cancer care, screening, diagnosis, quality of care and treatment; biological differences; lifestyle/behavioural differences; and differences in comorbidities. To investigate explanations for inequalities in survival for women with breast cancer, a conceptual model was used to illustrate potential pathways, and studies conducted to isolate which pathways could explain ethnic and socioeconomic differences in survival.

The substantive body of this work comprises a systematic review, and analyses of datasets from England and New Zealand. Firstly, breast cancer survival differences between ethnic minority and majority groups are reviewed to examine the relationship between social determinants and behavioural factors. Secondly, inequalities by socioeconomic position (SEP) in screen-detected breast cancer survival in the South West of England are presented to examine social determinants and healthcare systems. Next, prognostic factors for New Zealand women with breast cancer by ethnicity and SEP are presented to examine the relationship between social determinants and biological factors. Finally, two separate analyses examine the relationship between ethnicity and SEP respectively, and biological factors and healthcare systems, as determinants of breast cancer survival in New Zealand.

SEP was found to explain a sizeable proportion of ethnic inequalities in breast cancer survival; however other factors were also identified as important. The largest contributors to ethnic inequalities appear to be factors associated with access to timely healthcare. There are considerable SEP inequalities in breast cancer survival, which are independent of ethnicity. A large proportion of the observed deprivation-gap in breast cancer survival can be accounted for by early detection.

Efforts to eliminate inequalities in breast cancer survival should focus on increasing attendance at breast screening for women of lower SEP. However efforts should also be made to ensure equal access through the secondary care system to address the attenuated survival inequalities that remained even among screen-detected women. Both timely access to and through healthcare will likely have an important impact on ethnic survival disparities. Biological tumour differences, which indicate breast cancer subtype, do not appear to explain survival inequalities, between women of different ethnicity or different SEP.

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CHAPTER ONE

Introduction

The burden of cancer has been steadily increasing over the past few decades.[1] There are significant differences in outcomes along the cancer continuum among various social groups. In particular there has been much descriptive work documented for cancer inequalities in incidence, mortality, and survival among ethnic and socioeconomic groups, both around the world,[2-6] and in New Zealand.[7-9] Cancer is a leading cause of death in New Zealand, and about one in four people will be affected at some time in their lives.[10] Yet the burden is far from equal with indigenous Māori, Pacific, and people from low socioeconomic backgrounds carrying a disproportionate cancer burden.[11,12]

Health is a fundamental human right for all people. This is understood internationally, by the World Health Organisation and governments around the world, which recognise that reducing disparities in health is a priority. Not only are inequalities unjust, they are unnecessary, avoidable, and they affect everyone.[13,14] Disparities in health between Māori, the indigenous people of Aotearoa/New Zealand, and non-Māori have been evident for all of its colonial history which dates back to the early 19th century. In 1840, the Treaty of Waitangi, a formal agreement for British settlement and a guarantee of protection of Māori interests, was signed by representatives of the British crown and Māori. The treaty's intention was to protect and maintain the well-being of all citizens, and its health implications relating to processes of good government and notions of participation and equity are important.[15] Reducing disparities has been recognized as a key goal in the health sector since the 1990s although by a number of measures, this has not necessarily translated into actual health gains for Māori.[9,16,17] Māori currently comprise approximately 15% of the total population of just over 4 million people. Pacific (7%), Asian (9%) and peoples of British/European descent (68%), make up the majority of the remaining population.[18]

Ethnicity is a complex social construct whose definition varies according to the political, social and historical circumstances of the particular country or region. An ethnic group is made up of people who may share characteristics including religion, customs or language; unique community of interests, feelings and actions; a shared sense of common origins or ancestry; and a common geographic origin.[19,20] The Statistics New Zealand definition of ethnicity states that: ethnicity is the ethnic group or groups that people identify with or feel they belong to; ethnicity is a measure of cultural affiliation as opposed to race, ancestry, nationality or citizenship; ethnicity is self perceived and people can belong to more than one ethnic group.[19] The way in which ethnic groups in New Zealand have been classified has changed over time. In 1986 the census changed the way it defined Māori from a biological (50% or more Māori blood) and ancestry (descendant of a Māori) definition to one based on an ethnic / cultural affiliation.[21] There are also variations in frameworks used to classify ethnicity. For example, work by Ajwani et al [16] has utilised sole ethnicity measures applied to those people who identify with a single ethnic group only, alongside a total ethnicity measure, which counts multiple ethnic affiliations for each person and has been a standard classification used by Statistics New Zealand.[19] Additionally, ethnicity has also often been assigned using a prioritised system in other government datasets such as the New Zealand Cancer Registry.[22]

Socioeconomic position (SEP) can be measured in many ways; at the individual level, the household level, and the area or neighbourhood level (e.g. education, occupation, income, wealth, postcode). There are strengths and limitations of all measures of SEP, and these can vary by age, gender, ethnicity, and country. Education has been considered to be a more stable indicator, but it does not capture significant life or income changes that can alter SEP. Norms for highest educational attainment also change with time and location, and earnings can be vastly different among people with

the same qualifications.[23] Occupational measures cannot readily be used for people outside the paid labour force such as homemakers (chiefly women) and unemployed persons. Furthermore, an individual marker of SEP would not necessarily provide an accurate picture of combined household SEP, or standard of living.[23] Area-based measures of SEP represent those aspects of people's living conditions which are not captured by individual or household measures. They can be used for all ages and can be applied in the same way to men and to women. They may provide a more stable estimate of relevant economic circumstance, as compared to income or education. An example of an area-based SEP measure is the New Zealand Deprivation Index which was developed in 1991 and .has been utilised extensively in the research and government policy environment since that time.[24,25] It uses a weighted average of nine census indicators (benefit income, employment, household income, communication, transport, support, qualifications, living space, and home ownership) which reflect eight dimensions of deprivation. The index provides a deprivation score for each meshblock which are geographical units defined by Statistics New Zealand, containing a median of approximately 87 people.[25] A score of 10 represents the most deprived 10% of New Zealand areas, while 1 represents the 10% least deprived areas.[25]

This thesis addresses the social determinants of survival from breast cancer. Although there is evidence of disparities in cancer outcomes across ethnic and socioeconomic groups in New Zealand, very little work has gone beyond descriptive analyses. This research further examines the causes of disparities for women with breast cancer in an effort to identify possible strategies for intervention. The focal point of this investigation of disparities is survival. In order to ascertain the best pathways and points along the cancer continuum to focus interventions to reduce disparities in survival I used this as an outcome measure but looked at possible modifiable behaviours and exposures across the length of the continuum.

A special report on the unequal impact of cancer on Māori found Māori women were 21% more likely to be diagnosed with breast cancer and 68% more likely to die from breast cancer than non-Māori women in New Zealand.[9] Five-year relative survival (RS) has been estimated at 0.74 (95% confidence interval (CI) 0.71 to 0.78) for Māori, 0.72 (CI 0.67 to 0.78) for Pacific, and 0.83 (CI 0.82 to 0.84) for non-Māori/non-Pacific women diagnosed with breast cancer.[8] Similarly for women diagnosed with breast cancer living in the most deprived areas of New Zealand, RS has been estimated at 0.77 (CI 0.75 to 0.70), compared with 0.84 (0.82 to 0.85) for their counterparts in the most affluent areas.[7]

One of the two overall purposes of the New Zealand Cancer Control Strategy is to reduce cancer inequalities.[26] To develop strategies to diminish ethnic and socioeconomic inequalities, we first need to understand the aetiology of these differences. We need to distinguish which factors are involved in the establishment of differences and what the relative contribution of each of these factors is. The likelihood is that there are many contributing factors to cancer inequalities and the most commonly theorised include: differences in access or quality of care; detection (screening and diagnosis); treatment; tumour biology; genetic differences, lifestyle and behavioural differences; differences in comorbid conditions, and underlying racism.

Conceptual model

It is useful to employ a comprehensive framework for examining disparities in cancer outcomes.[27] There are many frameworks dedicated to understanding the social determinants of health such as those used by the WHO and their Commission for Social Determinants of Health [28,29] and others adopted for use in New Zealand.[13,30]

There are also frameworks which specifically focus on the social determinants of cancer inequalities.[31,32]

For the purpose of this investigation I have developed a conceptual model to illustrate the potential pathways by which ethnicity and SEP could influence outcomes for women with breast cancer. Figure 1.1 shows how ethnicity may have a direct influence on individual and health system factors, or these factors could be influenced via socioeconomic pathways. Potential key pathways of ethnic and socioeconomic inequalities may travel through individual risk factors to affect points along the cancer continuum, or there could be important routes via the health care system. Possible mediating pathways include differences in tumour biology, prognostic factors, and comorbid conditions. It may be that there are one or two key pathways influencing ethnic and socioeconomic inequalities, or that there are many pathways in play.

The term ‘access’, relates to a person’s entry both into, and appropriate progression through, the health care system.[33] Screening coverage is known to differ between social groups[34,35] and early detection is positively related to improved survival. Early diagnosis is also important for symptomatic women, and therefore access to primary care, which can differ by social grouping,[36] could be a contributing factor to cancer outcomes. There have been reported discrepancies in both the choice of cancer treatments between social groups,[37] and in the efficacy of the same treatments,[38] which could be critical to survival inequalities. Research examining racism and discrimination as important mediators in health care access, alongside the interpersonal and population health effects resulting from racism, is still relatively new both internationally and in New Zealand.[39-41]

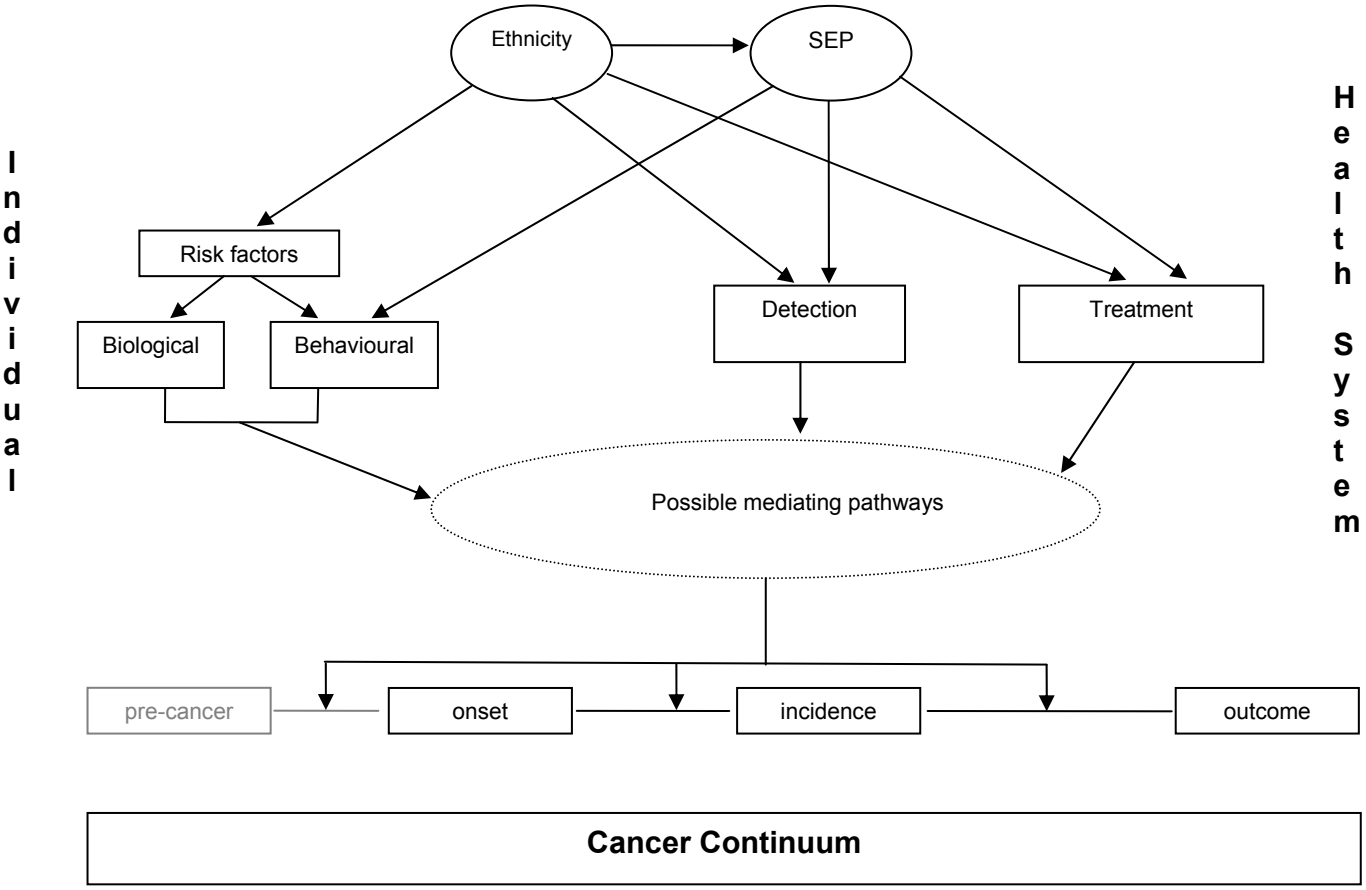

Figure 1.1 Conceptual model of potential pathways influencing ethnic and socioeconomic inequalities in breast cancer survival

Breast cancer is a heterogeneous disease. It has a range of features, pathological and clinical, which can have an effect on the disease and its treatment including tumour grade, extent of disease (stage), tumour size, oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor-type 2 (HER2) statuses. Tumour grade relates to the extent of cell differentiation in the cancer tissue and is an indicator of disease aggressiveness. Extent of disease indicates the stage of development, or spread, that the tumour has reached at the time of diagnosis. The size of the tumour at the widest point is also of clinical importance as large tumours have a worse prognosis than small tumours. Breast tumours that are positive for oestrogen receptors or

progesterone receptors are not as fast growing as hormone receptor negative tumours; they are responsive to hormonal treatments and are associated with improved survival. HER2 positive cancers tend to be more aggressive than HER2 negative cancers, and are associated with poor survival and increased rates of cancer recurrence. Differences in tumour biology among ethnic groups may be genetically determined, although they may also be due to differences in environmental exposure, which is the likely explanation for observed differences in tumour biology between socioeconomic groups. Behavioural factors such as smoking, diet, exercise, body weight, and reproductive history both influence cancer incidence and differ between social groups. These factors could also play a role in determining tumour biology, prognosis, and survival inequalities. Other important factors that notably influence both decisions along the cancer continuum and cancer outcomes are age and co-morbidity. Age and co-morbidity limit options for diagnostic tests and treatment for breast cancer.[42] Furthermore co-morbidity is positively associated with mortality.[43] To achieve a complete picture, in principle, all prognostic factors should be considered as potential explanatory variables in social differences of cancer outcomes.[44]

The overall objective of this body of work is to investigate explanations for ethnic and socioeconomic inequalities in survival for women with breast cancer.

Thesis structure

Chapter 2 systematically reviews breast cancer survival differences between ethnic minority and majority groups, and attempts to quantify the contribution of factors to these differences. This section examines the relationship between social determinants (ethnicity and SEP) and behavioural factors (smoking, alcohol consumption, and BMI) to establish whether intervening at the individual level would affect ethnic disparities in survival from breast cancer.

Chapter 3 investigates SEP inequalities in screen-detected breast cancer survival in the South West of England, UK. This section examines social determinants (SEP) and healthcare systems (breast screening programme) to ascertain whether SEP is still a determinant among women diagnosed with breast cancer within the same screening system.

Chapter 4 explores prognostic factors for New Zealand women with breast cancer by ethnicity and SEP. This section examines the relationship between social determinants and prognostic tumour factors (extent of disease, tumour grade, size, hormonal status, and HER2 status) to ascertain whether these vary by social groups.

Chapters 5 and 6 present associations between ethnicity and SEP in breast cancer survival in New Zealand. These sections examine social determinants, healthcare systems, and tumour factors in an effort to further isolate pathways and effective points of intervention for both ethnic and SEP inequalities in breast cancer survival.

Chapter 7 reviews the results, strengths and limitations of the complete body of work presented. Key findings and implications of the research are discussed, leading to further research and suggested recommendations in order to address disparities in breast cancer survival in New Zealand.

CHAPTER TWO

Do lifestyle or social factors explain ethnic/racial inequalities in breast cancer survival? A systematic review and meta-analysis

Fiona McKenzie and Mona Jeffreys

Despite numerous studies documenting ethnic inequalities in breast cancer survival between minority/majority ethnic groups worldwide, reasons for these inequalities remain unclear. We performed a systematic review of published literature to identify studies which investigated the explanatory power of smoking, alcohol consumption, body mass index (BMI) and socioeconomic position (SEP) on ethnic inequalities in breast cancer survival. Sixteen studies were included in the review. From five studies, we found that differences in breast cancer survival between ethnic groups may be in part explained by BMI, but there was little evidence to implicate smoking or alcohol as explanatory factors of this inequality. From 12 studies we found that SEP explains part of the ethnic inequality in all-cause survival, but that this was not evident for breast cancer-specific survival. SEP explains more of the disparities in African American versus white women in the US, compared to other ethnic comparisons. Furthermore, given social patterning of BMI and other lifestyle habits, it is possible that our results for SEP and BMI are measuring the same effect. We make suggestions regarding the role of epidemiology in facilitating further research to better inform the development of effective policies with which to address ethnic differences in survival.

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The manuscript which appears here reflects what was published, and also incorporates comments received by the examiners as part of the PhD conferment process

Introduction

Ethnicity and race are complex constructs whose definitions vary from country to country. The constructs can include shared history, cultural affiliation and practice, language, religion, lifestyle, and sometimes biology [45,46]. For the purpose of this review, we will use the word ethnicity to cover race and/or ethnicity. Due to different definitions of ethnicity, we would not necessarily expect to see the same ethnic differences in survival in different countries. However, lower breast cancer survival has consistently been found not only in African American compared to white American women [47-49], but also between other racial/ethnic groups in the US [48,50,51], and between indigenous and other groups in New Zealand [8,9] and Australia [52]; while South Asian women in the UK appear to have a better survival profile than white women [53,54]. Many possible reasons for these disparities have been suggested, which fall into the following broad categories: (a) structural barriers / system factors; (b) physician / clinical factors; and (c) patient factors [55-57]. Within the first two categories fall factors such as access to health care and screening, receipt of optimum treatment, and grade / disease stage at diagnosis. However, there is little empirical evidence regarding the role that patient factors play in explaining ethnic inequalities in breast cancer survival. We need to pinpoint the causes of ethnic differences in survival to create effective policies with which to address them. Policy options would be very different depending on whether ethnic differences are due to socioeconomic factors, lifestyle, treatment, or access to care.

There has been some work done which seeks to separate socioeconomic status from other influences on ethnic differences in survival. Newman and colleagues reviewed literature to investigate whether ethnic inequalities exist after accounting for socioeconomic position (SEP) in 2002 [58] and further updated their findings in 2006 [59]. The 2006 review included 20 studies which estimated survival for African American and

white American breast cancer patients. Newman's pooled analysis found African American ethnicity to be an independent predictor of worse overall survival, showing a 28% excess risk of death after adjustment for SEP measures (hazard ratio (HR) 1.28; 95% confidence interval (CI): 1.18, 1.38).Disease-specific results were based on eight pooled studies which looked specifically at death from breast cancer and, while smaller, were also found to be statistically significant (HR 1.19; 95% CI: 1.09, 1.30).

While there is an increasing amount of data available on the association between personal risk factors and survival (e.g. smoking [60-65], alcohol [66-70], weight [61,71-77]), there is a paucity of evidence comparing the association between those risk factors and differences in survival between ethnicities. Several authors have postulated that these factors could explain some or all of the observed ethnic inequalities in breast cancer survival [5,78-83]. In an effort to identify possible means by which we can address survival disparities, our main interest is focused on investigating modifiable lifestyle risk factors in majority and minority populations, and to determine the magnitude of the part of the inequality attributable to individual risk factors. However, as many studies look at SEP, we also decided to include that risk factor in the review; despite it not being easily amenable to modification, it is highly relevant, given that the lifestyle factors in which we are interested are socially patterned. The previously reported meta-analysis [59] was restricted to only one ethnic comparison within one country, whereas the current review is more extensive and international, and investigates other ethnic minority populations as well.

The aim of this review is to summarise the evidence of whether lifestyle factors (smoking, alcohol consumption, body mass index (BMI) or SEP) explain some or all of the ethnic inequalities in breast cancer survival, and, where possible, to quantify this.

Methods

Search methodology

We conducted a systematic search of published English language studies indexed in MEDLINE (1966 to June 2008). We devised a search strategy based on both text and MeSH terms, to identify papers which investigated reasons for breast cancer survival in at least two ethnic groups. The search terms used were: ((mortality) OR (prognosis) OR (cohort studies) OR (follow-up studies) OR (survival analysis) OR (disease-free survival) OR (survival rate) OR ("survival") OR ("overall survival")) AND ((breast neoplasms) OR ("breast cancer") OR ("breast carcinoma") OR ("malignant breast tumor") OR ("mammary cancer")) AND ((ethnic groups) OR ("ethnic minority") OR ("ethnicity") OR ("race") OR (racial stocks)) AND (("alcohol consumption") OR (alcohol drinking) OR (smoking) OR (obesity) OR (body weight) OR (body mass index) OR ("BMI") OR (social class) OR (education) OR (income) OR ("SES") OR (Socioeconomic factors) OR (poverty) OR ("deprivation")) AND ((Humans[Mesh]) AND (English[lang])). The titles resulting from this search were reviewed independently by each author. Where either author thought the paper could be relevant, it was included. The abstracts of included papers were then independently examined by the same two authors. The full text of the paper was obtained if the abstract mentioned i) breast cancer survival, ii) ethnicity and iii) at least one risk factor (smoking, alcohol consumption, BMI or SEP). Disagreements were resolved by consensus. Hand searches of the bibliographies of review papers identified by the search, as well as relevant papers identified, were conducted, and these papers were subjected to the same relevance criteria as those found during the initial search process. In addition, a search of EMBASE (1980 to July 2008) was performed with a broader search terms than the MEDLINE search ((ethnicity or race) and breast and cancer and survival) by one reviewer (MJ), but this did not result in the identification of any further relevant papers.

Inclusion and exclusion criteria

Studies were included if they reported on breast cancer survival, defined as at least one of overall survival, excess mortality, disease-free survival, or mortality in a cohort of breast cancer patients. Studies which reported breast cancer mortality in a healthy cohort (i.e. not in a cohort of patients with breast cancer) were excluded, since this endpoint is a combination of incidence and survival. Where the same study was reported on in more than one publication, we included the data from the more recent publication.

Studies were included if they either i) presented data for at least two racial/ethnic groups or ii) reported data for a minority racial/ethnic group, and compared it to comparable published data from another other racial/ethnic group in the same country.

We realised from the first search that there would be very few studies investigating the effects of smoking, alcohol and BMI, and therefore two different approaches were used: i) narrative synthesis that was applied to studies investigating BMI, smoking and/or alcohol use. The small number of studies examining these factors in relation to ethnic differences in breast cancer survival precluded use of statistical methods of synthesis. ii) meta-analysis of studies from which it was possible to extract the effect of the ethnic inequality attributable to SEP. The following inclusion criteria were applied only to studies which reported the effect of SEP on ethnic inequalities in breast cancer survival. Only studies that reported results from which we could extract the association between SEP and inequalities in breast cancer survival were eligible for inclusion. Data could be extracted if two comparable models were presented, comparing the survival in one ethnic group to another, with the two models differing only by the inclusion of one or more SEP parameter(s). Methods to extract crude survival for the purposes of meta-analyses have been described [84]. We used these methods, where possible, with the

exception of studies which only presented crude survival data in graphical form, because of the difficulties in extracting data from such studies [84]. Studies in which non-comparable estimates for crude and adjusted survival measures, such as crude relative survival followed by adjusted hazard ratios, were not eligible for inclusion.

Data extraction

A proforma was developed in order to ensure consistent and accurate data extraction from included papers. Bibliographic information, study setting and source of patients, age range of patients, years of diagnosis and length of follow-up, ethnicity information (including number in each ethnic group), outcome of interest, crude and adjusted hazard ratios, adjustment parameters, exposure variable measurement, and whether the study was conducted in an equal access healthcare system were all recorded. Data were extracted to exact number of decimal places as reported in the original papers.

Pooling of results

As few studies investigated the effect of BMI, smoking or alcohol as explanations of ethnic inequalities in breast cancer survival, these studies were combined using a narrative synthesis. The studies which investigated the role that SEP plays in determining ethnic inequalities in breast cancer survival were combined using a DerSimonian & Laird [85] random effects meta-analyses. Separate models were run for each of three outcome measures: (i) overall survival; (ii) breast cancer specific survival; and (iii) excess mortality (a multivariable extension of relative survival). For each outcome, hazard ratios comparing the outcome between a minority and the majority ethnic group were obtained from the individual studies. For each outcome, separate pooled estimates were estimated for: (i) the crude (or age-adjusted) effect of ethnicity on outcome; (ii) the effect of ethnicity having additionally adjusted for clinical factors,

but not SEP; and (iii) the effect of ethnicity having adjusted for clinical factors and SEP. Inter-study heterogeneity was quantified using the Q statistic.

To investigate the magnitude of the effect of SEP on ethnic inequalities in survival, we estimated, for each study, the percentage change in the minority vs. majority survival disparity as follows: $(HR_{model1} - HR_{model2})*100/(HR_{model1}-1)$, where Model 2 is an estimate of survival disparity adjusted for age, clinical factors and SEP, and Model 1 is the same model, but without SEP. For papers in which a Model 1 was not presented, the two models used for this analysis were a crude model, and an SEP-adjusted model. In all instances, because of our inclusion criteria, the models compared differed only by one or more SEP parameter(s).

A linear regression model was used to estimate the effect of the following variables on the change in ethnic inequality following adjustment for SEP: (i) whether the comparison was between African American and White women in the US, since these formed the bulk of the evidence, or between other ethnic groups; (ii) whether they were set in the context of an equal access healthcare system; and (iii) decade of publication. Each of these models was run using all available comparisons, since some publications made comparisons between several pairs of ethnic groups. The standard errors of this regression were adjusted for this clustering effect.

To assess whether the results could have been affected by publication bias, we used funnel plots and Egger's regression asymmetry test [86]. All analyses were performed using Stata Statistical Software version 10.0 (StataCorp, College Station, TX).

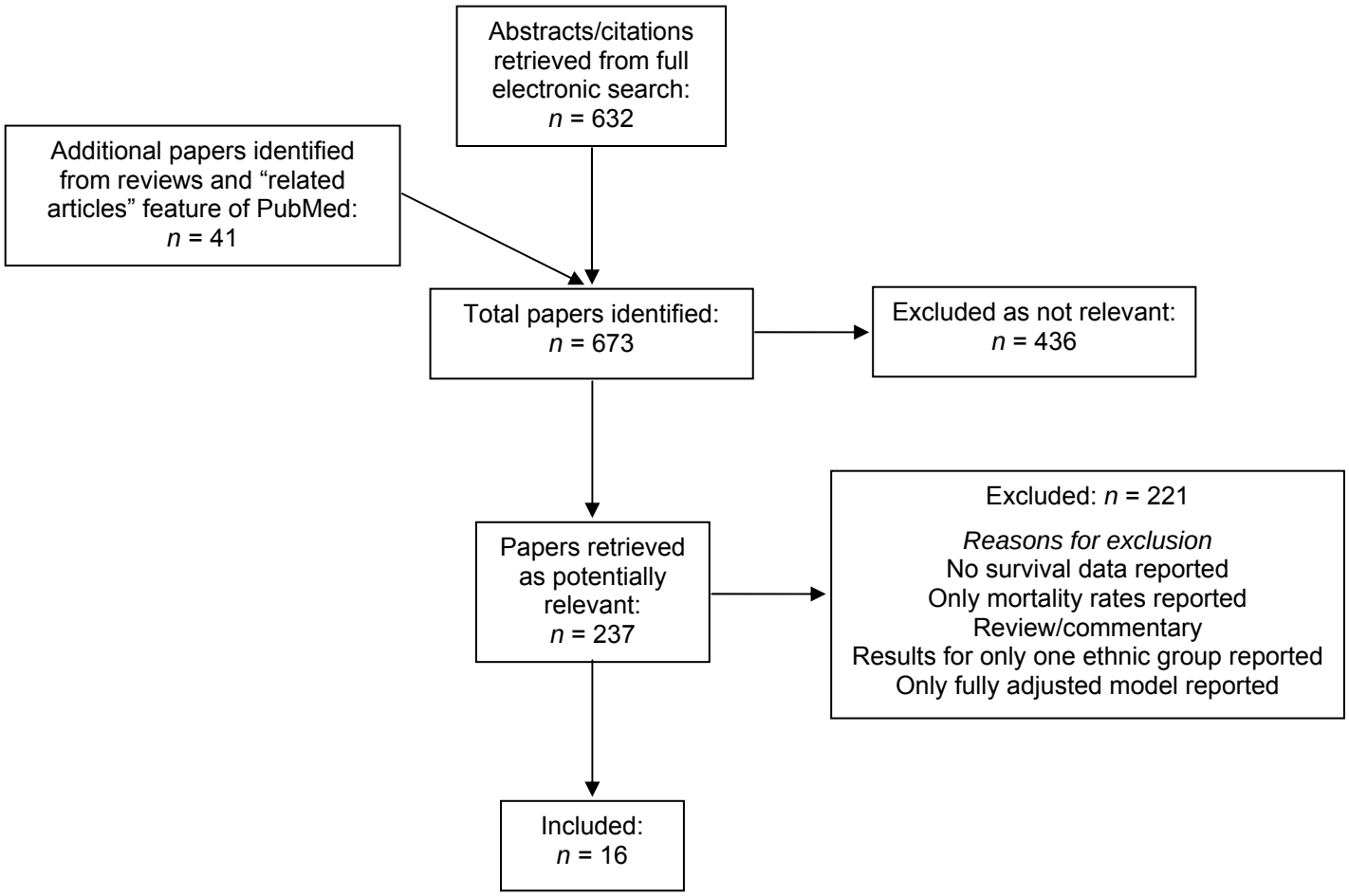


Figure 2.1: Flow diagram showing the selection of papers to be included in the review

Results

A total of 16 papers were included in this review, see Figure 2.1. The majority of these investigated the association between SEP and breast cancer survival, primarily using census-derived SEP measures.

Smoking, alcohol and BMI

The studies which investigated modifiable risk factors are described in Table 2.1 and the results are presented in Table 2.2. Only two studies could be identified in which the effects of smoking and alcohol on ethnic inequalities in survival were considered. In one [87], 698 African American women with breast cancer were compared with 5,879

white women. All women were treated in a US Department of Defense equal-access health care system. The crude association between race and all cause mortality showed a 40% higher risk in African American women. This association was unchanged by the simultaneous effect of adjusting for several factors, including clinical factors, smoking and alcohol consumption.

In the Black/White Cancer Survival Study [88], the two fold excess risk of both all cause and breast cancer specific survival among Black compared to White women in the US was not altered following simultaneous adjustment for comorbidities, smoking and BMI. In a relatively small study (n = 325), BMI was found to explain a small proportion of the Black/White breast cancer survival inequalities in women with Stage III cancer [89]. Tammemagi and colleagues investigated whether or not low BMI could be an explanation of ethnic inequalities in breast cancer mortality and non-breast cancer mortality [43]. Controlling for low BMI left the hazard ratio essentially unchanged. One final study, which followed up women diagnosed with breast cancer in the Women's Health Initiative, found that after adjusting for age, stage of disease, BMI, and whether the women was in the clinical or observational arm of the study, there still remained a statistically significant increased risk of death for African American compared to white women [90].

Taken together, these studies suggest, with a very limited evidence base, that it is unlikely that either smoking or alcohol can explain ethnic inequalities in breast cancer survival. It is possible that BMI may play some role in explaining these inequalities, but further research evidence is required. From our review, there do not appear to be any studies which have investigated whether these lifestyle factors could explain inequalities in breast cancer survival between groups other than African American and white American women.

Table 2.1. Description of studies investigating the effect of health behaviours (smoking, alcohol, BMI) on ethnic inequalities in breast cancer survival

First author	Publication year	Source of patients	Years of diagnosis	Age range of patients	Setting	Length of follow-up	Source of ethnicity data	Ethnicity 1	Ethnicity 2	Number of patients: ethnicity 1	Number of patients: ethnicity 2	Managed care/ equal access system
Coates [89]	1990	From 14 public and private hospitals. Stage III cases only	1975 to 1979	All	Georgia, US	Minimum of 5 years	Interview	Black	White	132	193	No
Tammemagi [43]	2005	Henry Ford Health System	1985 to 1990		Detroit, US	To 2002, median follow up 10 years	Self reported (registration forms)	Black	White	264	642	No
Eley [88]	1994	Black White Cancer Survival Study	1985 to 1986	20 to 79 years	Georgia, Louisiana, California, US	To December 1990 (median 59 months)	Not stated	Black	White	612	518	No
Chlebowski [90]	2005	Women's Health Initiative trial or observational study		50 to 79	40 centres in US	Medium follow up 3.1 years	Questionnaire	African American	White	242	3455	No
Wojcik [87]	1998	DoD central tumor Registry	1975-94	All	US (Dept of Def)		Not stated	White	African American	5879	698	Yes (DoD)

Table 2.2. Results from studies investigating the effect of health behaviours (smoking, alcohol, BMI) on ethnic inequalities in breast cancer survival

First author	Publication year	Outcome	Crude Model		Model 1		Model 1 Parameters	Model 2		Model 2 Parameters
			HR	95% CI	HR	95% CI		HR	95% CI	
Coates [89]	1990	All cause mortality	1.61	1.02, 2.53	1.54	0.89, 2.66	Age, education, occupational status, time to care, breast self-examination, menopausal status, personal cancer history, lymph node status, radiation treatment, chemotherapy, hormonal therapy.	1.44	0.82, 2.52	Model 1 plus BMI
Tammemagi [4;	2005	Non breast cancer mortality	1.27	1.00, 1.63				1.26	0.98, 1.63	Crude model plus low BMI
		Breast cancer mortality	1.47	1.08, 2.00				1.49	1.07, 2.07	
Eley [88]	1994	Breast cancer mortality	2.1	1.6, 2.8	2.2	1.7, 2.9	Age, location	2.0	1.5, 2.7	Model 1 plus comorbidities, smoking, BMI
		All cause mortality	2.2	1.7, 2.7	2.2	1.7, 2.7	Age, location	1.9	1.5, 2.4	
Chlebowski [90]	2005 [a]		1.57	0.95, 2.47				1.79	1.05, 3.05	Age, BMI, tumor stage, study component
Wojcik [87]	1998	All cause mortality	1.41	1.17, 1.70	1.41	1.16, 1.70	Age, stage	1.41	1.16, 1.71	Model 1 plus wait time, tumor pathology, family history, marital, dependent, alcohol, tobacco

[a] This paper did not report a crude hazard ratio of ethnicity on mortality, but noted the cumulative mortality was 21/242 for black and 191/3455 for white women. The crude effect given is therefore a RR not a HR

Table 2.3. Description of studies investigating the effect of socioeconomic factors on ethnic inequalities in breast cancer survival

First author	Publication year	Source of patients	Years of diagnosis	Age range of patients	Setting	Length of follow-up	Source of ethnicity data	Ethnicity 1	Ethnicity 2	Number of patients: ethnicity 1	Number of patients: ethnicity 2	SEP measure	Managed care/ equal access system
dos Santos Silva [54]	2003	Cancer Registry	1986-1993	All (range not stated)	SE England	31-Dec-97	Assigned based on name	South Asian	Non-South Asian	1,037	50,201	Census (Carstair's index)	Yes (UK)
Perkins [91]	1996	One Cancer Centre	Treated between 1958 to 1987	All (range not stated)	Texas, US	5 years (range 0.1-416 months)	Patient's self-report	Black	White	801	2,581	Insurance pay code	No
Bassett [92]	1986	Western Washington Cancer Surveillance System	1973 to 1983	All (range not stated)	Washington, US	To December 1983 (667 black woman-years and 3,156 white woman-years)	Not stated	Black	White	251	1,255	Race-specific census block group social class indicators (several)	No
Ansell [93]	1993	Hospital / University cancer registry	1973 to 1985	All (range not stated)	Chicago, US	8.3yr mean / up to 13 yrs	Not stated	Black	White	887	265	Race-specific (where available) census tract information on income, education, employment, and poverty status	No

First author	Publication year	Source of patients	Years of diagnosis	Age range of patients	Setting	Length of follow-up	Source of ethnicity data	Ethnicity 1	Ethnicity 2	Number of patients: ethnicity 1	Number of patients: ethnicity 2	SEP measure	Managed care/ equal access system
O'Malley [49]	2002	Greater San Francisco Bay Area Cancer Registry (part of SEER)	1988 to 1992	All (range not stated)	California, US	up to July 2001	From medical records	Black	White	940	10,414	Race-specific measures for census block on income, education, poverty and employment	No
								Hispanic		1,100			
								Asian / Pacific Islander		1,180			
Velikova [53]	2004	Yorkshire Cancer Registry	1986 to 1994	All (range not stated)	England	01/01/1999	Nam Penchan algorithm, place of birth, name	South Asian	Non-South Asian	120	16,759	Carstairs index	Yes (UK)
Franzini [94]	1997	The University of Texas M. D. Anderson Cancer Center	1987 to 1991	All (range not stated)	Texas, US	To Sept 1992, mean follow-up 30 months	Not stated	Black	White	163	964	Ability to pay for their treatment based on actual household income adjusted for number of dependents and insurance coverage.	No
El-Tamer [95]	1999	Cancer registry (two breast cancer centres)	1982 to 1995	All	US	Median follow-up 36 months	Self-identification	Afrian American	Caucasian	1,297	448	Median income based on zip code	No

First author	Publication year	Source of patients	Years of diagnosis	Age range of patients	Setting	Length of follow-up	Source of ethnicity data	Ethnicity 1	Ethnicity 2	Number of patients: ethnicity 1	Number of patients: ethnicity 2	SEP measure	Managed care/ equal access system
Du [50]	2008	SEER stage I–IIIA	1992 to 1999	65+ years	US	To Dec 2002, up to 11 years	Not stated	African American (Non-Hispanic Black)	White	1971	30484	Census tract data on education, poverty and income	All cases had full coverage of both Medicare Part A & Part B (& not enrolled with HMOs)
								Other		2574			
Greenwald [96]	1996	Centralized Cancer Patient Data System	1977 to 1981	Under 100 yrs	US	To Feb 1985	Not stated	Black	White	6896 total, not stated by ethnicity		Median education (% with high school grades) based on postcode	No
Curtis [48]	2008	SEER	1994 to 1999	68 years and over			Not stated	Black	White	2479	35878	Median income based on zip code	No
								Hispanic		1172			
								Asian / PI		1086			
Eley [88]	1994	Black White Cancer Survival Study	1985 to 1986	20 to 79 years	Georgia, Louisiana, California, US	To December 1990 (median 59 months)	Not stated	Black	White	612	518	Individual' s poverty index (based on income and dependents), occupation	No

Table 2.4. Results from studies investigating the effect of socioeconomic factors on ethnic inequalities in breast cancer survival

First author	Publication year	Outcome	Crude Model		Model 1		Model 1 Parameters	Model 2		Model 2 Parameters
			HR	95% CI	HR	95% CI		HR	95% CI	
dos Santos Silva [54]	2003	Excess mortality rate ratio	0.82	0.72, 0.94				0.77	0.67, 0.87	Crude model plus deprivation
Perkins [91]	1996	All cause mortality (5 years)	1.63	147, 1.82	1.35	1.21, 1.51	Stage	1.15	1.03, 1.29	Model 1 plus pay code
Bassett [92]	1986	All cause mortality	1.31	1.03, 1.67	1.35	1.05, 1.72	Age, stage, histology	1.10	0.83, 1.46	Model 1 plus social class (poverty, education and households on public assistance)
Ansell [93]	1993	All cause mortality	1.20	1.00, 1.41	1.26	1.02, 1.57	Age, stage	1.17	0.95, 1.38	Model 1 plus income
O'Malley [49]	2002	Death from breast cancer	1.81	1.59, 2.07	1.28	1.12, 1.46	Age, stage, clinical factors	1.22	1.05, 1.38	Model 1 plus SES
			1.39	1.22, 1.59	1.05	0.92, 1.20		1.01	0.87, 1.17	
			1.14	0.99, 1.31	0.98	0.85, 1.13		0.96	0.83, 1.11	
Velikova [53]	2004	5 year risk of death (all cause)	0.74	0.54, 0.99				0.68	0.50, 0.91	Crude model plus SES
Franzini [94]	1997	All cause mortality	1.98	1.40, 2.81				1.54	1.06, 2.23	Crude model plus SES
El-Tamer [95]	1999	BC death (paper states death from disease)	1.27	1.05, 1.55				1.16	0.95, 1.42	Crude model plus income

First author	Publication year	Outcome	Crude Model		Model 1		Model 1 Parameters	Model 2		Model 2 Parameters
			HR	95% CI	HR	95% CI		HR	95% CI	
Du [50]	2008	All cause mortality	1.35	1.27, 1.45	1.07	0.99, 1.15	Age, stage, grade, size, hormone receptor status, comorbidity, year of diagnosis, SEER region, primary surgery, radiotherapy, chemotherapy, marriage status	1.02	0.84, 1.10	Model 1 plus SES
		Breast cancer mortality	1.83	1.56, 2.16	1.25	1.05, 1.49		1.21	1.01, 1.46	
		All cause mortality			0.83	0.77, 0.90		0.81	0.75, 0.88	
		Breast cancer mortality			0.90	0.72, 1.13		0.89	0.70, 1.11	
Greenwald [96]	1996	All cause mortality			1.542	1.365, 1.741	Age	1.483	1.303, 1.687	Model 1 plus SES
Curtis [48]	2008	Breast cancer mortality	1.63	1.48, 1.80	1.10	1.00, 1.22	Age, stage, grade, ER status, tumor characteristics, SEER site, screening status, treatment, comorbidities	1.08	0.97, 1.20	Model 1 plus community, income
			1.24	1.06, 1.46	0.88	0.75, 1.04		0.88	0.75, 1.04	
			0.59	0.45, 0.77	0.62	0.47, 0.80		0.61	0.47, 0.79	
Eley [88]	1994	Breast cancer mortality	2.1	1.6, 2.8	2.2	1.7, 2.9	Age, location	2.0	1.5, 2.7	Model 1 plus marital status, education, poverty index, usual source of care
		All cause mortality	2.2	1.7, 2.7	2.2	1.8, 2.8		2.0	1.6, 2.6	

Socioeconomic position

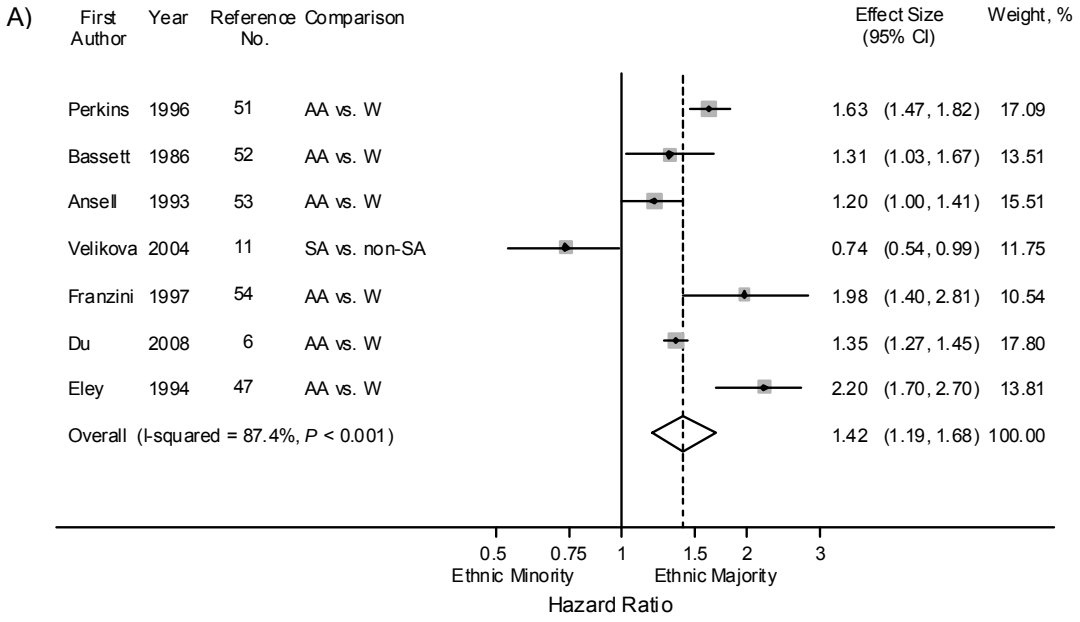
The studies which investigated socioeconomic position are described in Table 2.3 and the results are presented in Table 2.4.

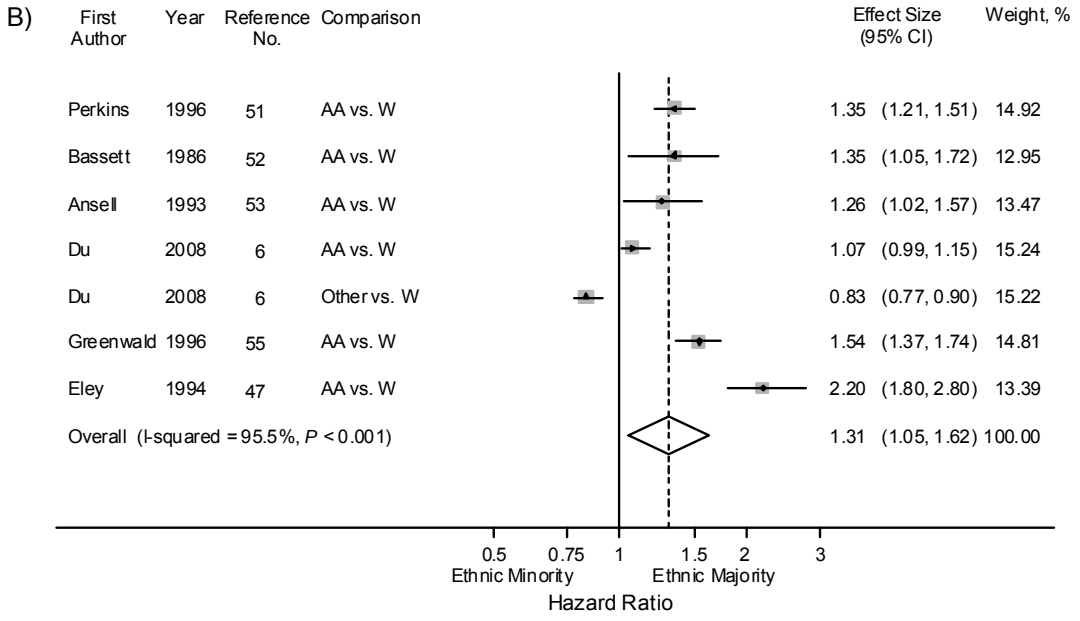
Excess mortality. Only one study used excess mortality modeling [54] to investigate ethnic inequalities in survival. In this study, women were assigned to South Asian ethnicity by a computerized algorithm. South Asian women were less likely to die during the follow-up period, crude excess mortality rate ratio (RR) 0.82 (95% CI: 0.72, 0.94). Adjusting for a census-derived measure of deprivation strengthened this association (0.77, CI: 0.67, 0.87).

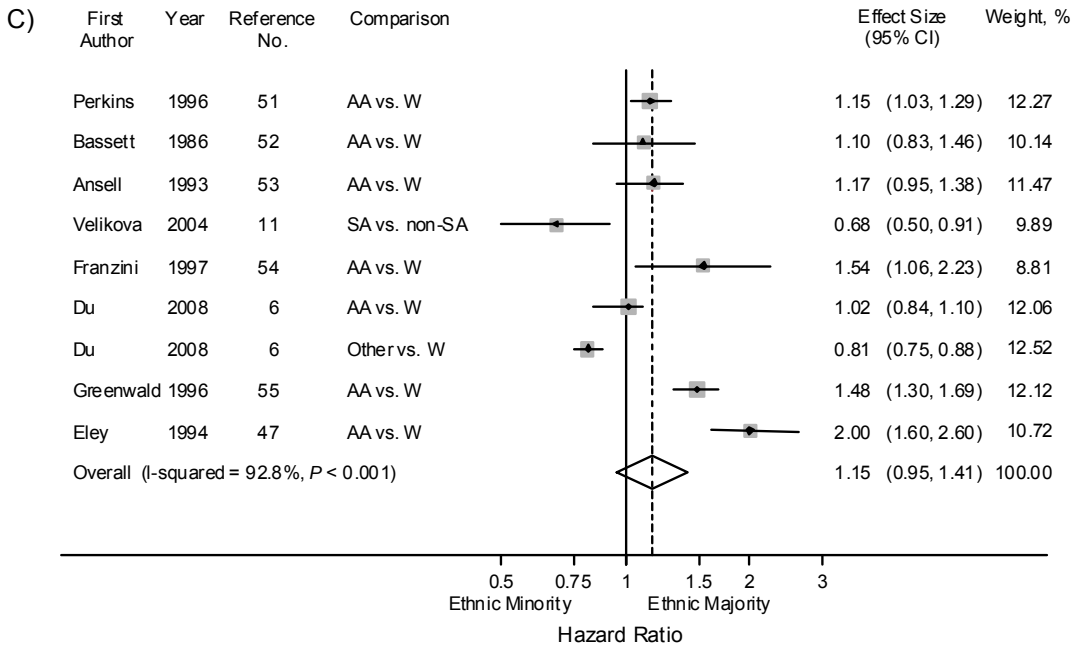
All cause mortality. Eight studies (nine comparisons) [50,53,88,91-94,96] investigated ethnic inequalities in all cause mortality in cohorts of women with breast cancer. Seven of these compared African American to white women in the US, one compared other (non African American) to white women in the US, and one compared South Asian to non-South Asian women in the UK. Seven studies contributed to the overall crude analyses. The pooled hazard ratio showed that women in the minority ethnic groups were more likely to die during the follow-up time (HR 1.42, 95% CI: 1.19, 1.68), see Figure 2.2a. However, there was significant heterogeneity among studies, $p < 0.001$. The exclusion of the one study which showed considerable difference in its results, with better survival in the ethnic minority population [53], slightly strengthened the pooled hazard ratio but did not remove the inter -study heterogeneity. Six studies (seven comparisons) adjusted for factors other than SEP [50,88,91-93,96]. The pooled hazard ratio was reduced to 1.31 (95% CI: 1.05, 1.62), see Figure 2.2b. Further adjusting for SEP reduced the hazard ratio to 1.15 (95% CI: 0.95, 1.41), see Figure 2.2c.

Figure 2.2: Association between ethnicity (minority vs. majority ethnic groups) and all cause mortality in women with breast cancer.

A) Crude association; B) Adjusted association, adjusted for "Model 1 parameters", see Table 2.4; C) Adjusted association, further adjusted for socioeconomic position, see "Model 2 parameters", Table 2.4. AA, African-American; W, White; SA, South Asian. The area of each square is proportional to the precision of the estimate and hence to the weight that the individual study contributed to the meta-analysis.





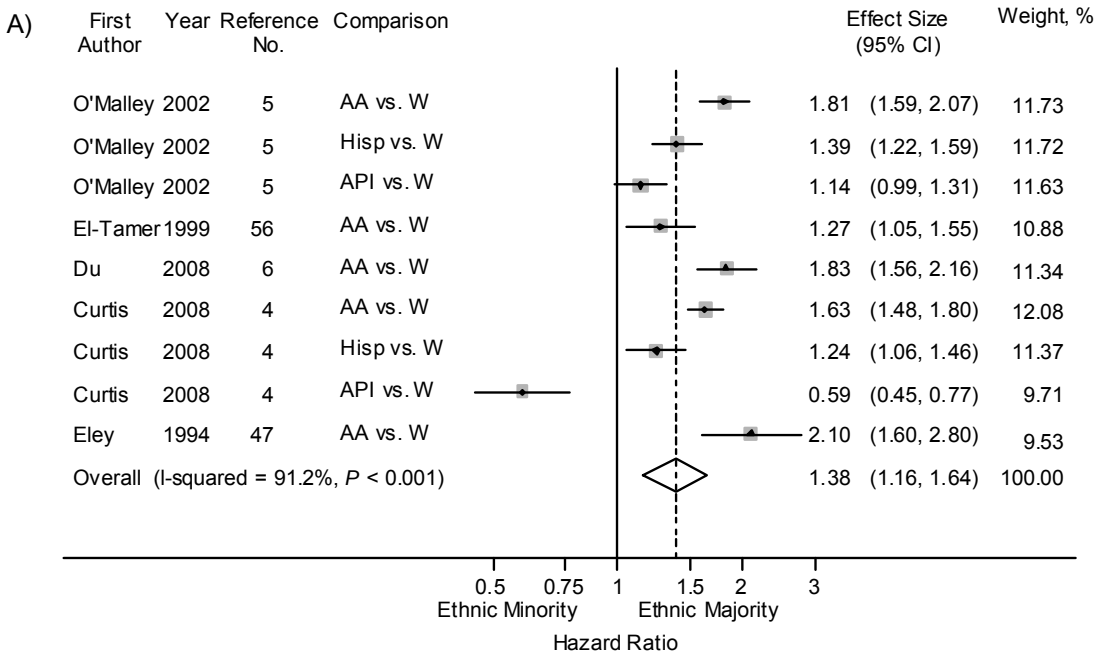


Breast cancer mortality. Five studies (ten comparisons) [48-50,88,95] investigated ethnic inequalities in breast cancer mortality in cohorts of women with breast cancer, all based in the US. Five of these compared African American, two compared Hispanic, two Asian/Pacific Islander and one non-African America women to white women. Five studies (nine comparisons) contributed to the overall crude analyses. The pooled hazard ratio showed that women in the minority ethnic groups were more likely to die during the follow-up time (HR 1.38, 95% CI: 1.16, 1.64), see Figure 2.3a. However, there was significant heterogeneity among studies, $p < 0.001$. The exclusion of the one comparison which showed considerable difference in its results, with better survival in the ethnic minority (Asian/Pacific Islander vs. white American) population [48], slightly strengthened the pooled hazard ratio but did not remove the inter-study heterogeneity. All but one comparison [95] provided results adjusted for factors other than SEP. The pooled hazard ratio was substantially reduced to 1.08 (95% CI: 0.93, 1.25), see Figure

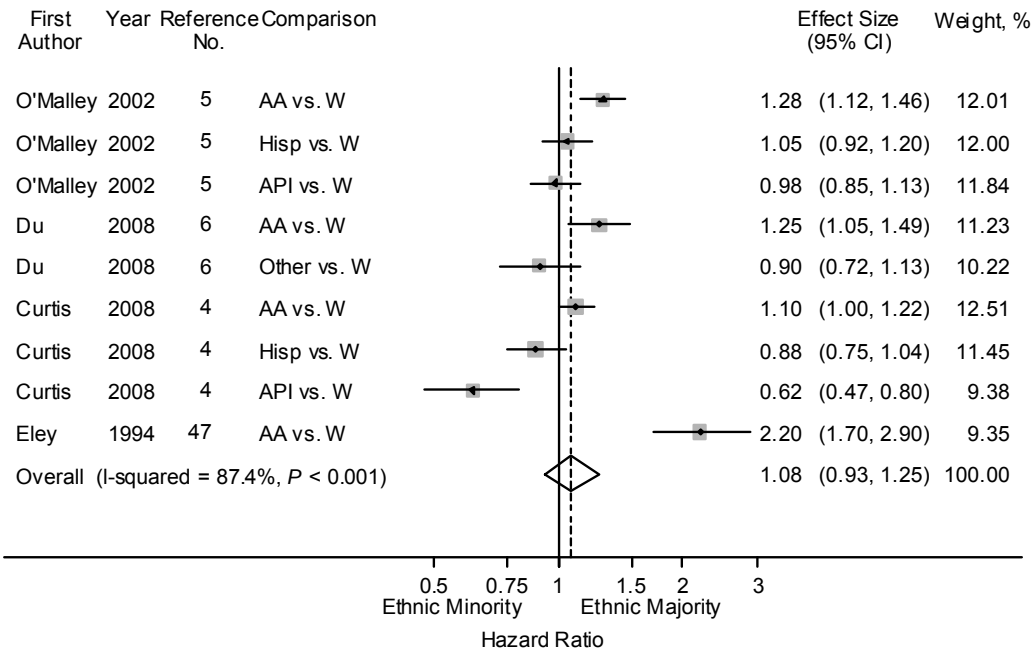
2.3b, indicating that almost all of the ethnic inequalities were due to adjustment variables (primarily clinical factors) other that SEP. Further adjusting for SEP reduced the hazard ratio to 1.05 (95% CI: 0.92, 1.20), see Figure 2.3c.

Figure 2.3: Association between ethnicity (minority vs. majority ethnic groups) and breast cancer survival.

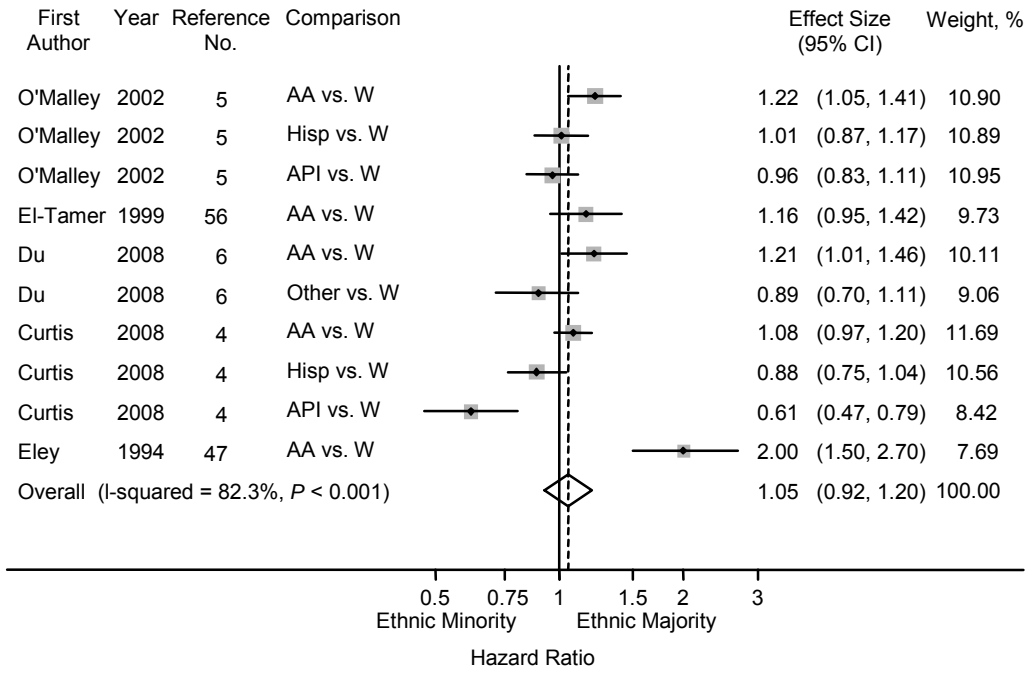
A) Crude association; B) Adjusted association, adjusted for "Model 1 parameters", see Table 2.4; C) Adjusted association, further adjusted for socioeconomic position, see "Model 2 parameters", Table 2.4. AA, African-American; W, White; Hisp, Hispanic; API, Asian/Pacific Islander. The area of each square is proportional to the precision of the estimate and hence to the weight that the individual study contributed to the meta-analysis.



B)


First Author
Year
Reference No.
Comparison
Effect Size (95% CI)
Weight, %
O'Malley 2002 5 AA vs. W 1.28 (1.12, 1.46) 12.01
O'Malley 2002 5 Hisp vs. W 1.05 (0.92, 1.20) 12.00
O'Malley 2002 5 API vs. W 0.98 (0.85, 1.13) 11.84
Du 2008 6 AA vs. W 1.25 (1.05, 1.49) 11.23
Du 2008 6 Other vs. W 0.90 (0.72, 1.13) 10.22
Curtis 2008 4 AA vs. W 1.10 (1.00, 1.22) 12.51
Curtis 2008 4 Hisp vs. W 0.88 (0.75, 1.04) 11.45
Curtis 2008 4 API vs. W 0.62 (0.47, 0.80) 9.38
Eley 1994 47 AA vs. W 2.20 (1.70, 2.90) 9.35
Overall (I-squared = 87.4%, P < 0.001) 1.08 (0.93, 1.25) 100.00
0.5 0.75 1 1.5 2 3
Ethnic Minority
Ethnic Majority
Hazard Ratio

C)


First Author
Year
Reference No.
Comparison
Effect Size (95% CI)
Weight, %
O'Malley 2002 5 AA vs. W 1.22 (1.05, 1.41) 10.90
O'Malley 2002 5 Hisp vs. W 1.01 (0.87, 1.17) 10.89
O'Malley 2002 5 API vs. W 0.96 (0.83, 1.11) 10.95
El-Tamer 1999 56 AA vs. W 1.16 (0.95, 1.42) 9.73
Du 2008 6 AA vs. W 1.21 (1.01, 1.46) 10.11
Du 2008 6 Other vs. W 0.89 (0.70, 1.11) 9.06
Curtis 2008 4 AA vs. W 1.08 (0.97, 1.20) 11.69
Curtis 2008 4 Hisp vs. W 0.88 (0.75, 1.04) 10.56
Curtis 2008 4 API vs. W 0.61 (0.47, 0.79) 8.42
Eley 1994 47 AA vs. W 2.00 (1.50, 2.70) 7.69
Overall (I-squared = 82.3%, P < 0.001) 1.05 (0.92, 1.20) 100.00
0.5 0.75 1 1.5 2 3
Ethnic Minority
Ethnic Majority
Hazard Ratio

The usefulness of the funnel and regression asymmetry plots in determining the possibility of publication bias was limited by the small numbers of studies included. Given this limitation, there was no evidence of publication bias for either outcome, based on the fully adjusted models; p = 0.81 for breast cancer mortality and p = 0.14 for all cause mortality (plots not shown).

Overall, these results indicate that SEP may explain approximately half of the inequality in breast cancer survival (all causes) between ethnic groups, but that SEP is not an important determinant of breast cancer specific survival inequalities, once clinical factors such as grade and stage have been accounted for.

The percentage change in the minority vs. majority survival disparity following SEP adjustment ranged from -100% (i.e. a doubling of the strength of association) to 80% (i.e. adjusting for SEP explained 80% of the disparities), with a median of 16.7% and interquartile range (IQR) of –2.6% to 44.9%. It was clear that the impact of SEP adjustment was more pronounced for studies of all cause mortality (median: 34.6%, IQR 10.9% to 57.1%) than for studies of breast cancer mortality (16.3%, IQR -2.6% to 21.4%). In all cases of comparisons of African American and White women in the US, adjustment for SEP resulted in an attenuation of the hazard ratio, whereas in comparisons of other ethnicities, adjustment tended to have small or negligible effects. For all cause mortality, the impact was 45% vs. –17% (i.e. a strengthening of effect following SEP adjustment), and for breast cancer mortality it was 20% vs. -3%. It appeared that the impact of adjusting for SEP on ethnic inequalities was weaker in studies where there was more equal access to health care, defined as studies based in the UK, or in a US HMO or DoD setting. For all cause mortality, the impact was 40% vs. -12%, and for breast cancer mortality it was 18% vs. 3%. There was also a

suggestion that those papers published in earlier years were more likely to demonstrate that SEP had a greater impact on explaining ethnic inequalities than those papers published in later years. For all cause mortality, the impact was 40% prior to the year 2000 compared to -12% in later studies, and for breast cancer mortality it was 29% vs. 8%. It is important to note that these differences are not weighted by the size of the study (as would be the case in meta-regression).

Discussion

In this systematic review, we have found that SEP explains part of the ethnic inequality in survival from all causes, but that this was not evident for breast cancer specific survival. SEP explains more of the disparities in African American versus white women in the US, compared to other ethnic comparisons. The role of SEP appears to be smaller in more recently published papers. We also found that the differences in breast cancer survival seen between ethnic groups may be in part explained by BMI, but there is little evidence to implicate smoking or alcohol as explanatory factors of this inequality. Furthermore, given social patterning of BMI and other lifestyle habits, it is possible that our results for SEP and BMI are measuring the same association.

This is the first review to attempt to quantify the effect of specific lifestyle factors on ethnic differences in survival. The study was strengthened by the carefully conducted review process, which attempted to minimize bias and error at all stages. A further strength of the review is the inclusion of various ethnic groups, treated in a range of health care systems. Given that there is minimal evidence of a genetic basis for inequalities in breast cancer survival, as discussed below, there may be lessons to be learnt from comparisons of survival between majority and minority ethnic populations.

Our findings were limited by the insufficient detail reported in many of the published studies. It is very common for papers to adjust for many factors simultaneously, which does not allow for an investigation of which specific factors could be important determinants of ethnic inequalities in survival. Furthermore, several papers had to be excluded as the results were not reported in a way whereby the effect of a variable could be quantified for extraction. We did not search the grey literature such as technical reports and unpublished work, nor did we attempt to contact authors to request that data be presented in a different manner. We cannot, therefore, rule out the possibility of selection or publication bias in the review, although there was no evidence of the latter from the relevant statistical tests that we performed.

In attempting to quantify the effect of the contribution of variables to ethnic inequalities in survival, it is important that these variables are accurately measured. Most studies investigating the effect of excess weight have used BMI, however, this is unlikely to be sufficient, and may not be the most pertinent measure of overweight. BMI and waist/hip ratio (WHR) affect all cause and breast cancer specific mortality independently [71] and to a similar degree [61], although this may be restricted to younger women. Almost all the studies that were included in the review used an ecological measure of SEP, based on area of residence and census information. This method assumes socioeconomic homogeneity within residential areas. Such measures underestimate socioeconomic disparities in breast cancer survival in the UK by up to 25% [97]. In the US, census-derived area-based SEP measures that estimate proportion below the poverty line at the census tract level, rather than using block group or ZIP codes, have been advocated as the most useful measure of SEP at a small area level [98]. Ideally, individual-based measures of socioeconomic position would be used; for example car access and housing tenure have been identified in the UK as more sensitive measures of deprivation than area-based measures [99]. Furthermore, Nazroo [100] has argued that

traditional socioeconomic groupings are not useful to investigate the impact of SEP on ethnic inequalities, because within socioeconomic ethnic groups, people in ethnic minorities are likely to be the most deprived (in terms of income, housing tenure, employment etc).

In population-based studies of cancer survival, as many of the included studies were, it has been argued that the preferred statistical measure is relative survival [101], with the complementary excess mortality modeling. This method compares the survival experience of a group of patients with cancer to the survival of the general population, and does not require cause of death information. Only one of the included studies used this method [54], but to adequately adjust for background mortality, it is preferable that ethnic-specific life tables are used; however these are not available in the UK. In cohort studies, when excess mortality modeling is not appropriate (e.g. unavailability of population specific life tables), it is important to distinguish cause of death. Inequalities in all-cause mortality will be larger than those in breast-cancer-specific mortality due to the strong effect of socially patterned variables such BMI and smoking on non-breast-cancer deaths. A follow-up of over 233,000 women with breast cancer found ethnic inequalities in mortality from breast cancer were of similar magnitude to the inequalities in mortality from four obesity-related outcomes [102].

The source of the ethnicity data used was not reported in the bulk of the papers that we reviewed. Cancer ethnicity data is abstracted from medical records, and this information may have been self identified from the patient; however it may also have just been assigned on the assumption of a health professional. Consequently the accuracy of ethnicity recording on registries is likely to differ by ethnic group. Specifically, high rates of misclassification have been reported for Hispanic, Asian and Pacific Island ethnicities in the US [103-106]. Despite these limitations, the collection of

ethnicity data in many countries outside the US is less well advanced. In the UK, ethnicity data has not, until very recently, been mandatory in NHS datasets, and is not available in the UK's cancer registries. For this reason, computerized algorithms have been used to assign South Asian ethnicity to individuals based on their name [53,54]. Despite relatively high sensitivity and specificity, there are limitations of this method. Furthermore, no similar method is available to identify Black Caribbean and Black African women, who form a substantial proportion of the non-white UK population.

Many US studies relied on SEER data, which are not representative of the minority populations in terms of ethnicity or SEP [103]. This selection bias introduced by using the SEER data is reflected in the higher relative survival noted in the SEER areas compared to those 11 states that contributed to the CONCORD programme [2] and emphasises the importance of nationwide cancer survival analyses. In a study of predominantly low socioeconomic, uninsured, uneducated, rural women, no difference in overall survival or survival by stage was found between African American and white women diagnosed with breast cancer throughout the 1990s [107]. This suggests that in the absence of privilege, ethnic inequalities in survival are no longer apparent, adding further weight to the argument that it is socially patterned differences that drive these inequalities.

A suggestion frequently made regarding ethnic inequalities in health is that there may be an underlying genetic basis for these. While there is a lack of major systematic genetic differences between ethnic groups, there are extensive differences in lifestyle suggesting that health disparities are most likely driven by environmental factors [45,46]. In relation to breast cancer survival, although differences in certain allele frequencies have been related to prognosis, we are not aware of any studies which demonstrate that these differences could explain ethnic inequalities in survival. On the contrary,

there are numerous studies that point to equally plausible, and more coherent, alternative explanations for the observed inequalities. The majority of this evidence relates to Asian women. Comparisons within one ethnic group cannot be explained by differences in genetic make-up. Chuang [108] found that Chinese women born in the US had better survival than Chinese women born in East Asia, hazard ratio 1.22 (95% CI: 1.06, 1.40). Similarly, changes in survival across generations among immigrant women are an indicator of the importance of environmental and cultural factors. Pineda [109] demonstrated such changes for Chinese and Japanese, although not for Filipino, women. These variations were almost fully explained by demographic, stage and treatment related factors.

Some environmental exposures that are culturally related are likely to persist across generations. Furthermore, living as a first generation immigrant in a country poses its own challenges, and linguistic and cultural barriers in access to care which are likely to be important [108]. The evidence above is supplemented by observations of changes over time in survival inequalities between ethnic groups. Jatoi [110] documented a widening inequality in all cause mortality following breast cancer between Black and White women in the US. This effect was driven by the most recently diagnosed cohort of women (1995 to 1999). Such changes are more plausibly explained by improvements in the health system that is better tailored to a dominant ethnic group. Finally, the importance of SEP and BMI in explaining inequalities, as shown in this review, adds to the evidence that genetic differences between ethnic groups are unlikely to be important determinants of inequalities.

There is accumulating evidence that women of different ethnicities experience disproportionate risks of various breast cancer subtypes. For example, we have shown that in New Zealand, Māori and Pacific women are more likely to have HER-2 positive

breast cancer than non-Māori/non-Pacific women [111]. Māori women were less likely and Pacific women more likely than non-Māori/non-Pacific women to have negative estrogen (ER) and progesterone receptor (PR) status. In the US, Hispanic women are more likely to have ER and PR negative breast cancer compared to non-Hispanic white women [112] and Black women more likely than white women to have triple negative breast cancer [113]. Comparing Chinese with white American women, no differences in ER or PR status were found [108]. Since receptor negative breast cancer is not amenable to hormonal therapy, these ethnic differences could explain some of the inequalities in survival. However, even among women with triple negative breast cancer, the five year relative survival was lowest in the non-Hispanic Black women [113]. The presence of differential subtypes of disease could be due to differential risk factors, and breast cancer epidemiologists should refine their outcomes to account for these differences.

Our final analysis showed that adjusting the breast cancer survival inequalities for measures of SEP had a greater impact in studies of African American versus white women compared to other ethnic comparisons. This is partly due to the higher crude inequality in survival between African American and white women (see Figure 3a), so there was more inequality to "explain" through adjustment. However, it is probably also partly due to the higher proportion of African American (compared to other ethnic minorities) living in poverty (25% vs. 8%) [114], and the probable higher level of resulting socioeconomic homogeneity in the census groups used to assign SEP in the studies included in this review. The effect of adjusting ethnic inequalities in health for SEP is strongly affected by the choice of SEP measure, and health inequalities between different ethnic groups respond in different ways to this adjustment [115]. Therefore the aggregation of different ethnic groups, as seen in several of the included studies (such as the grouping "Asian/Pacific Islander" in the US and "South Asian" in the UK) could

be masking the real effect that various individual level measures of SEP would have on ethnic inequalities in survival.

Despite several of the studies that we included in the review, and others which did not meet our inclusion criteria [52,116] being set in "equal access" health care systems, ethnic inequalities in breast cancer outcomes were still evident. However, it is important to point out that in these contexts, "equal access" means "equal cost", or "no cost at the point of access". This does not necessarily mean that all ethnic or socioeconomic groups will perceive the access equally, or indeed utilize the health service equally according to need. Underserved/minority ethnic groups may have had previous negative experiences within health systems causing mistrust. For example, we have demonstrated that in New Zealand, Māori are more than twice as likely to have experienced unfair treatment by a health professional because of their ethnicity compared to European New Zealanders [40]. Since health systems are generally run by and tailored to the majority population, the system can be hard to navigate and may be culturally inappropriate for patients from minority ethnic groups.

Differential access to treatment is likely to play an important role in ethnic survival disparities, especially in the light of continuing treatment advances. There is some evidence that clinicians' perceptions about patients, and their diagnostic and treatment decisions are affected by the patients' ethnicity and socioeconomic position [117]. In the US, even when comparing those of the same socioeconomic and health insurance status, African Americans are less likely to receive optimum or curative treatment for cancer [41]. A study of the follow-up of abnormal mammogram results in the US found that being of African American ethnicity was an independent predictor of inadequate follow-up [118]. An American review found evidence of ethnic disparities between those in receipt of definitive primary therapy, conservative therapy, and adjuvant therapy, which

were not explained by clinical variations [56]. Even after adjusting for multivariable factors including stage and comorbidity, Bicknell and colleagues [119] found women from minority populations (African American and Hispanic) with early stage breast cancer were twice as likely to experience underuse of necessary adjuvant treatments (HR 2.0; 95% CI: 1.3, 3.1). This was slightly higher than the risk of not receiving appropriate therapies for women without insurance (HR 1.9; 95% CI: 0.9, 4.0). These results together indicate that at least part of the ethnic inequalities in breast cancer survival is attributable to unequal care.

Differential exposure to risk factors and unequal access to and through a health care pathway can be considered as manifestations of racism [39], pervading not only the health system but society itself. A third manifestation in Krieger's proposed framework is economic/ social deprivation itself, which, as we have shown, is related to all cause mortality in women with breast cancer. The importance of the macrosocial determinants of inequity and their impact on health has been discussed by Nazroo [120]. It is easy to conceive that living as an ethnic minority woman in a society where the health system is dominated by a different cultural framework could lead to less easy access into and through the health system, resulting in suboptimal care and outcomes. However, it is identifying points along the pathway that are amenable to immediate change that is the challenge for public health and allied professionals. As noted in the recent WHO Report *Closing the Gap in a Generation* [28], ensuring heath equity is the responsibility of the highest level of government, which must be addressed through coherent, cross-policy agendas.

In addition to such high-level action, there is a substantial role for epidemiology in the concerted action to eliminate inequalities in cancer survival. Specifically, we suggest bivariate as well as multivariable results should be presented, and that statistical

models are presented in a transparent way, (e.g. see [48]), with specific factors or groups of factors entered sequentially into models. This method will allow researchers investigating ethnic inequalities in cancer survival to use evidence-based approaches to identify how, and at what point on the care pathway, we can focus interventions specifically to reduce inequalities.

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CHAPTER THREE

Socio-economic inequalities in survival from screen-detected breast cancer in South West England: population-based cohort study

Fiona McKenzie, Alexander Ives and Mona Jeffreys

Socioeconomic inequalities in breast cancer survival have been reported worldwide, but whether these exist in screen-detected as well as symptomatic women has not been established. Making this distinction will allow inferences about the relative contributions of pre- and post-diagnostic delay to these inequalities. Screening-eligible women diagnosed with breast cancer in South-West England (2002 to 2006) were followed-up to 2007. Five-year relative survival ratios (RSR) were calculated for each deprivation quintile, using deprivation-specific life-tables and a period approach. The "deprivation gap" in survival was calculated as the slope index of inequality between least and most deprived. The study included 11,018 women, of whom 1,176 died during follow-up period. Screening status of 54% of women was missing in the cancer registry. A clear gradient in survival across deprivation groups ranged from 83.6% (95% confidence interval (CI) 80.0, 86.6) in the most deprived to 90.8% (CI 89.0, 92.3) in the least deprived group. Comparing the hypothetically most deprived to least deprived women, the estimated deprivation gap was –9.42% (95% CI –12.80, –6.04, p=0.003). Among screen-detected women, inequalities were attenuated, but persisted, ranging from 95.6% (CI 90.6, 98.0) in the most deprived to 98.2% (CI 95.9, 99.2) in least deprived; the estimated deprivation gap was –3.03% (95% CI –5.75, –0.85, p=0.023). The deprivation gap in survival does not appear as marked with screen-detected breast cancer as the other groups, though still apparent. Efforts to eliminate inequalities should consider both increasing breast screening participation and ensuring equal access through secondary care systems for women of lower socioeconomic position.

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Introduction

The UK's Cancer Reform Strategy [121] highlights the importance of reducing inequalities in cancer incidence and outcome. Two important developments in a first step to achieve this have been the launch of the National Cancer Equality Initiative, and the National Awareness and Early Diagnosis Initiative. Both initiatives acknowledge the paucity of evidence on which recommendations to reduce cancer inequalities can be based.

Socioeconomic inequalities in cancer survival have been reported in different countries and are a global concern. [3,122-127] An analysis of cancer survival in England and Wales has shown that survival from breast cancer is lower in women of lower socioeconomic position. [4] A similar pattern of survival has also been described specifically in the South West region of England.[128] A key factor in explaining poorer breast cancer survival for less affluent women is likely to be related to screening coverage. Women from low socioeconomic groups are less likely to access mammography services than their more affluent counterparts [129], and therefore may receive delayed diagnosis and treatment.

It has not been established whether the same pattern of survival, or deprivation gap, which is seen for all women diagnosed with breast cancer, is also seen just within screen-detected women. A UK report on women diagnosed with breast cancer in 2001/02 indicated a 12.2 percentage point difference in 5-year relative survival between the most affluent and most deprived quintiles of women diagnosed symptomatically, compared to a 6.6 percentage point difference for screen-detected women.[130] If inequalities in survival are evident among women with screen-detected cancer, then investigations of differences in treatments and prognostic factors are needed to explain observed disparities. However, if the inequalities are limited to only those women who do not attend screening, then the efforts to reduce inequalities

should be more focussed on improving screening and uptake among the most deprived women.

In this study we estimated 5-year relative survival from breast cancer by screening status and deprivation quintile among women diagnosed with breast cancer between ages 50 and 70, in the South West region of the UK.

Materials and methods

All women diagnosed with invasive breast cancer between January 2002 and December 2006 registered on the South West Cancer Registry were included in our study. Age was restricted to only include women within the screening age range of 50 to 70 years of age. Deprivation was measured using the income domain of the 2007 Index of Multiple Deprivation (IMD), [131] an area-based measure of socio-economic position (SEP), derived from a woman's place of residence at time of diagnosis, and calculated at the Lower Super Output Area (LSOA) level. Income scores were categorised into quintiles of the English population. Follow-up was to the end of 2007.

Screening status was classified into five categories. The screen-detected category included women who were diagnosed through the breast screening programme. The interval cancer category included women who belonged to the screening programme but who were diagnosed symptomatically between screens. The non-/lapsed attenders category included women who have been invited to the screening programme but are not current participants. The uninvited category includes women who have never been invited to the screening programme, such as those not registered with a GP. The unknown category included women whose screening status was not recorded on the cancer registry. No other information for women in this category was available.

Analysis

Descriptive data were presented and compared across deprivation / screening categories. Categorical variables were cross-tabulated and compared using chi squared tests; Kruskal-Wallis tests were used to compare the median age across deprivation / screening categories.

Relative survival ratios (RSRs) are defined as the ratio of observed survival of the patients with cancer to the expected survival of the general population; this, in effect, ‘‘adjusts’’ the mortality patterns of cancer patients for the background population rates of mortality in the same demographic group [101]. Expected survival was estimated for each of the five deprivation categories, based on region-, period- deprivation- and sex-specific life tables for the period by single year of age (15-99 years). All RSRs were estimated using a maximum likelihood approach [101] in the Stata program strel. [132] Survival probabilities were estimated at three month intervals in the first year, six month intervals in years 2 and 3, and yearly intervals thereafter. The assumption behind the model is that the modelled hazard is constant within these time intervals. Five-year RSRs are presented for simplicity.

Relative survival analyses were performed, using the period approach, [133] to estimate RSRs and associated 95% confidence intervals (CI) across deprivation groups. The period approach has been shown to provide more accurate predictions of survival for newly diagnosed patients compared with the cohort approach.[134] Survival curves are compiled from the most recent cohort with full follow up time to reflect recent improvements in survival. Data for women diagnosed between 1998 and 2006 was used to estimate the five year relative survival of those diagnosed from 2002 to 2006.

To estimate the survival gap between the least and the most deprived women, survival gradients across the five categories of deprivation were calculated. This measure is also known as the slope index of inequality. [135] We performed linear regression of RSRs on a score for each of the deprivation categories, the score being equivalent to its midpoint on a cumulative rank scale (i.e. 0.1 for the most affluent quintile, and 0.3, 0.5, 0.7 and 0.9 for successively more deprived groups). Thus, the regression estimates the difference between the hypothetically most deprived (score = 1.0) and least deprived (score = 0) women. The P values for the Wald test statistic from these regressions were reported. These estimates were repeated for total population and for the screen-detected population. The percentage difference between these two sets of regression estimates gave the contribution of screen-detected breast cancer to deprivation differences in survival.

Results

A total of 11,018 women with breast cancer were included in the study, all of whom were diagnosed between 2002 and 2006 and registered on the South West Cancer Registry. During the follow-up period, a total of 1,176 deaths were recorded. The median age at diagnosis in the whole cohort was 60 years (inter-quartile range (IQR): 55 to 65 years), which did not differ by deprivation categories (see Table 1). From the available data, fewer than half the women (45%) were detected at screening although, for 54% of women screening status was unknown. Among those with missing data on screening, the median age at diagnosis across deprivation categories was similar. The distribution of women across deprivation categories according to whether or not they had missing screening data was similar (data not shown).

Table 3.1. Description of women diagnosed with invasive breast cancer in the South West region, 2002-2006

	N (%)	Median age (P-value)
Screening status		
Screen-detected cancers	4,965 (45.1)	60
Interval cancers	45 (0.4%)	57
Cancers in non-attenders	12 (0.1)	58
Cancers in uninvited	39 (0.4)	63
Unknown status	5,957 (54.1)	60
		P=0.14
Deprivation *		
1 (least deprived)	2,098 (19.0)	60
2	3,077 (27.9)	60
3	3,099 (28.1)	60
4	2,039 (18.5)	60
5 (most deprived)	705 (6.4)	60
		P=0.67
Deprivation **		
1 (least deprived)	1,191 (20.0)	59
2	1,601 (26.9)	59
3	1,656 (27.8)	60
4	1,113 (18.7)	60
5 (most deprived)	396 (6.7)	60
		P=0.040

* All women; ** Women with missing screening data

Table 3.2. Five-year relative survival for breast cancer cases in the South West region by screening status

Screening status	Women	Deaths	5-year RSR	95% Confidence Interval	
Screen-detected cancers	4,965	164	96.88	95.97	97.58
Interval cancers	45	9	84.94	75.09	91.12
Cancers in non-attenders	12	2	84.59	64.14	93.89
Cancers in uninvited	39	5	90.05	79.23	95.39
Unknown status	5,957	996	80.43	79.24	81.56

Table 3.2 shows five-year relative survival estimates for each screening category. Women who had breast cancer detected through screening had the highest survival estimates (96.88; 95% CI 95.97 to 97.58). The lowest survival was seen for women in the unknown screening category (80.43; 95% CI 79.24 to 81.56). Five-year relative survival estimates for each deprivation quintile and all screening groups combined are shown in Table 3.3. As expected, survival is better among women in the least deprived group (90.79; 95% CI 88.97 to 92.32) and poorer among women in the most deprived group (83.56; 95% CI 79.98 to 86.55). There is a clear deprivation gradient for survival; comparing the most deprived to the least deprived women, the modelled deprivation gap was –9.42% (95% CI –12.80 to –6.04, p=0.003).

Table 3.3. Five-year relative survival for breast cancer cases in the South West region by deprivation quintile

Deprivation	Women	Deaths	5-year RSR	95% Confidence Interval	
1 (least deprived)	2,098	187	90.79	88.97	92.32
2	3,077	313	89.45	87.97	90.75
3	3,099	357	86.04	84.50	87.45
4	2,039	227	85.07	83.03	86.89
5 (most deprived)	705	92	83.56	79.98	86.55

This same analysis was repeated among only the screen-detected women; the five-year relative survival estimates for each deprivation quintile are shown in Table 3.4. The results show that, while the deprivation survival differences for the subset of screen-detected women are smaller than those for the whole dataset, they nevertheless illustrate a deprivation gradient from better survival among affluent women (98.16; 95% CI 95.88 to 99.18) to poorer survival among their less affluent counterparts (95.60; 95% CI 90.63 to 97.96). The deprivation gap was estimated as –3.03% (95% CI –5.75 to –0.85, p=0.023). Thus approximately 68% of the socio-economic inequalities in survival in the total population who are eligible for screening could be attributable to not having cancer detected through screening.

Table 3.4. Five-year relative survival for screen-detected breast cancer cases in the South West region by deprivation quintile

Deprivation	Women	Deaths	5-year RSR	95% Confidence Interval	
1 (least deprived)	880	33	98.16	95.88	99.18
2	1,435	51	97.53	95.66	98.60
3	1,420	44	95.91	93.93	97.25
4	922	24	96.05	93.48	97.62
5 (most deprived)	308	12	95.60	90.63	97.96

Discussion

In this study of breast cancer registrations in the South West we have shown that deprivation survival disparities are evident for the complete cohort of women diagnosed. They are also evident, albeit attenuated, for women diagnosed within the screening programme, indicating that lack of earlier detection could account for much of the inequality within the general population. However as there was still a clear gradient of deprivation survival disparity within the screen-detected population, there

are also other factors affecting inequalities in breast cancer outcomes between women of different socioeconomic positions.

The strengths of this study lie in the population-based nature of the cancer registry and the complete outcome (death) ascertainment through record linkage. One of the biggest limitations of the study is the large degree of missing screening data in the cancer registry. Following our analysis, this was investigated. It appears likely that we are, to some extent, under-ascertaining screen-detected cancers; in the South West, we would expect approximately 1,200 screen-detected invasive breast cancers per year, whereas in the five-year period of our study, we identified 5,000; the remaining 1,000 women could be included in the 6,000 for whom we had missing screening data. From a detailed analysis of the figures, it appears most likely that a substantial proportion of the women with unknown screening status in this analysis had an interval cancer (C Rocha, South West Cancer Intelligence Service, personal communication 2009). This also fits with the rather low 5-year survival reported among these women. The primary concern regarding the degree of missing data is whether it is randomly missing or not; if so, it has the potential to bias the association between deprivation and relative survival, when stratified by screening status. The lack of an association between deprivation group and missing screening data is reassuring. However, it is still possible that the relative survival in the people with missing data does not follow the same pattern by deprivation category as does the screen-detected data, although it is hard to conceive why this might be so. Cancer registries in the UK are continuing efforts to improve linkage between data sources, and it is likely that the proportion of missing data in key variables such as diagnosis route will be lower in future.

A second limitation of the analysis is the use of an area-based deprivation index to measure socioeconomic position. This does not capture individual socioeconomic

position as well as an individual marker would. However, Woods et al have previously shown that the income domain of the IMD index, when calculated at the LSOA level, is more strongly associated with breast cancer survival than most other commonly used area-based measures of deprivation in the UK, which are based on larger geographic areas. [97] Measurement error could only have attenuated, rather than artificially created, the observed inequalities. We may therefore have under-estimated the deprivation gap to some degree but this is likely to have occurred equally in the screened and unscreened populations, and therefore unlikely to have substantially affected our conclusions. Research in the US has highlighted the importance of considering social context when examining health outcomes. Specifically investigating non-adherence to mammography screening, Dailey et al found that neighbourhood level socioeconomic factors were associated with regular screening, independent of individual level factors. [136] Ideally, we would use both individual and area-based measures to characterise SEP, the latter capturing broader context of neighbourhoods which is not measured with individual level exposures.

Systematic reviews of interventions to increase mammography uptake [137,138] arrive at different conclusions to those specifically assessing interventions for women with low rates of screening. [139,140] The latter find that approaches which include access-enhancing interventions produce the greatest increase in mammography uptake. However, the majority of the evidence is US-based, and the interventions are not necessarily applicable to the UK. Within the National Health Service (NHS), local efforts have been made to increase mammography uptake in women with low rates of screening, but are not always evidence-based, nor do they have their effectiveness evaluated. [141,142] The acceptability of interventions needs to be assessed in the diverse populations in the UK, and cost-effectiveness should be considered before interventions can be recommended.

Of importance is to consider reasons for the remaining survival disparity that we observed in screen-detected women. Within our dataset, we could not investigate this further. One possibility is that this could be due to higher co-morbidity among lower SEP women. Previous research has found that women from lower socioeconomic groups diagnosed with breast cancer are more likely to have at least one other chronic condition (hypertension, diabetes, previous myocardial infarction, chronic obstructive pulmonary disease) than their counterparts from higher socioeconomic groups. [143,144] Although neither of these studies specifically investigated screen-detected breast cancers, it is likely that similar patterns may be evident in that group of women. The excess mortality we observed in the women from more deprived areas cannot be directly attributed to the effects of higher co-morbidities, since we have effectively controlled for this using deprivation-specific life tables in our analyses. However, it is possible that co-morbidities could affect treatment options in a woman's cancer care, and thus indirectly affect her survival. Clearly, further work, perhaps using prospectively collected data rather than routinely collected data, is required to investigate this further.

The possibility that there are inequalities in the treatment of women from different socioeconomic groups [145] should also be considered. It has been proposed [146] that higher educated and affluent women are more adept at navigating through the secondary care system. Again, further research is needed to investigate this, and if substantiated, to identify strategies to improve access for all women through the system.

Screening programmes are usually attended more regularly by affluent people;[129,147] therefore, while they may improve survival overall, they can also increase disparities between deprived and affluent people [148] due to differential uptake; a phenomenon

referred to as intervention-generated inequalities. Although there was a considerable amount of missing data in this study, a large proportion of the observed deprivation gap in breast cancer survival appeared to be accounted for by lack of early detection. Therefore efforts to eliminate inequalities in breast cancer among 50 to 70 year old women should focus on increasing breast screening participation for women of lower socioeconomic position. However efforts should also be made to ensure equal access through the secondary care system to address the attenuated survival inequalities that remained even among screen-detected women with breast cancer.

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CHAPTER FOUR

Prognostic factors in women with breast cancer: inequalities by ethnicity and socioeconomic position in New Zealand

Fiona McKenzie, Mona Jeffreys, Andrea 't Mannetje and Neil Pearce

To investigate differences in breast cancer prognostic factors among ethnic and socioeconomic groups in New Zealand, we analysed all 21,586 breast cancer cases on the New Zealand Cancer Registry (July 1994 to June 2004). Māori, Pacific, and non-Māori/non-Pacific women were categorised according to ethnicity on the Registry. Deprivation was analysed as quintiles of the New Zealand Deprivation Index 2001, an area-based measure of socioeconomic position. Logistic regression was used to estimate age-adjusted odds ratios (OR) (95% confidence intervals (CI)). Māori and Pacific women were more likely to have non-local stage, less well differentiated cancer, larger tumours and positive human epidermal growth factor receptor-type 2 (HER-2) status than non-Māori/non-Pacific women. Māori were less likely and Pacific women more likely than non-Māori/non-Pacific women to have negative oestrogen (ER) and progesterone receptor (PR) status. Adjusting for deprivation did not materially alter the results. Women living in more deprived areas had a higher risk of non-local stage and larger tumours. These associations were only partially explained by ethnicity. There was no relationship between tumour grade, ER, PR or HER-2 status and deprivation. Our results confirm that Māori, Pacific and low socioeconomic women present with poor prognosis breast tumours.

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Introduction

The incidence and mortality rates of breast cancer in New Zealand are high in comparison to the rest of the developed world [149,150]. It is the most common site of cancer registration and death for females in New Zealand, with more than 2300 breast cancer registrations and 600 deaths each year.

The burden of breast cancer in New Zealand is not shared equally among ethnic groups [9,16,151]. Ethnic disparities in breast cancer mortality have increased since 1980: rates in non-Māori/non-Pacific women decreased during the 1980s and 1990s, while during the same period, Pacific and Māori rates increased. By the late 1990s, cancer mortality rates for Māori and Pacific women were 1.5 to 2 times greater than non-Māori/non-Pacific rates [16]. Therefore, although the incidence of breast cancer is slightly higher for Māori [9] and Pacific [152], compared to non-Māori/non-Pacific women, Māori and Pacific women are twice as likely to die from this cancer [16], indicating that much of the mortality disparities are due to inequalities in survival rather than risk.

Breast cancer has traditionally been considered as a disease of affluence, but while higher mortality has previously been observed among high-income women [153], New Zealand currently shows more of a trend towards higher breast cancer mortality in lower socioeconomic women [151,154]. Furthermore, because of low coverage of breast screening for Māori and Pacific women [155], inequalities in breast cancer mortality have been predicted to increase [156].

Overseas studies have reported that both socioeconomic factors [55,157-159] and ethnicity [41,160,161] are associated with disparities in cancer survival. Differences have been observed using a variety of measures of socioeconomic position, including income,

education, occupation and deprivation indices [159,162-164]. Factors relating to socioeconomic position have been shown to account for many observed ethnic differences in breast cancer stage and tumour size at the time of diagnosis [91,92,165]. There is some evidence to suggest that differences in socioeconomic position may explain part of the differences in breast cancer survival between ethnic groups [91], but other studies examining the combined effects of ethnicity and socioeconomic position have found that they have independent effects on survival [166].

Only a proportion of the lower survival rates for Māori and Pacific women compared with non-Māori/non-Pacific in New Zealand can be attributed to the stage of the cancer at the time of diagnosis [8]. Similarly inequalities in survival between socioeconomic groups in New Zealand are not attributable to ethnicity or stage of disease [154]. Differential access to treatment is likely to have a considerable impact on these inequalities, especially in light of continuing treatment advances. However, demographic differences in breast cancer survival could also be attributable to more aggressive tumours which have different tumour biology. Numerous studies have provided evidence that African-American women are diagnosed more frequently with larger tumours, higher grade tumours, more advanced stage tumours, and hormone receptor negative tumours than white American women [90,160-162,167-171].

This study explores prognostic factors which may contribute to ethnic or socioeconomic inequalities in breast cancer survival in New Zealand. The factors investigated were stage, grade, and size of tumour at time of diagnosis, hormone receptor statuses and human epidermal growth factor receptor-type 2 (HER-2) status, and these characteristics were compared among ethnic and among deprivation index groups.

Materials and methods

All women with a primary breast cancer diagnosed between July 1994 and June 2004 registered on the New Zealand Cancer Registry [55] (NZCR) were identified. Pathology laboratories are the primary source of registrations to the NZCR and have been required by law since 1994 to report any new diagnosis of cancer in New Zealand (excluding squamous and basal cell skin cancers). Data are also collected from Medical Certificates of Causes of Death, Coroners' Findings, hospital discharge data, and private hospital discharge returns. The NZCR is primarily intended for New Zealand residents and the Registry attempts to distinguish between residents and non-residents. Prognostic variables (grade, stage, size, oestrogen receptor (ER), progesterone receptor (PR), and HER-2 status) were extracted from the NZCR data.

Tumour grade is recorded on the NZCR in four categories: well differentiated, moderately differentiated, poorly differentiated, and not known. Extent of disease was recorded up to and including 1998 as a numeric code. Since 1999 the Surveillance, Epidemiology and End Results (SEER) Guide to Summary Staging was adopted at the NZCR [172]. Combining these two systems, extent of disease was grouped into four stage categories: local, regional, distant, and unknown.

Size of tumour is measured at the widest point. This field was introduced to the NZCR in 1998 and has been mandatory since 2002 [172]. The data provided in millimetres (mm) were grouped into six categories for analyses: less than 10mm, 10-19mm, 20-29mm, 30-49mm, 50mm and larger, and missing.

Hormone receptor status information has been available on the NZCR since 2002 [172]. Measurement of receptor status is based on an immunochemistry test. ER status is

routinely tested, but PR status is not always tested [172]. HER-2 status is based on a test of gene amplification, but is not always tested. Missing data and data which were coded as “not known” were combined into one unknown category; leaving three categories for analysis: positive status, negative status, and unknown.

Age at diagnosis was divided into five categories for analysis: less than 40 years, 40-49 years, 50-59 years, 60-69 years, and 70 years and older.

Ethnicity data was provided grouped into only three categories: Māori, Pacific Island (combining the codes for Pacific Island not further defined, Samoan, Cook Island Māori, Tongan, Niuean, Tokelauan, Fijian, and Other Pacific Island not listed), and Other (combining the codes for European not further defined, NZ European, Other European, Asian not further defined, South East Asian, Chinese, Indian, Other Asian, Middle Eastern, Latin American/Hispanic, African, Other, and Not stated). Since July 1996 up to three ethnic group codes can be collected for cancer registrations [172]. Recording ethnicity on the Cancer Registry is done using a prioritisation system. Māori ethnicity has highest priority, followed by the Pacific Islands ethnicities. In practical terms this system records anyone who identifies with Māori ethnicity as Māori, regardless of any other ethnic identities, and anyone who identifies with a Pacific Islands ethnicity is recorded as Pacific, unless they also identify with Māori ethnicity.

The New Zealand Deprivation Index 2001 (NZDep01) was used as a measure of socioeconomic position based on place of residence at the time of cancer registration. The Domicile code provided by the NZHIS was used by the Public Health Intelligence (PHI) unit of the Ministry of Health to calculate the NZDep01 index. The index uses nine variables (benefit income, employment, household income, communication, transport, support, qualifications, living space, and home ownership) from the 2001

census to place mesh-block areas on a deprivation scale from 1 to 10 [24]; 10 represents the most deprived 10% of New Zealand areas, while 1 represents the 10% least deprived areas. Deciles were combined into five categories for analyses: 1-2 (least deprived); 3-4; 5-6; 7-8; 9-10 (most deprived).

Analyses

All analyses were performed using Stata software, version 8.0. Descriptive analyses were initially conducted to explore the variable values and summarise the data. Logistic regression was used to estimate the associations between the prognostic factors and ethnicity and/or deprivation index. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the associations between ethnicity and having worse prognostic factors. Stage was defined as local or non-local, grade as well differentiated or moderately to poorly differentiated, size as <20mm or ≥20mm, and ER, PR and HER-2 statuses as positive or negative.The reference group for each dependent variable was the most favourable prognostic outcome in each case.

For NZDep01, data were missing when domicile codes could not be matched to the index due to input and coding errors. These 1,301 women were therefore excluded from the NZDep01 analyses. The analyses by ethnicity were conducted twice, once for all women (n=21,586), and once for the subset of women who had NZDep01 available (n=20,285).

Table 4.1: Distributions of breast tumour characteristics by ethnicity, 1994-2004

		Māori (n=1,674)		Pacific (n=564)		NMNP (n=19,348)		All women (n=21,586)	
		n	%	n	%	n	%	n	%
Age	median	52.7		52.3		60.1			
	<40	244	14.6	94	16.7	1,213	6.3	1,551	7.2
	40-49	448	26.8	151	26.8	3,525	18.2	4,124	19.1
	50-59	465	27.8	156	27.7	4,896	25.3	5,517	25.6
	60-69	339	20.3	100	17.3	3,996	20.7	4,435	20.6
	70+	178	10.6	63	11.2	5,718	29.6	5,959	27.6
p<0.001									
NZDep	1-2	72	4.5	29	5.6	3,282	18.1	3,383	16.7
	3-4	136	8.6	39	7.5	3,619	19.9	3,794	18.7
	5-6	227	14.3	58	11.2	4,102	22.6	4,387	21.6
	7-8	342	21.6	116	22.4	4,295	23.6	4,753	23.4
	9-10	810	51.0	276	53.3	2,882	15.9	3,968	19.6
	missing	87		46		1,168		1,301	
p<0.001									
stage	local	648	46.4	183	40.0	8,638	55.0	9,469	53.9
	regional	664	47.5	220	48.1	6,249	39.8	7,133	40.6
	distant	86	6.2	54	11.8	834	5.3	974	5.5
	unknown	276		107		3,627		4,010	
p<0.001									
grade	well diff	136	20.6	21	9.7	1,765	26.6	1,922	25.6
	moderately	294	44.6	112	51.6	2,923	44.0	3,329	44.3
	poorly	229	34.8	84	38.7	1,957	29.5	2,270	30.2
	unknown	1,015		347		12,703		14,065	
p<0.001									
size (mm)	<10	67	6.6	25	8.3	1,589	14.4	1,681	13.6
	10-19	334	33.0	64	21.3	4,253	38.6	4,651	37.8
	20-29	279	27.6	82	27.3	2,797	25.4	3,158	25.6
	30-49	229	22.7	77	25.7	1,724	15.7	2,030	16.5
	50+	102	10.1	52	17.3	647	5.9	801	6.5
	missing	663		264		8,338		9,265	
p<0.001									
ER status	neg	126	22.0	71	32.3	1,546	24.1	1,743	24.2
	pos	447	78.0	149	67.7	4,862	75.9	5,458	75.8
	unknown	139		47		1,281		1,467	
	missing	962		297		11,659		12,918	
p=0.009									
PR status	neg	174	31.0	94	43.7	2,276	36.2	2,544	36.1
	pos	388	69.0	121	56.3	4,004	63.8	4,513	64.0
	unknown	150		51		1,369		1,570	
	missing	962		298		11,699		12,959	
p=0.003									
Her2 status	neg	140	66.4	47	59.5	1,461	72.6	1,648	71.6
	pos	71	33.7	32	40.5	551	27.4	654	28.4
	unknown	405		146		4,397		4,948	
	missing	1,058		339		12,939		14,336	
p=0.008									

p chi2 test of association excluding unknown and missing data

NMNP non-Māori/non-Pacific

NZDep New Zealand Deprivation Index 2001 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

Results

There were 21,586 women who had a breast tumour registration between 1994 and 2004, comprising 19,348 non-Māori/non-Pacific, 1,674 Māori and 564 Pacific women. Table 4.1 shows the distributions of age and tumour features by ethnic group. The median age at diagnosis was 52.7 years for Māori women, 52.3 years for Pacific women, and 60.1 years for non-Māori/non-Pacific women. There were greater proportions of younger women (less than 50 years old) registered in the Māori and Pacific groups compared with non-Māori/non-Pacific women. Māori and Pacific women were also over-represented in the more deprived groups. All differences between ethnic groups were highly statistically significant. Tumour grade, size, ER, PR, and HER-2 status all showed high proportions of missing data. For most variables, the percentage with missing data was greatest for non-Māori/non-Pacific women. Across NZDep01 categories there appeared to be greater proportions of data missing in the more deprived groups.

Table 4.2 shows the age-adjusted ORs for deprivation groups (in comparison with the least deprived group) and the six prognostic factors. Women living in more deprived areas were more likely to have non-local stage breast tumours than those living in less deprived areas (NZDep 9-10 OR 1.22, 95% CI 1.10-1.35). Women living in more deprived areas were also more likely to have moderate to poorly differentiated and larger tumours than those living in more affluent areas. The greatest differences between deprivation groups were seen in the findings for tumour size, which were all statistically significant at the 5% level. There was only a small attenuation of the ORs when they were adjusted for ethnicity in addition to age (results not shown). Attenuation was most notable for tumour size, but there remained statistically significant differences across deprivation groups. There was no association between

deprivation and ER, PR, or HER-2 status. Repeating the analyses for the non-Māori/non-Pacific group only did not alter the results, indicating that confounding by ethnicity was not a major concern. This was not done for Māori or Pacific women due to the smaller numbers in each deprivation stratum.

Table 4.3 shows the age-adjusted and age- and deprivation-adjusted ORs for ethnicity and the six prognostic factors. There was little difference in the age-adjusted odds ratios between the analyses involving all women and those with available NZDep01 (results not shown). Māori and Pacific women were more likely to have non-local stage, less well differentiated cancer and larger tumours than non-Māori/non-Pacific women. Māori women were less likely than non-Māori/non-Pacific women to have negative ER and PR status, while Pacific women were more likely to have negative ER and PR status. Both Māori and Pacific women were more likely to have positive HER-2 status than non-Māori/non-Pacific women. Further adjusting for deprivation did not substantially alter any of the ORs, indicating that differences in prognostic variables by ethnicity are largely independent of this measure of socioeconomic status.

Table 4.2: Odds ratios for selected tumour features by deprivation

Stage - nonlocal compared to local stage breast cancer (n=16,546)			
	OR*	**95% CI**	**P-trend**
NZDep 1-2	1.0		
NZDep 3-4	1.07	0.96 - 1.19	
NZDep 5-6	1.15	1.04 - 1.27	
NZDep 7-8	1.22	1.10 - 1.35	
NZDep 9-10	1.22	1.10 - 1.35	<0.001

Grade - moderately/poorly compared to well differentiated tumours (n=7,257)			
	OR*	**95% CI**	**P-trend**
NZDep 1-2	1.0		
NZDep 3-4	1.11	0.94 - 1.33	
NZDep 5-6	1.03	0.87 - 1.21	
NZDep 7-8	1.15	0.97 - 1.36	
NZDep 9-10	1.16	0.98 - 1.39	0.086

Size - 20mm+ compared to <20mm tumours (n=11,858)			
	OR*	**95% CI**	**P-trend**
NZDep 1-2	1.0		
NZDep 3-4	1.31	1.16 - 1.48	
NZDep 5-6	1.35	1.20 - 1.52	
NZDep 7-8	1.51	1.35 - 1.70	
NZDep 9-10	1.58	1.40 - 1.79	<0.001

ER status - negative compared to positive status (n=8,390)			
	OR*	**95% CI**	**P-trend**
NZDep 1-2	1.0		
NZDep 3-4	1.10	0.92 - 1.31	
NZDep 5-6	0.98	0.82 - 1.16	
NZDep 7-8	0.97	0.82 - 1.16	
NZDep 9-10	0.99	0.83 - 1.19	0.465

PR status - negative compared to positive status (n=6,822)			
	OR*	**95% CI**	**P-trend**
NZDep 1-2	1.0		
NZDep 3-4	1.00	0.86 - 1.18	
NZDep 5-6	1.02	0.88 - 1.19	
NZDep 7-8	0.87	0.74 - 1.01	
NZDep 9-10	0.96	0.81 - 1.13	0.180

HER2 status - positive compared to negative status (n=2,255)			
	OR*	**95% CI**	**P-trend**
NZDep 1-2	1.0		
NZDep 3-4	1.00	0.74 - 1.36	
NZDep 5-6	1.22	0.91 - 1.63	
NZDep 7-8	0.92	0.68 - 1.24	
NZDep 9-10	1.05	0.78 - 1.43	0.995

*age adjusted

NZDep New Zealand Deprivation Index 2001 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

NB: The numbers of women analysed for each variable differ due to the differing amounts of missing data

Table 4.3: Odds ratios for selected tumour features by ethnicity

Stage - nonlocal compared to local stage breast cancer (n=16,546)				
	OR*	**95% CI**	**OR****	**95% CI**
NMNP	1.0		1.0	
Māori	1.38	1.23 - 1.55	1.35	1.20 - 1.52
Pacific	1.75	1.43 - 2.13	1.72	1.41 - 2.11

Grade - moderately/poorly compared to well differentiated tumours (n=7,257)				
	OR*	**95% CI**	**OR****	**95% CI**
NMNP	1.0		1.0	
Māori	1.26	1.03 - 1.55	1.26	1.02 - 1.55
Pacific	3.16	1.98 - 5.05	3.15	1.96 - 5.05

Size - 20mm+ compared to <20mm tumours (n=11,858)				
	OR*	**95% CI**	**OR****	**95% CI**
NMNP	1.0		1.0	
Māori	1.79	1.57 - 2.06	1.71	1.41 - 1.96
Pacific	3.05	2.34 - 3.96	2.90	2.23 - 3.79

ER status - negative compared to positive status (n=8,390)				
	OR*	**95% CI**	**OR****	**95% CI**
NMNP	1.0		1.0	
Māori	0.80	0.65 - 0.99	0.81	0.65 - 1.01
Pacific	1.38	1.03 - 1.85	1.40	1.03 - 1.89

PR status - negative compared to positive status (n=6,822)				
	OR*	**95% CI**	**OR****	**95% CI**
NMNP	1.0		1.0	
Māori	0.79	0.66 - 0.96	0.81	0.66 - 0.98
Pacific	1.40	1.06 - 1.85	1.43	1.07 - 1.90

HER2 status – positive compared to negative status (n=2,255)				
	OR*	**95% CI**	**OR****	**95% CI**
NMNP	1.0		1.0	
Māori	1.26	0.92 - 1.71	1.29	0.94 - 1.78
Pacific	1.76	1.11 - 2.81	1.86	1.16 - 2.99

*age adjusted

**age and NZDep adjusted - New Zealand Deprivation Index 2001 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

NMNP non-Māori/non-Pacific

NB: The numbers of women analysed for each variable differ due to the differing amounts of missing data

To investigate whether the associations between ethnicity and tumour grade and size were explained by stage at diagnosis, we ran another model for these two prognostic variables which included adjustment by age, NZDep01 and stage. These results (not shown) were not materially different from the age- and deprivation- adjusted results, indicating that ethnic differences in grade and size are independent of cancer stage at diagnosis.

To investigate whether the association between deprivation and tumour grade and size was explained by stage at diagnosis, we ran another model for these two prognostic variables which included adjustment by age, ethnicity and stage. These results (not shown) were not materially different from the age- and deprivation- adjusted results, indicating that socioeconomic differences in grade and size are independent of cancer stage at diagnosis.

Discussion

In this study of breast cancer registrations in New Zealand women, we found differences in factors associated with poorer survival, including stage, grade, and size of breast tumours, ER and PR status and HER-2 status among ethnic groups. In addition we found differences in tumour stage and size among deprivation index groups.

This is the first population-based study to examine breast tumour characteristics/prognostic features by ethnicity and deprivation index in New Zealand. The age structures of the various ethnic populations in New Zealand are quite different.

The European population has a much higher proportion of older women with a median age of 35 years; whereas the Māori and Pacific populations have higher proportions of younger women with median ages of 22 and 21 years, respectively [173].

We used data from the New Zealand Cancer Registry, which is estimated to be about 98% complete (S. Hanna, personal communication, 2007). Nevertheless, our results should be interpreted with caution as there are small numbers in some categories, especially among Pacific women. There were also large amounts of missing data, most notably in the grade, hormone receptors, and HER-2 variables. Importantly, the proportion of missing data for these variables differed systematically across deprivation categories, with higher proportions of missing data seen in women living in more deprived areas. Therefore, we cannot exclude the possibility that the results which we found for deprivation were biased, and these findings should be regarded as preliminary requiring further exploration.

There are also concerns regarding the collection and accuracy of ethnicity information in New Zealand. In particular, routinely collected health datasets in New Zealand have been found to contain poor quality, unreliable ethnicity data [174]. However bias would only be introduced if the misclassification of ethnicity was related to tumour characteristics. Since ethnicity data are collected independently of the tumour data, it is unlikely that the misclassification of ethnicity could be differential with respect to the tumour markers in this study. Therefore, any misclassification of ethnicity would be non-differential, thus diluting the observed differences rather than producing spurious results [175].

Our findings indicated that Māori and Pacific women were more likely to have further advanced, higher grade, larger tumours at time of cancer registration than non-

Māori/non-Pacific women. Previous overseas studies have documented similar ethnic differences in breast cancer, which include African-American, Hispanic, and Hawaiian women being diagnosed more frequently with advanced stage and larger tumours than white women in America, while Japanese women are diagnosed less frequently with larger, advanced tumours [162,168]. Higher grade tumours have also been found to be more common in African-American women compared with white women in America [162,168].

Our study found that hormone receptor positive tumours were more common in Māori women than non-Māori/non-Pacific women, and they were less common in Pacific women. Previous overseas studies have found that ER and PR positive tumours are more common in white American women compared to African-American women [160,168,170]. The opposite patterns of the Māori and Pacific hormone receptor ORs indicate that these receptors do not explain the observed lower survival in both these groups of women. Hormone receptors have been identified as independent indicators of breast cancer prognosis, with ER negative tumours being associated with more aggressive cancers. Hormone receptors are also crucial to treatment options, with ER positive patients being suitable for anti-oestrogen treatments such as tamoxifen. Our results suggest that Māori may have a better prognosis for hormonal treatments than Pacific or non-Māori/non-Pacific women.

We also found that HER-2 positive tumours were more common in Māori and Pacific women than non-Māori/non-Pacific women. The overseas literature on HER-2 overexpression is inconsistent with regard to ethnic differences. Some previous studies have shown no differences in HER-2 status between ethnic groups [167,169,176], while others have found HER-2 positive breast tumours to be more common among Asian women [177,178]. HER-2 positive cancers tend to be more aggressive than HER-2

negative cancers, and are associated with poor survival [179,180], and increased rates of cancer recurrence. Our findings indicate ethnic differences in breast cancer HER-2 status, which suggest that Māori and Pacific women are more often diagnosed with the type of breast cancer that may benefit from Herceptin treatments compared with non-Māori/non-Pacific women. The current funding of Herceptin in New Zealand is limited; as at March 2007, the government drug funding agency Pharmac is proposing to fund nine weeks of treatment for women with early HER-2 positive breast cancer. Private funding of a 12 month course is well beyond the financial means of most women, particularly Māori and Pacific women.

The associations found between deprivation and disease spread, stage, grade and tumour size, generally show the same patterns, with women in the most deprived areas having tumour features associated with poorer prognosis. However, this pattern is more pronounced for tumour size than for the other markers, possibly as a result of less access to screening or poorer access to primary care for women in low socioeconomic groups. There did not appear to be any associations with deprivation and hormone receptor or HER-2 statuses in our study. Previous studies have found an association between socioeconomic status and ER/PR statuses [159,181]. ER status has also been associated with social class in American women independent of ethnicity [182].

In contrast with previous studies [91], ethnic differences in prognostic factors were not explained by socioeconomic status in our study. The associations between the prognostic variables and ethnicity were different than the associations between the prognostic variables and deprivation, which indicate that, in this context, ethnicity is not just a marker of socioeconomic status. This may in part be a result of using an area-based deprivation index to measure socioeconomic status. It is recognised that such indices do not capture individual socioeconomic position as well as an individual

marker would [183]. Nevertheless, it is notable that the ethnic differences barely change at all after adjustment for socioeconomic status; thus it may be that true differences in these prognostic factors exist among ethnic groups which are independent of socioeconomic position.

It was not possible in this study to consider the role of the menopause on the observed associations, and it is possible that our results are confounded by menopausal status. There are no data available to indicate whether age of menopause differs by ethnicity in New Zealand. However, factors which influence age at menopause, such as smoking, parity and obesity [184,185] differ by ethnicity in New Zealand, suggesting that there may also be important differences among ethnic and socioeconomic groups in age at menopause. An ongoing case-control study will allow these gaps in our information to be filled.

In general, our findings indicated that poorer prognostic breast cancer characteristics are more common in Māori and Pacific women than non-Māori/non-Pacific women in New Zealand. These findings are consistent with previous studies conducted in the United States, which have found tumour features associated with poorer prognosis are more common in underserved ethnicities than white American women [90,160-162,167-171]. Possible reasons for the poorer prognosis profiles of Māori and Pacific women could be related to lower rates of mammography screening. BreastScreen Aotearoa reports more than 20% higher coverage rates for non-Māori/non-Pacific women than Māori and Pacific women [155]. The consequences of lower screening rates for Māori and Pacific women are later cancer detection and a more advanced disease at diagnosis. Adjustment in this study for cancer stage at diagnosis did not account for the ethnic differences found in tumour grade or size. However, this could be partially accounted

for by the limitations of the use of SEER summary staging, which might have resulted in residual confounding due to the imprecise nature of the staging system.

Another possible explanation for variations in prognostic profiles could be differences in tumour biology. The differences regarding ER, PR and HER-2 status could be due to genetic or differential lifestyle risk factors, whereas the other differences in tumour characteristics are most likely to be due to environmental and lifestyle patterns associated with ethnicity. As most genetic variation is random [45], ethnicity may be a marker for environmental risk factors related to poor prognosis tumours.

Obesity has been reported as both a risk factor for breast cancer and as a contributing factor to poorer prognosis [89]. This may be due to the effect of obesity on hormone levels which are also associated with cancer progression [167]. It is possible that obesity could play a role in some of the observed ethnic differences. Māori, Pacific and lower socioeconomic women all tend to have higher rates of obesity [186]. However, this study does not have any information on Body Mass Index (BMI) or obesity. Nor does it have information on reproductive risk factors such as age at menarche and nulliparity.

There is clear evidence of differential survival from breast cancer in New Zealand by ethnicity [8]. While access to services undoubtedly plays a significant role in disparities, this does not mean that other possible contributing factors should be ignored. In particular, if Māori and Pacific women are more likely to develop a different subtype of breast cancer than the non-Māori/non-Pacific population, they may need differently targeted and customised therapies and management.

In summary, we have found that Māori and Pacific women are at a greater risk than non-Māori/non-Pacific women of presenting with poorer prognosis breast tumours.

Advanced stage, higher grade, larger tumours, and HER-2 status could explain some of the survival disparities in Māori and Pacific women, whereas hormone receptor status could be associated with the lower survival in Pacific women but not in Māori women. It is likely that a combination of factors, including lifestyle and environment, may account for these differences. Future investigations could explore the reasons for the differences between ethnicities in tumour characteristics, including reproductive and anthropometric factors, as well as a more comprehensive investigation of reasons for the high levels of missing data in the NZCR, and methods of improving the accuracy of the information on ethnicity.

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CHAPTER FIVE

Investigating reasons for ethnic inequalities in breast cancer survival in New Zealand

Fiona McKenzie, Lis Ellison-Loschmann and Mona Jeffreys

This study investigated the role that demographic and tumour factors play in explaining ethnic inequalities in breast cancer survival. Breast cancer cases notified to the New Zealand Cancer Registry (NZCR) from April 2005 to April 2007 were followed up to April 2009. Māori, Pacific and non-Māori/non-Pacific women were categorised according to ethnicity on the NZCR. Deprivation was analysed as quintiles of the New Zealand area-based index of socioeconomic position. Relative survival was estimated using ethnic-specific life tables. Missing values were imputed and excess mortality modelling was used to estimate the contribution of demographic and tumour factors to ethnic inequalities in survival. There were 2,968 breast cancer cases (76.5% non-Māori/non-Pacific, 17% Māori, and 6.5% Pacific) included and 433 recorded deaths. Relative survival at 4 years was 91.45% (CI 89.68 to 92.93) for non-Māori/non-Pacific, 86.15 (CI 80.33 to 90.36) for Māori, and 79.56% (CI 68.17 to 87.24) for Pacific women. Using non-Māori/non-Pacific as the reference group, the age-adjusted hazard ratio (HR) dropped for Māori from 1.76 (CI 1.22 to 2.48) to 1.43 (CI 0.97 to 2.10) when further adjusted by deprivation. For Pacific, the HR dropped from 2.49 (CI 1.57 to 3.94) to 1.94 (CI 1.20 to 3.13). Inequalities persisted after adjustment for subtype variables (ER/PR/HER2), but adjusting for access to care variables (extent/size) eliminated the ethnic inequalities in excess mortality. Ethnic disparities in breast cancer survival in New Zealand can be attributed to deprivation and differential access to health care rather than differences in breast cancer subtypes.

Ethnicity and Health, in press

The manuscript which appears here reflects what was published, and also incorporates comments received by the examiners as part of the PhD conferment process

Introduction

Breast cancer is the most common female cancer in the New Zealand Cancer Registry (NZCR). It is also a leading cause of cancer death for women worldwide. Previous research has described survival differences between indigenous Māori and non-Māori New Zealanders [8,9]. Other evidence of differential survival between ethnic groups has primarily been produced in the United States, where African American women have poorer survival than white women [48-50]. In other countries, ethnic differences have also been found, with lower survival in Indigenous compared to white Australians,[52] and better survival in South Asian and Chinese compared to other women in UK [53,54,187].

Although these descriptive studies documenting ethnic inequalities in survival are useful, it is necessary to take such research to the next level, investigating possible reasons for these inequalities, to allow translation into public health interventions which could reduce inequalities. Few studies have investigated reasons for these inequalities. A meta-analysis indicated that socio-economic position explains only part of the excess mortality experienced by African American compared to white women with breast cancer [59]. We have suggested that life-style factors (body mass index, smoking and alcohol) similarly explain only some of the differences in survival inequalities between ethnic groups [188]. Other studies have highlighted the importance of screening, [48] late presentation (stage), [8,91,93] comorbidities [48] and treatment patterns [41,118]. This study aims to investigate the role that demographic and tumour factors play in explaining breast cancer survival inequalities among women from three ethnic groupings in New Zealand.

Materials and methods

Information from the New Zealand Cancer Registry (NZCR) was used to identify all women with a primary breast cancer diagnosed between April 2005 and April 2006. A further year of registrations, to April 2007, was used to identify additional Māori and Pacific women to ensure enough cases for analyses for these ethnic groups. The reason for restricting cases to these years is that these women formed the basis of a case-control study (to be reported elsewhere). Furthermore, we have previously documented a high level of missing data on pertinent factors in earlier NZCR data extracts, [111] but, because the missing data are less of a problem in recent years, we decided to restrict analyses to the time period above.

Demographic and prognostic variables of interest were extracted from the NZCR data. Age at diagnosis was divided into five categories for analysis: less than 40 years, 40-49 years, 50-59 years, 60-69 years, and 70 years and older. Tumour grade is recorded as well differentiated, moderately differentiated, poorly differentiated, or unknown. Extent of disease is recorded on the NZCR as local, regional, distant, or unknown. Size of tumour is measured at the widest point and recorded in millimetres (mm). For analysis, tumour measurements were grouped into four categories: less than 10mm, 10-19mm, 20-39mm, 40mm and larger. These two variables (extent and size) each reflect the progression of the tumour at presentation and are referred to below as markers of timely access to care.

Hormone (oestrogen and progesterone) receptor and human epidermal growth factor receptor-type 2 (HER2) status information are recorded as negative status, positive status, or unknown. The unknown category does not differentiate between women whose tumour was not tested and those for whom the test was indeterminate. These

fields have only recently become mandatory and, as yet, the reasons why the unknown category is utilised is unclear i.e. we don't have further information to look at which of the reasons above apply to which women. The interest in these variables is that their different distribution across ethnic groups may reflect differential risk factor exposures, and are referred to below as "sub-types".

Up to three ethnic affiliations can be collected for cancer registrations in New Zealand [189]. For people who reported more than one ethnic affiliation, ethnicity was assigned using a prioritisation system. The highest priority was assigned to Māori ethnicity, followed by the Pacific Islands ethnicities. This method records anyone who identifies with Māori ethnicity as Māori, regardless of other ethnic identities, and anyone who identifies with a Pacific Islands ethnicity is recorded as Pacific, unless they also identify with Māori ethnicity. Ethnicity information was grouped into three categories: Māori, Pacific Island (combining Samoan, Cook Island Māori, Tongan, Niuean, Tokelauan, Fijian, and Other Pacific Island), and non-Māori/non-Pacific (predominantly European but also including South East Asian, Chinese, Indian, Other Asian, Middle Eastern, Latin American/Hispanic, African, Other, and Not stated).

The New Zealand Deprivation Index 2006 (NZDep06) was used as a measure of socioeconomic position based on place of residence at the time of cancer registration. The index uses nine variables (benefit income, employment, household income, communication, transport, support, qualifications, living space, and home ownership) from the 2006 census to place small areas (mesh-blocks) on a deprivation scale from 1 to 10; 10 represents the most deprived 10% of New Zealand areas, while 1 represents the 10% least deprived areas. For analysis, deciles were combined into five categories: 1-2 (least deprived); 3-4; 5-6; 7-8; 9-10 (most deprived).

Analyses

Descriptive analyses were initially conducted to explore the values of variables and to summarise the data. All cause mortality was ascertained from the Information Directorate of the New Zealand Ministry of Health. Patients were followed up until 07 April 2009.

Since cause of death is not available for several years following the event in routinely collected NZ data, relative survival and excess mortality modelling (instead of cause-specific survival analysis) were used to estimate net effects attributable to cancer. Relative survival was performed using the maximum likelihood approach for individual records.[101] Unadjusted relative survival was first estimated for all women by each variable of interest relative to the total New Zealand female population. Ethnic-specific life tables sourced from Statistics New Zealand were then used to estimate relative survival for Māori, Pacific, and non-Māori/non-Pacific women at each year of follow-up, censored at 4 years. The use of ethnic-specific life tables accounts for the differential mortality patterns of the three ethnic groups.

Due to the significant degree of missing or unknown data for some variables, multiple imputation was performed on the dataset. This method assumes that the data are missing at random (MAR), i.e. that missing values are randomly distributed within one or more strata of the data, and can hence be predicted using imputation. Multiple imputation was performed by chained equations (MICE) [190]. Twenty-five complete datasets were generated using a model that included incomplete variables (stage, grade, size, ER, PR, HER2), complete variables (ethnicity, age, deprivation), vital status, and follow-up time.

Excess mortality modelling with the MIM program [191] was performed to fit multivariable regression models, using a generalised linear model with a Poisson error structure to estimate excess mortality hazard ratios. An age- and deprivation-adjusted base model was used, to which other prognostic variables, or variable groupings, were added singly, and then in progression.

All analyses were performed using Stata software, version 10.1.

Results

There were 2,968 breast cancer cases registered with a New Zealand address within the study period (11 cases had an overseas/not applicable domicile code recorded on the register), comprising 2,271 (76.5%) non-Māori/non-Pacific, 506 (17%) Māori, and 191 (6.5%) Pacific women. Table 5.1 shows the distributions of age, deprivation and tumour features by ethnic group. The median age at diagnosis was 53.7 years for Māori women, 50.1 years for Pacific women, and 58.7 years for non-Māori/non-Pacific women. There were smaller proportions of older women (70 years of age and above) registered in the Māori and Pacific groups compared with non-Māori/non-Pacific women. Māori and Pacific women were over-represented in the most deprived socioeconomic group and under-represented in the least deprived. Pacific women were also over-represented in the distant extent, high grade, and large size tumour groups. Māori and Pacific women were more likely than non-Māori/non-Pacific women to be HER2 positive.

Table 5.1. Distributions of age, deprivation and breast tumour features for women diagnosed 2005-2007 by ethnic group in New Zealand

		Total (n=2,968)			Māori (n=506)			Pacific (n=191)			NMNP (n=2,271)		
		n	%	*%	n	%	*%	n	%	*%	n	%	*%
age	median		57.2			53.7			50.1			58.7	
	<40	209	7.0		43	8.5		28	14.7		138	6.1	
	40-49	690	23.3		138	27.3		66	34.6		486	21.4	
	50-59	777	26.2		160	31.6		34	17.8		583	25.7	
	60-69	663	22.3		110	21.7		40	20.9		513	22.6	
	70+	629	21.2		55	10.9		23	12.0		551	24.3	
P < 0.001													
NZDep	1-2	478	16.1		25	4.9		8	4.2		445	19.6	
	3-4	468	15.8		46	9.1		12	6.3		410	18.1	
	5-6	580	19.5		67	13.2		22	11.5		491	21.6	
	7-8	712	24.0		120	23.7		46	24.1		546	24.0	
	9-10	730	24.6		248	49.0		103	53.9		379	16.7	
P < 0.001													
extent	local	1,317	53.4	52.9	203	49.0	48.4	61	42.4	42.3	1,053	55.1	54.7
	regional	1,044	42.3	42.1	186	44.9	44.7	69	47.9	47.4	789	41.3	41.1
	distant	107	4.3	5.0	25	6.1	6.9	14	9.7	10.3	68	3.6	4.2
	unknown	500			92			47			361		
P < 0.001													
size (mm)	<10	374	14.9	14.1	38	9.1	8.8	12	8.7	8.1	324	16.6	15.8
	10-19	865	34.4	31.8	118	28.2	26.1	33	23.9	21.0	714	36.5	34.0
	20-39	996	39.7	39.8	204	48.8	47.2	48	34.8	36.3	744	38.1	38.6
	40+	276	11.0	14.1	58	13.9	17.9	45	32.6	34.6	173	8.8	11.6
	unknown	457			88			53			316		
P < 0.001													
grade	well diff	625	23.1	22.5	90	19.4	18.9	28	17.3	16.2	507	24.3	23.8
	moderately	1,201	44.3	44.4	225	48.5	48.1	70	43.2	42.9	906	43.5	43.7
	poorly	885	32.6	33.1	149	32.1	33.0	64	39.5	40.9	672	32.2	32.5
	unknown	257			42			29			186		
P = 0.025													
ER	negative	558	20.7	20.6	83	18.3	18.5	42	26.1	25.8	433	20.8	20.6
	positive	2,139	79.3	79.4	371	81.7	81.5	119	73.9	74.2	1,649	79.2	79.4
	unknown	271			52			30			189		
P = 0.107													
PR	negative	941	35.3	35.4	133	30.0	30.6	62	39.0	39.1	746	36.2	36.2
	positive	1,722	64.7	64.6	311	70.0	69.4	97	61.0	60.9	1,314	63.8	63.8
	unknown	305			62			32			211		
P = 0.027													
HER2	negative	1,494	81.6	82.9	246	74.3	76.1	90	72.0	72.3	1,158	84.3	85.3
	positive	336	18.4	17.1	85	25.7	23.9	35	28.0	27.7	216	15.7	14.7
	unknown	1,138			175			66			897		
P < 0.001													

P calculated excluding missing data
*% from all imputed datasets (all *P < 0.001)
NMNP non-Māori/non-Pacific (women diagnosed 2005-2006 only)
NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

Table 5.2. Unadjusted relative survival (RS) and 95% confidence intervals (CI) for demographic and tumour features

		1-yr RS	CI		4-yr RS	CI	
ethnicity	NMNP	98.29	97.45	98.86	91.87	90.09,	93.35
	Māori	95.20	92.73	96.85	83.47	77.88,	87.76
	Pacific	95.20	90.46	97.62	78.35	67.26,	86.07
	ALL	97.47	96.70	98.07	89.68	88.02,	91.12
age	<40	96.73	93.14	98.45	86.18	79.10,	91.00
	40-49	98.02	96.57	98.86	89.43	86.11,	91.99
	50-59	97.00	95.38	98.06	91.24	88.40,	93.40
	60-69	99.24	97.00	99.81	92.30	88.40,	94.93
	70+	94.39	91.32	96.40	83.12	76.89,	87.80
NZDep	1-2	98.83	96.07	99.06	93.91	89.18,	96.61
	3-4	97.62	95.26	98.81	92.55	88.56,	95.18
	5-6	98.61	96.93	99.37	92.90	89.27,	95.34
	7-8	97.49	95.62	98.57	86.22	82.39,	89.27
	9-10	95.56	93.52	96.97	84.89	80.71,	88.24
extent	local	99.99	-	-	98.13	95.97,	99.14
	regional	98.75	97.60	99.35	85.53	82.30,	88.21
	distant	48.83	38.79	58.13	23.98	15.01,	34.13
(missing=16.9%)		94.78	91.83	96.68	86.64	81.84,	90.25
size (mm)	<10	99.99	-	-	97.35	91.42,	99.20
	10-19	99.96	58.54	99.99	98.11	95.66,	99.18
	20-39	99.51	98.07	99.87	90.78	87.69,	93.13
	40+	95.28	91.73	97.33	76.56	68.98,	82.55
(missing=15.4%)		83.97	79.89	87.29	66.14	60.21,	71.39
grade	well diff	99.99	-	-	99.72	8.14,	99.99
	moderately	99.08	97.97	99.59	93.03	90.49,	94.91
	poorly	96.00	94.27	97.22	82.22	78.57,	85.30
(missing=8.7%)		85.46	79.86	89.60	70.15	62.46,	76.56
ER status	negative	95.38	92.94	96.99	79.38	74.66,	83.32
	positive	98.82	98.06	99.28	93.25	91.44,	94.68
(missing=9.1%)		89.77	84.90	93.13	82.20	75.22,	87.38
PR status	negative	96.17	94.47	97.36	83.19	79.80,	86.07
	positive	99.26	98.47	99.64	94.18	92.19,	95.68
(missing=10.3%)		89.14	84.50	92.46	81.75	75.09,	86.78
HER2 status	negative	98.71	97.73	99.27	92.71	90.48,	94.44
	positive	96.18	93.11	97.90	80.62	73.92,	85.76
(missing=38.3%)		96.11	94.53	97.24	88.56	85.72,	90.86

NMNP non-Māori/non-Pacific

NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

Calculated from total female population life tables

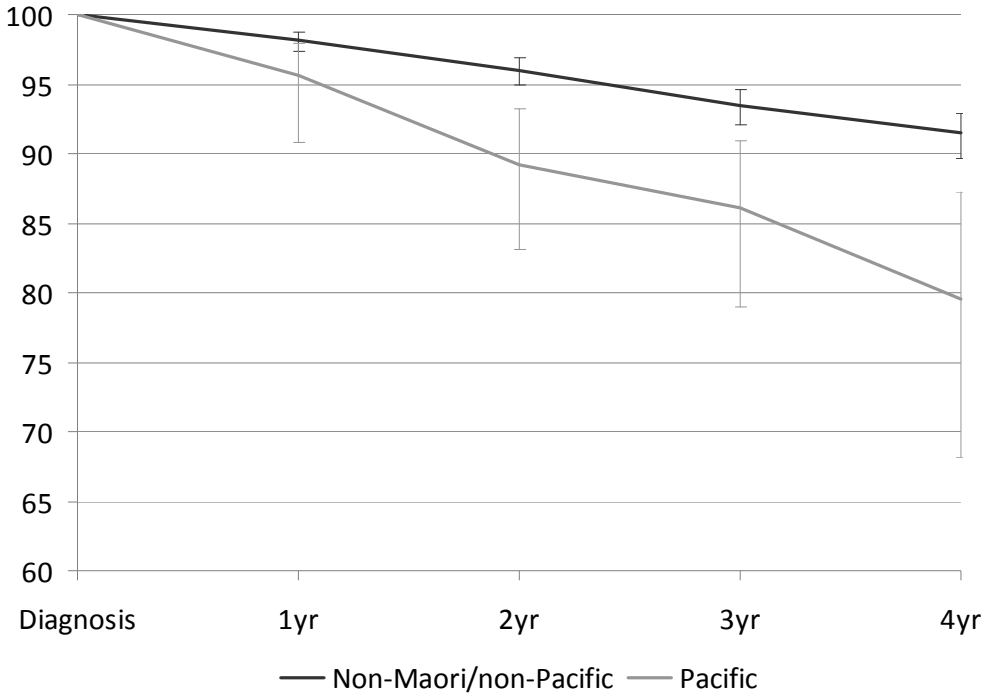
Tumour extent, size, grade, ER, PR, and HER2 status all included notable proportions of missing data. With the exception of HER2, the greatest proportions of missing data were seen among Pacific women and the most complete data among non-Māori/non-Pacific women. Table 5.1 also shows the distribution of explanatory variables by ethnicity following the multiple imputation. These show a small shift in the distributions from those based on non-missing data.

Up to April 2009, there were 433 recorded deaths: 321 non-Māori/non-Pacific, 76 Māori and 36 Pacific women. Table 5.2 shows unadjusted relative survival estimates and 95% confidence intervals (CI) for each variable of interest, including estimates for each category of missing data. Relative to the total female population, non-Māori/non-Pacific women had the highest and Pacific women the lowest 4-year survival. Deprived women had lower survival than their more affluent counterparts. As expected, women with more favourable tumour features had higher relative survival than those with poor prognostic features. Women who had missing information for grade and tumour size had noticeably low survival.

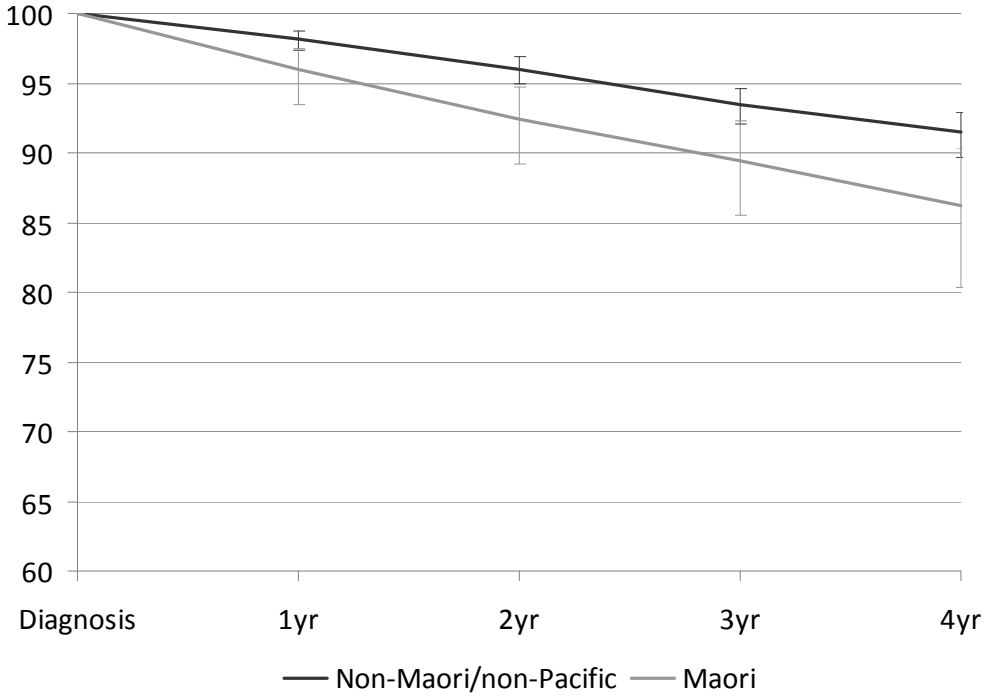
Figure 5.1(a) and figure 5.1(b) show relative survival for Māori and Pacific women compared with non-Māori/non-Pacific women, estimated from ethnic-specific life tables. Non-Māori/non-Pacific women show higher survival estimates than Māori and Pacific women at all points after diagnosis.

Figure 5.1 Relative survival and 95% confidence intervals estimated from ethnic-specific life tables for (A) Pacific women compared with non-Māori/non-Pacific women and (B) Māori women compared with non-Māori/non-Pacific women

A)



B)



The excess mortality hazard ratios for Māori and Pacific women compared with non-Māori/non-Pacific women are given in Table 5.3. Adjusting for deprivation attenuated the excess mortality observed for both Māori and Pacific women. For Māori, the age-adjusted HR dropped from 1.76 (CI: 1.22, 2.48) to 1.43 (CI: 0.97, 2.10) when further adjusted by deprivation. For Pacific, the same adjustment reduced the HR from 2.49 (CI: 1.57, 3.94) to 1.94 (CI: 1.20, 3.13).

The access to care variables (extent and size) appeared to individually account for large proportions of the ethnic inequalities in excess mortality. Adjusting for these two variables at once (Model C) further attenuated the excess mortality HRs and additionally adjusting for deprivation (Model D) eliminated the ethnic inequalities. To investigate whether tumour sub-types (and hence risk factor profiles) explained ethnic inequalities in survival, we assessed the individual and combined effect of adjusting for ER, PR and HER2. For Māori women, none of these factors appeared to modify the survival inequalities, although HER2 attenuated the excess mortality to a small degree. For Pacific women, adjusting for ER, PR and HER2 attenuated the excess mortality, although significant inequalities remained. Grade adjustment also attenuated the excess mortality for both Māori and Pacific women, but a degree of inequality persisted.

Table 5.3. Excess mortality hazard ratios (HR) and 95% confidence intervals (CI) for Māori and Pacific women compared with non-Māori/non-Pacific women, modelled on imputed data

		Māori			Pacific		
		HR	CI		HR	CI	
	***Crude/ethnicity**	1.71	1.18,	2.48	2.45	1.54,	3.89
A	**Age adjusted**	1.76	1.22,	2.55	2.49	1.57,	3.94
B	**A+NZDep**	1.43	0.97,	2.10	1.94	1.20,	3.13
	A+extent	1.25	0.87	1.80	1.30	0.80	2.12
	A+size	1.28	0.89	1.84	1.25	0.79	1.99
	A+grade	1.51	1.03	2.20	2.12	1.35	3.32
	A+ER	1.83	1.26	2.64	2.24	1.42	3.53
	A+PR	1.92	1.33	2.77	2.33	1.48	3.67
	A+HER2	1.62	1.12	2.34	2.20	1.39	3.51
	A+ER,PR	1.89	1.31	2.73	2.28	1.45	3.58
	A+ER,PR,HER2	1.76	1.21	2.56	2.11	1.33	3.34
C	**A+extent,size**	1.14	0.78	1.66	1.11	0.68	1.82
	C+grade	1.14	0.78	1.67	1.04	0.63	1.70
	C+grade,ER,PR	1.20	0.82	1.75	1.04	0.64	1.70
	C+grade,ER,PR,HER2	1.19	0.81	1.75	1.04	0.63	1.70
	B+extent	1.11	0.76,	1.62	1.07	0.76,	1.62
	B+size	1.12	0.77,	1.63	1.06	0.66,	1.70
	B+grade	1.31	0.89,	1.94	1.77	1.11,	2.83
	B+ER	1.49	1.01,	2.20	1.76	1.09,	2.83
	B+PR	1.55	1.05,	2.29	1.83	1.14,	2.94
	B+HER2	1.35	0.92,	1.99	1.78	1.10,	2.88
	B+ER,PR	1.54	1.04,	2.26	1.80	1.12,	2.88
	B+ER,PR,HER2	1.46	0.99,	2.16	1.69	1.05,	2.73
D	**B+extent,size**	1.02	0.69,	1.51	0.92	0.55,	1.55
	D+grade	1.01	0.68,	1.50	0.85	0.51,	1.44
	D+grade,ER,PR	1.03	0.68,	1.55	0.84	0.49,	1.42
E	**D+grade,ER,PR,HER2**	1.03	0.68,	1.55	0.83	0.49,	1.42

*Adjusted for follow up

NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

Calculated from ethnic-specific female population life tables

Table 5.4. Excess mortality hazard ratios (HR) and 95% confidence intervals (CI) for all explanatory variables adjusted for each other, modelled on imputed data and complete case data

Model E on imputed data (n=2968)					Model E on complete case data (n=1500)				
		HR	**CI**				**HR**	**CI**	
ethnicity	NMNP	1.00			**ethnicity**	NMNP	1.00		
	Māori	1.03	0.68,	1.55		Māori	1.43	0.74,	2.75
	Pacific	0.83	0.49,	1.42		Pacific	0.80	0.28,	2.25
age	<40	1.00			**age**	<40	1.00		
	40-49	1.41	0.83,	2.39		40-49	1.40	0.62,	3.16
	50-59	1.14	0.67,	1.93		50-59	1.27	0.55,	2.92
	60-69	1.20	0.66,	2.18		60-69	1.96	0.81,	4.77
	70+	2.14	1.20,	3.81		70+	1.49	0.50,	4.44
NZDep	1-2	1.00			**NZDep**	1-2	1.00		
	3-4	1.47	0.81,	2.67		3-4	1.45	0.51,	4.11
	5-6	1.32	0.73,	2.40		5-6	1.65	0.65,	4.19
	7-8	1.95	1.13,	3.38		7-8	2.16	0.87,	5.38
	9-10	1.96	1.12,	3.44		9-10	1.89	0.71,	4.86
extent	local	1.00			**extent**	local	1.00		
	regional	5.17	2.59,	10.30		regional	2.96	1.55,	5.63
	distant	52.77	25.32,	109.98		distant	10.97	2.76,	43.65
size (mm)	<10	1.00			**size (mm)**	<10	1.00		
	10-19	0.92	0.29,	2.91		10-19	0.30	0.09,	0.95
	20-39	1.62	0.54,	4.83		20-39	0.83	0.32,	2.15
	40+	2.72	0.93,	8.00		40+	1.17	0.43,	3.20
grade	well diff	1.00			**grade**	well diff	1.00		
	moderately	2.00	0.69,	5.79		moderately	4.13	0.32,	52.94
	poorly	**2.85**	1.00,	8.12		poorly	8.72	0.68,	111.39
ER	negative	1.00			**ER**	negative	1.00		
	positive	0.66	0.42,	1.02		positive	0.30	0.15,	0.61
PR	negative	1.00			**PR**	negative	1.00		
	positive	0.56	0.36,	0.85		positive	1.22	0.59,	2.54
HER2	negative	1.00			**HER2**	negative	1.00		
	positive	0.99	0.67,	1.46		positive	0.85	0.48,	1.52

NMNP non-Māori/non-Pacific

NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

Calculated from ethnic-specific female population life tables

Details of excess mortality hazard ratios for all explanatory variables adjusted for each other are shown in Table 5.4 based on the full imputed dataset. There remains a statistically significant excess mortality attributable to breast cancer among women 70 years and over compared to women less than 40 years. Mortality amongst more deprived women (deprivation 7-10) was also twice that of the most affluent women (deprivation 1-2). Other prognostic variables remained associated with survival in the expected directions, although the effect of tumour size was attenuated, after adjusting for age and extent of disease.

Details of excess mortality hazard ratios for all explanatory variables adjusted for each other based on only the cases with no missing data are also presented in Table 5.4. This analysis is restricted to complete-cases and resulted in exclusion of 50% of the study population. There are notable differences in excess mortality hazards for grade and extent between this complete-case analysis and the imputed data analysis, highlighting the possibility of bias in interpreting data from complete-case analyses.

To investigate the possibility of differential inequalities by pre- and post-menopausal breast cancer, we stratified the data, using age as a binary variable cut at 50 years. However, there was no evidence of interaction between age on ethnicity on excess mortality (data not shown).

Discussion

This study explored explanations for ethnic inequalities in breast cancer survival in New Zealand. We found that a large proportion of the observed differences were explained by deprivation. Socioeconomic position remained a strong predictor of poor survival for

deprived women compared with affluent women, even in the fully adjusted model. Variables which measured timely access to care accounted for most of the remaining survival disparity for both Māori and Pacific women, whereas hormonal receptor and HER2 status did not appear to have any impact on ethnic differences in survival. It is therefore likely that the observed survival differences can be attributed to differential access to/through health services, or to deprivation-associated differential risk factor profiles, and not due to biological differences of breast cancer sub-types across ethnic groups.

The dataset contained missing data for some variables of interest, particularly extent of disease, tumour size, and HER2 status. However rather than restricting analysis to complete cases, missing variables were imputed to obtain more reliable and unbiased estimates, though imputation can be problematic with high proportions of missing data. Restricting analysis to cases without missing data would be based on the supposition that the reason for unknown data is not linked in any way to the other variables of interest, i.e. that they were missing completely at random (MCAR). This is unlikely to be the case, since we have shown that the pattern of missingness does vary with ethnicity, as well as with relative survival. The social patterning of missing data has been reported in the US, [192] where data on cancer registries are more likely to be missing for women from more deprived areas, and for African-American and Hispanic women than white women. The social patterning of missing data is important evidence that there are disparities in the 'system' and this should be a priority area for future research.

There were small numbers of mortality events in some strata of our analyses, leading to wide confidence intervals and statistical uncertainty.

Only three ethnicity groupings were used for analysis. The non-Māori/non-Pacific category is an especially heterogeneous grouping, including all ethnicities other than Māori and Pacific. The inclusion of Asian ethnicities into this category should be considered when interpreting these results as, internationally, these women have been found to have better breast cancer survival than non-Asian women.[54,187,193]

An area based SEP measure derived from census indicators was used. There are limitations with using area-based measures and they may not be as accurate as some individual SEP measures. Previous work has shown that socioeconomic differences in breast cancer survival can be diluted when using large population areas, presumably due to increased social heterogeneity in larger areas.[97] Traditional socio-economic groupings may not be useful in investigating the impact of SEP on ethnic inequalities because ethnic minorities are likely to be the most deprived in terms of income, employment, etc [100]. Further work in this area is therefore necessary, using individually collected data rather than relying on routine data sources.

In the absence of individual measures, area-based measures can be an acceptable proxy while also having the added benefit of being able to capture the context of where a woman lives, for example, physical distance from health services, which is not captured by individual measures of SEP [194]. As the only SEP measure available was an area-based measurement, the smallest geographic unit available in New Zealand was used (median of 87 people) [25]. Previous studies (reviewed by Woods et al. [97]) have found substantial inequalities using both area-based and individual measures and our results are consistent with these findings. It is important to note, therefore, that the small area-based SEP measure that we used explained a large proportion of the observed ethnic inequities in survival, but that further exploration of this on an individual level is required to inform the design of possible interventions.

Measures of timely access to care accounted for survival disparities among ethnic groups in the current study. Our findings are consistent with international studies [8,91,93] showing that stage at presentation is an important explanation of survival inequalities. Simultaneous adjustment of clinical and tumour factors make it difficult to isolate important determinants of inequalities; however in general, markers of timely access to screening, diagnosis and/or care account for survival disparities [95,187,195] between ethnic groups. Nevertheless they did not eliminate the disparities shown in all studies. In particular, some US studies continued to show poorer survival following adjustment for socioeconomic position and tumour grade and stage for African American [94] and Hawaiian women [196] compared to white women.

We found markers of breast cancer subtypes did not appear to have any impact on ethnic differences in survival. Similarly, Braun et al. [197] found hormone status did not account for ethnic differences in survival for breast cancer patients in Hawaii. Although it has been suggested that inequalities in cancer incidence could be due to differences between ethnic groups in risk factors or tumour biology, [12] there is currently little evidence to suggest that this could explain ethnic inequalities in survival in New Zealand.

We performed relative survival analysis and complementary excess mortality modelling using ethnic-specific life tables, which account for differential mortality patterns in the ethnic groups. Few studies have used excess mortality modelling to investigate disparities in breast cancer survival. Dos Santos Silva et al. [54] used this method to investigate survival differences for South Asian compared to non South Asian women in the UK although ethnic-specific life tables were not available for this study. If ethnic groups have different underlying mortality rates (or life expectancies), using total

population life tables can bias the excess mortality models, resulting in an over-estimate of the proportion of the inequalities that are due to cancer.

As part of a previous cancer linkage study by Jeffreys et al., [8] similar ethnic disparities in survival were found for more than 16,000 New Zealand breast cancer cases. However, in that study, as stratification instead of modelling was used, Pacific women were not included in the stage-standardised analysis because of small numbers. Furthermore, cancer cases with missing stage data were excluded from the analysis, 35% overall. The study found that stage accounted for some, but not all of the estimated 5-year relative survival difference between Māori and non-Māori/non-Pacific women. There was also no deprivation or SEP measure provided in the study.

The current study did not have access to screening information. New Zealand has a national screening programme, BreastScreen Aotearoa (BSA), open to all women aged 45 to 69 years. However BSA participation is known to differ by ethnic group: for women aged 50 to 69 years, biennial participation is reported as 65% for non-Māori/non-Pacific women, 47% for Māori and 50% for Pacific women [35]. While screening programmes have the capacity to detect cancer earlier and improve survival, they also have the capacity to actually increase disparities as they are usually designed by, and hence more accessible to, the ethnic majority and more affluent within the population. This phenomenon is referred to as an intervention-generated inequality.

There was no information on comorbid conditions available for this cohort of women. Relative survival analysis using ethnic-specific life tables accounts for differential patterns of mortality between ethnic groups. However, it does not account for compounded effects of multiple comorbid conditions (i.e. in addition to the woman's breast cancer). Comorbidities can affect timely diagnosis or limit which treatments are

offered to women. Further investigation of these factors is warranted and is likely to only be possible in a prospective design.

In summary, this study has shown that ethnic disparities in breast cancer survival in New Zealand can be attributed to differential access to health care rather than differences in breast cancer subtypes. We have also highlighted the importance of using multiple imputation when large proportions of data are missing. However, further work in this area is required before appropriate interventions can be designed. It is important to know the contribution that access to screening makes to the late presentation of Māori and Pacific women. An ongoing study funded by the New Zealand Health Research Council is examining the role that access to care plays in explaining survival inequalities, through structured interviews with newly diagnosed women with breast cancer. This will examine the issues of patient and provider delay, [198,199] as well as barriers to accessing primary and secondary health services [200-203].

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CHAPTER SIX

Investigating reasons for socioeconomic inequalities in breast cancer survival in New Zealand

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This study investigated the role that demographic and tumour factors play in explaining socioeconomic inequalities in breast cancer survival. Breast cancer cases notified to the New Zealand Cancer Registry (NZCR) from April 2005 to April 2007 were followed up to April 2009. The New Zealand area-based deprivation index (NZDep) was used as a measure of socioeconomic position. Relative survival was estimated using sex-, deprivation- and ethnic-specific life tables. Multiple imputation was used to impute missing data. Excess mortality modelling was used to estimate the contribution of demographic and tumour factors to inequalities in survival. There were 2,968 breast cancer cases included and 433 recorded deaths. Relative survival at 4 years varied across deprivation groups. Using NZDep deciles 1-4 (least deprived) as the reference group, the age- and ethnicity-adjusted hazard ratio (HR) for NZDep deciles 7-8 was 2.03 (CI 1.36 to 3.04) and for NZDep deciles 9-10 was 1.93 (CI 1.28 to 2.92). In the fully adjusted model, there remained 50% excess mortality for the two most deprived groups compared to the most affluent. Variables which measured timely access to care (extent/size) accounted for more of the survival disparity than breast cancer subtype variables (ER/PR/HER2). Women from deprived areas in New Zealand who are diagnosed with breast cancer are less likely to survive as long as those from affluent areas. A substantial proportion of these socioeconomic disparities can be attributed to differential access to health care although other factors, currently unknown, are also likely to play an important role.

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Introduction

Breast cancer is the most common female cancer in New Zealand and a leading cause of cancer death for women. Previous research has described survival disparities by socioeconomic position (SEP) for women with breast cancer in numerous countries, with very different health care systems, including New Zealand,[7] Australia,[123] Denmark,[125] Sweden,[157,204] the United States (US),[92,182,205] and the United Kingdom (UK). [122,159,206]

Various measures of SEP include markers of education, occupation, income, assets, and area of residence. Some measures are volatile and can change rapidly such as income, while others are more static such as education. Varying benefits and limitations are associated with employing all markers of SEP and depend on what is specifically being investigated. For example, education may be a stable indicator which will never decrease, but it does not capture significant life or income changes that can alter SEP. Norms for highest educational attainment also change with time and location, and earnings are vastly different among people with the same qualifications.[23] Indices based on aggregated personal data can also be useful as a marker of SEP and these are commonly used in New Zealand. SEP and ethnicity have a close and complex relationship, and appear to affect health outcomes both independently and jointly.[207-209]

This study aims to investigate the role that demographic and tumour factors play in explaining breast cancer survival inequalities among women across levels of deprivation in New Zealand.

Materials and methods

Study population

Data for this study came from the New Zealand Cancer Registry (NZCR), a population-based country-wide cancer registry. Pathology laboratories have been required by law since 1994 to report any new diagnosis of cancer in New Zealand (excluding squamous and basal cell skin cancers), with additional data collected from death certificates, coroners' findings, and hospital discharge data. Women with a primary breast cancer diagnosed between April 2005 and April 2006 were identified. An additional year of registrations, to April 2007, was taken for Māori and Pacific cases to ensure a representative sample of the New Zealand population. These women formed the basis of a case-control study (to be reported elsewhere). We previously documented a large degree of missing data on pertinent factors in earlier NZCR data extracts;[111] however missing data is declining over time, which is why we have chosen to restrict analyses to this recent time period.

Study variables

Demographic and tumour features were extracted from the NZCR data. Age at diagnosis was divided into five categories for analysis: less than 40 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 years and older. The NZCR records tumour grade as well differentiated, moderately differentiated, poorly differentiated, or unknown. Extent of disease is recorded as local, regional, distant, or unknown. Tumour size is measured at the widest point and recorded in millimetres (mm). For analysis, tumour measurements were grouped into four categories: less than 10mm, 10-19mm, 20-39mm, 40mm and larger. Extent of disease and tumour size reflect the progression of the tumour at presentation, and these two variables are referred to below as markers of timely access to care.

Hormone (oestrogen and progesterone) receptor and human epidermal growth factor receptor-type 2 (HER2) status information are recorded as negative, positive, or unknown status (including both not tested and indeterminate results). These variables are often used to separate breast cancers into subtypes and may reflect differential risk factor exposures; we refer to these variables below as markers of subtypes.

The New Zealand Deprivation Index 2006 (NZDep06) [25] was used as a measure of socioeconomic position based on place of residence at the time of cancer registration. The index uses nine variables (benefit income, employment, household income, communication, transport, support, qualifications, living space, and home ownership) from the 2006 census to place small areas (mesh-blocks containing a median of 87 people [25]) on a deprivation scale from 1 to 10; 10 represents the most deprived 10% of New Zealand areas, while 1 represents the 10% least deprived areas. For this analysis, an a priori decision was made to combine deciles into four categories: 1-4 (least deprived); 5-6; 7-8; 9-10 (most deprived). As Māori (indigenous people of New Zealand) are underrepresented in the most affluent areas, the four least deprived deciles were combined for analysis.

Ethnicity on the NZCR is assigned using a prioritisation system.[189] The highest priority is assigned to Māori ethnicity, which records anyone who identifies with Māori ethnicity as Māori, regardless of other ethnic identities. Ethnicity information was grouped into the two categories: Māori, and non-Māori (predominantly European but also including Pacific Island, South East Asian, Chinese, Indian, Other Asian, Middle Eastern, Latin American/Hispanic, African, Other, and Not stated).

All cause mortality was ascertained from the Information Directorate of the New Zealand Ministry of Health. Patients were followed up until 07 April 2009.

Statistical analysis

Descriptive analyses were initially conducted to explore the values of variables and to summarise the data.

Cause of death is not available for several years following the event in routinely collected New Zealand data, and was not available for the cohort under study. To our knowledge, the accuracy of cause of breast cancer death has not been reported in New Zealand and may differ by SEP. Furthermore, even if cause of death is recorded accurately it is likely that cancer also increases other causes of death, e.g. those induced as a result of treatment. Therefore, relative survival and excess mortality modelling (instead of cause-specific survival analysis) were used to estimate net effects attributable to cancer. Relative survival was performed using the maximum likelihood approach for individual records.[101] Crude relative survival was first estimated for all women by each variable of interest relative to the total New Zealand female population. Deprivation- and ethnic-specific life tables were then used to estimate relative survival for Māori, and non-Māori women at each year of follow-up, censored at 4 years. The use of deprivation- and ethnic-specific life tables accounts for the differential mortality patterns of the socioeconomic/ethnic groups.

Due to the significant degree of missing or unknown data for some variables, multiple imputation was performed on the dataset. This method assumes that the data are missing at random (MAR), i.e. that missing values are randomly distributed within one or more strata of the data, and can hence be predicted using imputation. Multiple imputation was performed by chained equations (MICE).[190] Twenty-five complete

datasets were generated using a model that included incomplete variables (extent, size, grade, ER, PR, HER2), complete variables (deprivation, age, ethnicity), vital status and follow-up time.

Excess mortality modelling with the MIM program[191] was performed to fit multivariable regression models, using a generalised linear model with a Poisson error structure to estimate excess mortality hazard ratios. An age- and ethnicity-adjusted base model was used, to which other prognostic variables, or variable groupings, were added singly, and then in progression.

All analyses were performed using Stata software, version 10.1.

Results

There were 2,968 breast cancer cases registered with a New Zealand address within the study period (11 cases had an overseas/not applicable residential code recorded on the register), comprising 946 (31.9%) in the affluent group (NZDep 1-4), 580 (19.5%) in deprivation group 5-6, 712 (24.0%) in deprivation group 7-8, and 730 (24.6%) in the most deprived group (NZDep 9-10). Table 6.1 shows the distributions of age, ethnicity and tumour features by deprivation group. The median age at diagnosis was 57.2 years. The most deprived socioeconomic group had a higher proportion of Māori women who comprised 34.0% of the group, compared with only 7.5% of the affluent group. Deprived women were over-represented in the distant extent, and large size tumour groups. The most deprived women were also more likely than their affluent counterparts to be HER2 positive.

Table 6.1. Distributions of age, deprivation and breast tumour features by deprivation group in New Zealand

					Deprivation category										
		Total (n=2,968)			1-4 (n=946)			5-6 (n=580)			7-8 (n=712)			9-10 (n=730)		
		n	%	*%	n	%	*%	n	%	*%	n	%	*%	n	%	*%
age	Median		57.2			56.5			58.5			58.7			56.5	
	<40	209	7.0		70	7.4		47	8.1		39	5.5		53	7.3	
	40-49	690	23.3		232	24.5		126	21.7		158	22.2		174	23.8	
	50-59	777	26.2		259	27.4		143	24.7		182	25.6		193	26.4	
	60-69	663	22.3		185	19.6		146	25.1		160	22.5		172	23.6	
	70+	629	21.2		200	21.1		118	20.3		173	24.3		138	18.9	
p=0.129																
ethnicity	non-Māori	2,462	82.9		875	92.5		513	88.4		592	83.1		482	66.0	
	Māori	506	17.1		71	7.5		67	11.6		120	16.9		248	34.0	
p<0.001																
extent	Local	1,317	53.4	52.9	462	56.7	56.2	269	54.6	54.4	309	53.0	52.3	277	48.0	47.8
	Regional	1,044	42.3	42.1	323	39.6	39.6	213	43.2	43.0	246	42.2	42.0	262	45.4	45.0
	Distant	107	4.3	5.0	30	3.7	4.2	11	2.2	2.6	28	4.8	5.7	38	6.6	7.2
	Unknown	500			131			87			129			153		
p=0.002																
size (mm)	<10	374	14.9	14.1	135	16.5	15.7	83	16.4	16.1	76	12.7	12.1	80	13.5	12.4
	10-19	865	34.4	31.8	311	38.1	35.5	167	33.0	31.3	218	36.5	33.2	169	28.6	26.0
	20-39	996	39.7	39.9	306	37.5	38.1	202	39.9	40.3	235	39.3	39.7	253	42.8	42.3
	40+	276	11.0	14.2	64	7.8	10.7	54	10.7	12.3	69	11.5	15.0	89	15.1	19.3
	Unknown	457			130			74			114			139		
p<0.001																

grade	well differentiated	625	23.1	22.5	205	23.6	23.0	139	25.7	25.3	144	22.1	21.7	137	21.0	20.2
	moderately	1,201	44.3	44.4	405	46.7	46.6	235	43.5	43.7	264	40.6	41.0	297	45.5	45.5
	Poorly	885	32.6	33.1	257	29.6	30.4	166	30.7	31.0	243	37.3	37.3	219	33.5	34.3
	Unknown	257			79			40			61			77		
p=0.027																
ER status	Negative	558	20.7	20.6	172	19.9	19.9	106	20.1	19.7	145	22.1	22.0	135	20.9	20.9
	Positive	2,139	79.3	79.4	694	80.1	80.1	422	79.9	80.3	512	77.9	78.0	511	79.1	79.1
	Unknown	271			80			52			55			84		
p=0.738																
PR status	Negative	941	35.3	35.4	284	33.2	33.7	189	36.2	35.6	246	38.1	37.9	222	34.7	35.1
	Positive	1,722	64.7	64.6	571	66.8	66.3	333	63.8	64.4	400	61.9	62.1	418	65.3	64.9
	Unknown	305			91			58			66			90		
p=0.251																
HER2 status	Negative	1,494	81.6	82.9	518	86.9	87.5	277	79.6	82.8	353	79.9	81.5	346	77.9	78.6
	Positive	336	18.4	17.1	78	13.1	12.5	71	20.4	17.2	89	20.1	18.5	98	22.1	21.4
	Unknown	1,138			350			232			270			286		
p=0.001																

p calculated excluding missing data

*% from imputed data (all*p<0.001)

NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

Extent of disease, size, grade, ER, PR, and HER2 status all included notable proportions of missing data. With the exception of HER2, there appeared to be the greatest proportions of missing data for the women in the most deprived group. Table 6.1 also shows the distribution of explanatory variables by deprivation group following the multiple imputation. These were broadly similar to the distributions based on non-missing data.

Up to April 2009, there were 433 recorded deaths: 108 in the affluent group 1-4, 68 in deprivation group 5-6, 134 in deprivation group 7-8 and 123 in the most deprived group 9-10. Table 6.2 shows crude relative survival estimates and 95% confidence intervals (CI) for each variable of interest, including estimates for each category of missing data. Relative to the total female population, women from the affluent group had the highest survival whereas their most deprived counterparts had the lowest 4-year survival. Māori women had lower survival than non-Māori women. As expected women with more favourable tumour features had higher relative survival than those with poor prognostic features. Women who had missing information for grade, and tumour size had noticeably low survival.

Table 6.2. Crude relative survival and 95% confidence intervals for demographic and tumour features relative to the total female population of New Zealand

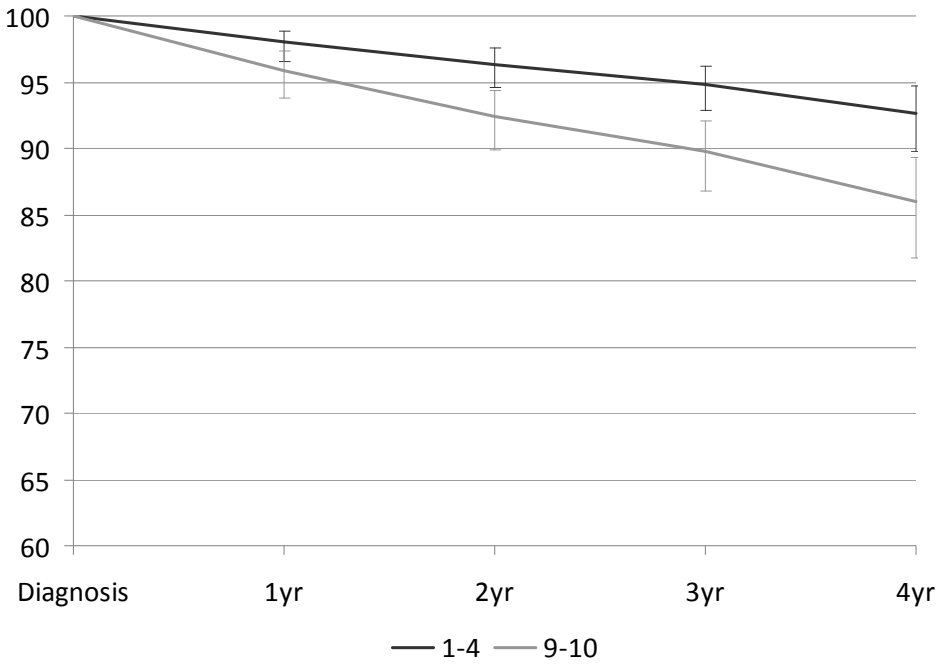
		4 year relative survival	Confidence interval		
NZDep	1-4	92.51	89.68	to	94.59
	5-6	92.29	88.78	to	91.73
	7-8	86.33	82.55	to	89.34
	9-10	84.19	80.06	to	87.52
	All	89.46	87.81	to	90.90
age	<40	85.98	79.23	to	90.66
	40-49	89.33	86.00	to	91.90
	50-59	90.70	87.88	to	92.89
	60-69	91.37	87.57	to	94.05
	70+	81.88	75.87	to	86.53
ethnicity	Māori	82.87	77.61	to	87.00
	non-Māori	90.74	88.99	to	92.23
extent	local	97.91	95.85	to	98.96
	regional	85.67	82.52	to	88.30
	distant	22.13	15.57	to	29.43
(missing = 16.9%)		86.16	81.58	to	89.68
grade	well diff	99.65	25.74	to	99.99
	moderately	92.21	89.71	to	94.12
	poorly	81.50	77.92	to	84.56
(missing = 8.7%)		70.06	63.33	to	75.80
size (mm)	<10	97.93	92.10	to	99.47
	10-19	97.99	95.62	to	99.08
	20-39	90.79	87.74	to	93.12
	40+	75.16	67.96	to	80.98
(missing = 15.4%)		64.82	59.07	to	69.98
ER status	neg	77.40	72.80	to	81.33
	pos	92.85	91.04	to	94.30
(missing = 9.1%)		79.49	72.80	to	84.70
PR status	neg	82.50	79.16	to	85.35
	pos	93.78	91.80	to	95.29
(missing = 10.3%)		78.76	72.28	to	83.89
HER2 status	neg	92.24	90.03	to	93.97
	pos	78.80	72.47	to	83.84
(missing = 38.3%)		88.26	85.47	to	90.55

NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

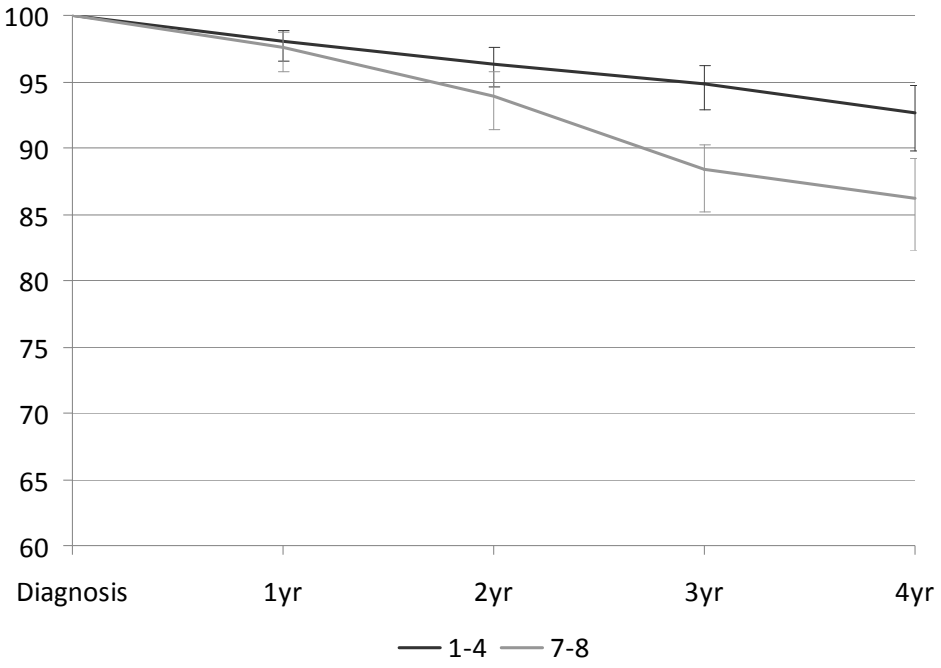
Figure 6.1 shows relative survival for women from the most deprived group compared with women from the least deprived group, estimated from sex-, deprivation- and ethnic-specific life tables. Deprived women show lower survival estimates than their more affluent counterparts across all time bands.

Figure 6.1 Relative survival and 95% confidence intervals estimated from deprivation- and ethnic-specific life tables for (a) deprivation group 9-10 (most deprived) compared with deprivation group 1-4 (least deprived), (b) deprivation group 7-8 compared with 1-4 and (c) deprivation group 5-6 compared with 1-4

a)



b)


100
95
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85
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75
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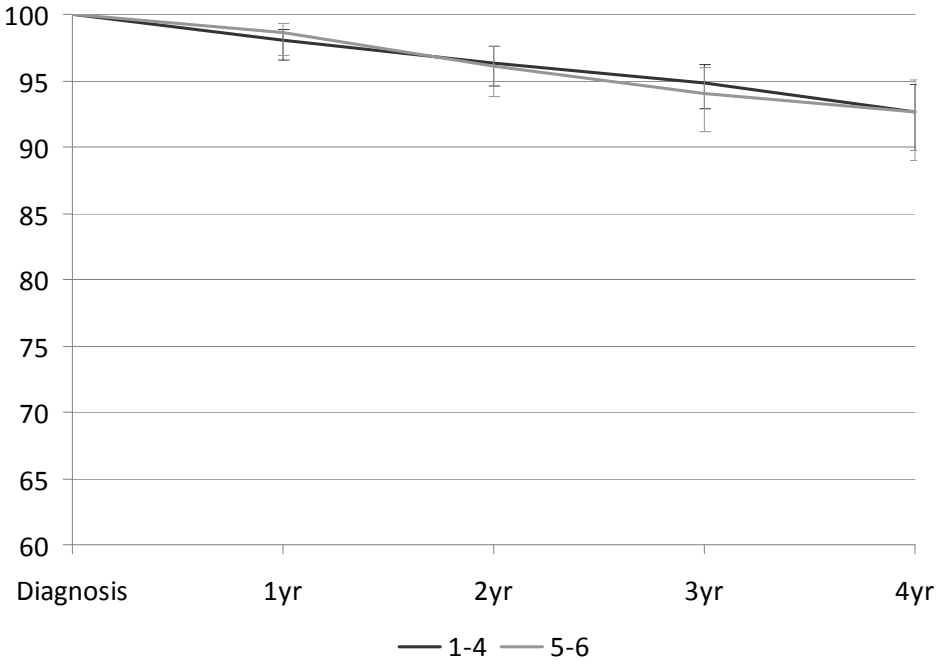
65
60
Diagnosis
1yr
2yr
3yr
4yr
1-4
7-8

c)


100
95
90
85
80
75
70
65
60
Diagnosis
1yr
2yr
3yr
4yr
1-4
5-6

The excess mortality hazard ratios for deprived women compared with affluent women are given in Table 6.3. Women in the deprivation group 5-6 showed no excess mortality compared to the affluent women. Adjusting for each of the access to care variables (extent and size) individually attenuated the socioeconomic inequalities in excess mortality. For Deprivation group 7-8 the age- and ethnicity-adjusted HR dropped from 2.03 (CI 1.36 to 3.04) to 1.59 (CI 1.07 to 2.35) when further adjusted by extent and size (Model C). For Deprivation group 9-10 the HR dropped from 1.93 (CI 1.28 to 2.92) to 1.42 (CI 0.97 to 2.10). To investigate whether tumour sub-types (and hence risk factor profiles) explained socioeconomic inequalities in survival we assessed the individual and combined effect of adjusting for ER, PR and HER2. Although subtype factors attenuated the excess mortality to a small degree, their impact was not as marked as the access to care variables. Even after adjustment for all variables (Model F), there remained significant excess mortality for Deprivation group 7-8 (HR 1.50, CI 1.02 to 2.21) and Deprivation group 9-10 (HR 1.48, CI 1.00 to 2.18).

Table 6.3. Excess mortality hazard ratios (HR) and 95% confidence intervals (CI) for women from deprived areas compared with women from affluent areas, modelled on imputed data

		1-4	5-6			7-8			9-10		
	Models on imputed data	**HR**	**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**	
	***Crude/deprivation**	1.00	1.08	0.65 to	1.80	2.16	1.43 to	3.25	2.06	1.36 to	3.11
A	**Age adjusted**	1.00	1.04	0.62 to	1.73	2.10	1.40 to	3.14	2.08	1.39 to	3.11
B	**A+ethnicity**	1.00	1.03	0.62 to	1.71	2.03	1.36 to	3.04	1.93	1.28 to	2.92
	B+extent	1.00	1.13	0.71 to	1.79	1.63	1.11 to	2.41	1.50	1.03 to	2.20
	B+size	1.00	0.89	0.55 to	1.43	1.58	1.07 to	2.34	1.46	0.99 to	2.16
	B+grade	1.00	1.00	0.62 to	1.61	1.75	1.19 to	2.56	1.67	1.12 to	2.49
	B+ER	1.00	1.02	0.62 to	1.67	1.96	1.32 to	2.90	1.88	1.25 to	2.82
	B+PR	1.00	0.99	0.61 to	1.61	1.82	1.22 to	2.69	1.89	1.26 to	2.82
	B+HER2	1.00	0.94	0.57 to	1.55	1.82	1.21 to	1.27	1.75	1.16 to	2.64
	B+ER,PR	1.00	0.99	0.61 to	1.62	1.84	1.24 to	2.73	1.87	1.25 to	2.79
	B+ER,PR,HER2	1.00	0.96	0.59 to	1.56	1.76	1.18 to	2.61	1.79	1.20 to	2.68
C	**B+extent,size**	1.00	1.11	0.70 to	1.76	1.59	1.07 to	2.35	1.42	0.97 to	2.10
D	**B+extent,grade,size**	1.00	1.08	0.69 to	1.71	1.51	1.02 to	2.22	1.43	0.97 to	2.10
E	**D+ER,PR**	1.00	1.05	0.67 to	1.65	1.51	1.03 to	2.22	1.48	1.00 to	2.18
F	**E+HER2**	1.00	1.05	0.66 to	1.65	1.50	1.02 to	2.21	1.48	1.00 to	2.18

NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

*Adjusted for follow up

Table 6.4. Excess mortality hazard ratios (HR) and 95% confidence intervals (CI) for all explanatory variables adjusted for each other, modelled on imputed data and complete case data

Model F on imputed data (n=2968)						Model F on complete case data (n=1500)					
		HR	95% CI					HR	95%CI		
NZDep	1-4	1.00				**NZDep**	1-4	1.00			
	5-6	1.05	0.66	to	1.65		5-6	1.32	0.66	to	2.62
	7-8	1.50	1.02	to	2.21		7-8	1.62	0.85	to	3.08
	9-10	1.48	1.00	to	2.18		9-10	1.32	0.66	to	2.63
age	<40	1.00				**age**	<40	1.00			
	40-49	1.38	0.82	to	2.33		40-49	1.42	0.63	to	3.17
	50-59	1.14	0.68	to	1.92		50-59	1.35	0.60	to	3.04
	60-69	1.21	0.67	to	2.19		60-69	2.05	0.85	to	4.93
	70+	2.25	1.30	to	3.91		70+	1.54	0.54	to	4.44
ethnicity	non-Māori	1.00				**ethnicity**	non-Māori	1.00			
	Māori	1.10	0.76	to	1.61		Māori	1.58	0.85	to	2.94
extent	Local	1.00				**extent**	local	1.00			
	Regional	5.03	2.57	to	9.84		regional	3.00	1.59	to	5.68
	Distant	48.53	23.89	to	98.60		distant	9.22	2.45	to	34.66
size (mm)	<10	1.00				**size (mm)**	<10	1.00			
	10-19	0.89	0.28	to	2.81		10-19	0.28	0.09	to	0.91
	20-39	1.62	0.55	to	4.81		20-39	0.81	0.32	to	2.07
	40+	2.68	0.92	to	7.84		40+	1.13	0.42	to	3.03

grade	well differentiated	1.00				**grade**	well differentiated	1.00			
	moderately	1.92	0.70	to	5.29		moderately	5.41	0.17	to	172.77
	Poorly	2.71	1.01	to	7.26		poorly	11.66	0.37	to to	370.60
ER status	Negative	1.00				**ER status**	negative	1.00			
	Positive	0.67	0.44	to	1.03		positive	0.30	0.15	to	0.62
PR status	Negative	1.00				**PR status**	negative	1.00			
	Positive	0.58	0.36	to	0.85		positive	1.23	0.60	to	2.54
HER2 status	Negative	1.00				**HER2 status**	negative	1.00			
	Positive	1.01	0.69	to	1.48		positive	0.86	0.49	to	1.52

NZDep New Zealand Deprivation Index 2006 is a scale based on census information, where 1 represents the 10% least deprived and 10 represents the 10% most deprived areas in New Zealand

Details of excess mortality hazard ratios for all explanatory variables adjusted for each other are shown in Table 6.4 based on the full imputed dataset. There remains a significant excess mortality attributable to breast cancer among women 70 years and over compared to women less than 40 years. Other prognostic variables remained associated with survival in the expected directions.

Restricting the analyses to women with no missing data (i.e. a complete-case only analysis) resulted in exclusion of 50% of the study population. The excess mortality hazard ratios for all explanatory variables adjusted for each other from this analysis are also presented in Table 6.4. There are notable differences in excess mortality hazards for extent of disease and grade between this complete-case analysis and the imputed data analysis, highlighting the possibility of bias in interpreting data from complete-case analyses.

To investigate the possibility of differential inequalities by pre- and post-menopausal breast cancer, we stratified the data, using age as a binary variable cut at 50 years. However, there was no evidence of interaction between age on excess mortality (data not shown).

Discussion

We have shown socioeconomic position remains a strong predictor of poor survival for deprived women compared with affluent women, even after adjustment for other known prognostic factors. Our results show that the two most deprived groups both have a 50% excess mortality compared to the affluent women. Only a small proportion of the observed differences were explained by ethnicity, highlighting the fact that these differences are independent of any ethnic differences in survival which we have previously described.[8] Variables which measured timely access to care accounted for more of the remaining survival disparity than breast cancer subtype variables.

Our results are consistent with other international findings.[122,123] In a systematic review of socioeconomic inequalities and cancer survival, in general, the most deprived groups had estimated increased relative risk of death at 1.3 to 1.5 times that of the most affluent groups.[124]

We used the New Zealand Deprivation Index as a measure of SEP. This is an area-based index derived from census information and there are limitations with using such aggregate measures. Woods et al showed socioeconomic differences in breast cancer survival can be diluted when using large population areas due to increased social heterogeneity in larger areas.[97] However, with no individual measures available, area-based measures can be an acceptable proxy. Such indices measure not only some aspect of a woman's individual SEP, but may also capture the context of where she lives, [194] and have been viewed as a marker of health service access in New Zealand.[210] As the only SEP measure available was an area-based measurement, the smallest geographic unit available in New Zealand was used (median of 87 people).[25]

This is considerably smaller than the small areas units used in other countries, such as the UK, where even the lower-level super output area (LSOA) has an average of 1,500 people. The larger the area, the more heterogeneity might be expected within each area, resulting in dilution of the measured effect due to non-differential misclassification. It is likely that our results are therefore affected by such measurement error to a smaller degree than studies which have based their results on larger areas.

Measures of timely access to care accounted for survival disparities between deprivation groups in the current study. Our findings from New Zealand are consistent with international studies[8,91,93] showing that extent of disease at presentation is an important explanation of survival inequalities. In a previous study, we have documented socioeconomic disparities in survival for New Zealand women with breast cancer.[7] However in that study, we controlled for the potential confounding factors of age and extent of disease by standardisation rather than excess mortality modelling, and had to exclude a total of 35% of cases from the analyses because of missing data on extent of disease. That study found that extent of disease accounted for 33.8% of the estimated deprivation gap in 5-year relative survival.

For all cancers combined, we have previously shown that there is a linear trend of lower survival across the whole NZDep distribution.[8] In this study, deprivation appeared to have a dichotomous effect on breast cancer survival, with the lower survival apparent only in the lower four deciles of the NZDep distribution. This finding seems in contrast to most other breast cancer studies, which tend to show more of a linear effect on survival.[54,122,211] However, to ensure Māori women were represented in all deprivation categories, we needed to combine the four least deprived groups into one category, which was used as the group of reference. This grouping may have diluted

the association that could have been seen if only the least deprived women, or smaller deprivation categories were used. However in that case, we would not have been able to adequately adjust for ethnicity.

As would be expected, we found that breast cancer subtypes are clearly related to survival, with women with ER and PR positive tumours having better survival than receptor-negative tumours, and women with HER2 negative having better survival than HER2 positive tumours. We have previously shown that these factors are not related to SEP, [111] and it is therefore not surprising that adjusting for these had little impact on socioeconomic differences in survival.

We found that tumour grade appeared to vary by SEP, which is consistent with our findings from a previous New Zealand study [111] and similar results have also been reported in the UK. [212,213] Variation in tumour grade between social groups could be associated with differential exposure to risk factors.

Relative survival analysis and complementary excess mortality modelling was performed to adjust for mortality from causes other than breast cancer. Our analysis used sex-, deprivation- and ethnic-specific life tables, which accounted for differential mortality patterns in these different groups. Few studies have used excess mortality modelling to investigate disparities in breast cancer survival, and even fewer have used population-specific life tables in their analysis. When specific groups have different underlying mortality rates (or life expectancies), total population life table rates can bias excess mortality models, and over-estimate the proportion of the inequalities that are due to cancer.[214]

The dataset included high proportions of missing data for variables, including extent of disease and tumour size. Imputation of missing data is preferable to complete case analysis as estimates are more reliable and unbiased [215] though it is acknowledged that imputation can be problematic with high proportions of missing data.[216] Restriction of analysis to cases without missing data would infer that the reason for unknown data is not linked in any way to the other variables of interest, i.e. that they were missing completely at random. This is unlikely in our dataset as the pattern of missingness did vary with deprivation, as well as with relative survival. Similar patterns of missing data have been reported in the US, [192] where data on cancer registries are more likely to be missing for women from more deprived areas.

Imputation relies on the assumption that variables are MAR, which can never be directly validated.[215] However, including in the imputation model as many predictive variables as possible makes the assumption of MAR more probable, and therefore less likely to produce biased results.[216,217]

The NZCR has been audited in relation other cancer sites and their accuracy was found to be similar to that of internationally comparable registries.[218] Extent of disease is the most difficult data for registries to collect accurately. A NZCR lung cancer audit found extent was recorded accurately for 77% of cases. [219] A further colon cancer audit found 80% accuracy for extent of disease recording on the NZCR [218]; however, this was noted to have improved over the time period studied, and is more accurate in later years.

Screening attendance information, which differs by SEP, was not available for this study. Breast screening programmes are often attended more regularly by affluent people[136,220], and although data from New Zealand are not available, it is likely that a

similar pattern exists. There is, however, data by ethnicity, which shows overall that breast screening coverage is higher for non-Māori than Māori women in New Zealand.[35,221] While breast screening programmes are an important contributor to the falling breast cancer mortality rate,[222] this benefit is not afforded to all women equally. Differential uptake of screening across SEP groups, followed by subsequent differential management (as evidenced by lower survival in screen-detected women from more deprived areas [223]) results in the programmes increasing disparities between deprived and affluent people[148], a phenomenon referred to as an intervention-generated inequality. A recent study of breast cancer registrations in the UK showed deprivation survival disparities were evident both in the general population (ranging from 83.6% (80.0, 86.6) in the most deprived to 90.8% (89.0, 92.3) in the least deprived) and in screen-diagnosed women (ranging from 95.6% (90.6, 98.0) in the most deprived to 98.2% (95.9, 99.2) in the least deprived). [223]

There was no information on comorbid conditions available for this cohort of women. Relative survival analysis using deprivation-specific life tables accounts for differential patterns of mortality between these groups. However, it does not account for compounded effects of several comorbid conditions in addition to the specific cancer. Comorbidities and underlying health problems can delay diagnosis, limit treatments, and affect survival. [224] Nor was there information on psychosocial issues,[225,226] some of which may differ by SEP and have an impact on survival. Further studies with intermediate variables will be helpful to elucidate the pathways through which the observed associations may be operating.

In summary, this study has shown that there remains a large excess in mortality for women diagnosed with breast cancer from deprived compared to affluent areas in New Zealand. A substantial proportion of socioeconomic disparities in survival can be

attributed to differential access to health care although other factors, currently unknown, are also likely to play an important role. This study has further shown the benefits of performing multiple imputation on datasets with high proportions of missing data.

An ongoing study funded by the New Zealand Health Research Council is examining the roles that access to primary and secondary care plays in explaining survival inequalities. This research examines the issues of patient and provider delay,[198,199] and barriers to accessing primary and secondary health services,[200-203] specifically for women diagnosed with breast cancer.

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CHAPTER SEVEN

Discussion

This thesis examines explanations for inequalities in outcomes for women with breast cancer. In summary, we found that individual level risk factors (BMI, smoking, alcohol and breast cancer sub-types) were not strongly associated with the social patterning of breast cancer survival. In contrast, early detection and markers of timely access to care were important determinants of inequalities in survival.

Introduction

One of the strengths of the body of work as a whole was the employment of various approaches to address the overall research aim of investigating explanations for ethnic and socioeconomic inequalities in survival for women with breast cancer, using different study designs, contexts, and data sources. A systematic review and meta-analysis was carried out among published English language studies which examined the contribution of behavioural factors to breast cancer survival differences between ethnic groups. Prognostic factors for New Zealand women with breast cancer were examined by ethnicity and SEP. Two general-population-based survival studies, which examined ethnic and SEP inequalities, used a New Zealand dataset to isolate contributions to inequalities by specific demographic and tumour factors. A further population-based study examined the social gradient of survival among screen-detected breast cancer the South West of England, UK. Thus, New Zealand, UK, and worldwide data; ethnic and SEP data; and review and empirical data were all used to investigate survival inequalities for women diagnosed with breast cancer.

Conceptual model

It is important to have a coherent and comprehensive framework for investigating disparities in cancer outcomes.[27] For this body of work a conceptual model was

designed to elucidate potential pathways by which ethnicity and SEP could influence outcomes for women with breast cancer (see Figure 1.1). The bolded arrows shown in Figure 7.1 illustrate those pathways found to be important through this research. Ethnicity is closely related to SEP. With regard to survival, ethnicity appeared to have both direct effects on health factors and indirect effects via SEP. The key pathway appears to be related to health system factors that are in effect prior to diagnosis, rather than health system factors operating post diagnosis. Thus, the detection pathway played a greater role in ethnic and socioeconomic inequalities in survival than the treatment pathway.

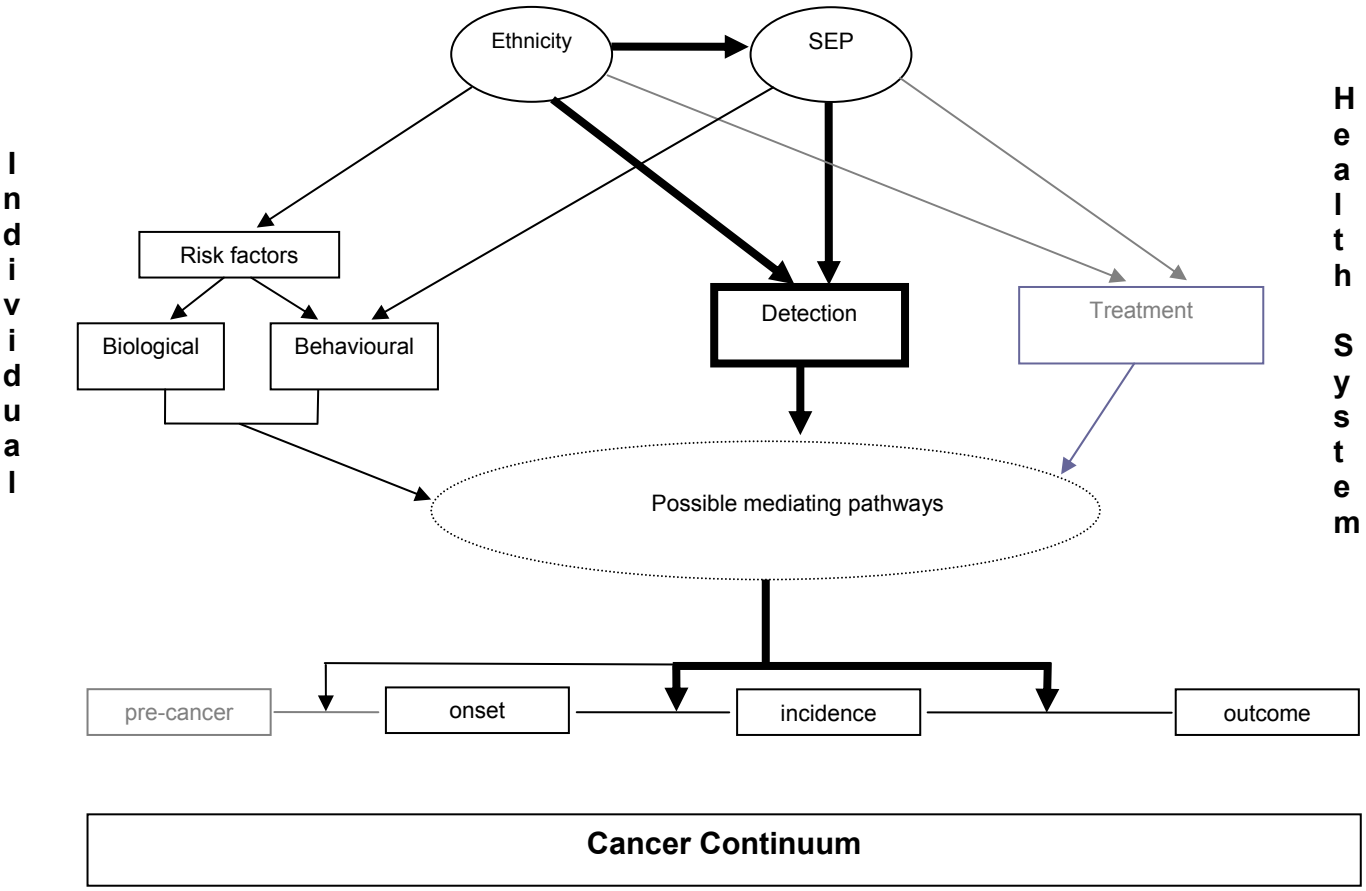

Figure 7.1. Conceptual model of pathways influencing ethnic and socioeconomic inequalities in breast cancer survival.

The focal point of this work was survival. In order to ascertain the best points along the cancer continuum to focus interventions to reduce disparities in survival, we used this as an outcome measure but looked at possible modifiable exposures across the continuum.

The Review paper (chapter two) examined the relationship between social determinants and behavioural factors to establish whether intervening at the individual level would affect ethnic disparities in survival from breast cancer. The differences in breast cancer survival seen among ethnic groups may be in part explained by BMI, but there was little evidence to implicate smoking or alcohol as explanatory factors of this inequality. SEP explained part of the ethnic inequality in survival from all causes, but this was not evident for breast cancer specific survival. Given the social patterning of BMI and other lifestyle habits, it is possible that results for SEP and BMI are measuring the same effect.

The screening paper (chapter three) examined SEP and a breast screening programme to ascertain whether SEP persisted as a determinant of survival among women diagnosed from within the same system. This population-based cohort study found that deprivation/SEP survival disparities were evident for women diagnosed with breast cancer. They were also evident, but substantially attenuated, for women diagnosed within the screening programme, indicating that earlier detection could account for much of the inequality within the general population. The clear gradient of deprivation-related survival disparity which remained within the screened population, however, suggests that other variables, potentially differential treatment, quality of care, or environmental or lifestyle factors, are additionally influencing inequalities in breast cancer outcomes between women of differing SEP.

Prognostic factors in women with breast cancer: inequalities by ethnicity and socioeconomic position in New Zealand (chapter four) found that Māori, Pacific and low socioeconomic women present with poor prognosis breast tumours. There were differences in factors associated with poorer survival, including stage, extent of disease, size of tumour, ER, PR, and HER2 status among ethnic groups. In addition differences were found in tumour stage and size among deprivation groups. Ethnic differences were not explained by socioeconomic status. Associations between ethnicity and prognostic factors differed from those between deprivation and prognostic factors, indicating other drivers of ethnic differences than purely socioeconomic considerations. These results showed that ethnicity and deprivation were separate exposures, which had independent effects on outcome.

The NZ ethnicity and SEP papers examined social determinants, indicators of timely access to healthcare and indicators of tumour subtype in an effort to further isolate effective levels and points of intervention. We considered extent of disease and size of tumour as measures of access to healthcare, since these are factors which could be mitigated by earlier presentation or diagnosis. It is possible that individual level factors such as obesity could be the more proximal cause of later diagnosis, rather than system level factors. However, without more information which was not available to us, this could not be investigated further.

Investigating reasons for ethnic inequalities in breast cancer survival in New Zealand (chapter five) found that a large proportion of the observed differences were explained by deprivation. Variables which indicated timely access to care accounted for most of the remaining survival disparity for both Māori and Pacific women, whereas hormonal receptor and HER2 status did not appear to have any impact on ethnic differences in survival. Therefore, it is likely that the observed survival differences can be attributed to

differential access to and through health services, or to deprivation-associated differential risk factor profiles, and not due to biological differences of breast cancer sub-types across ethnic groups.

Investigating reasons for socioeconomic inequalities in breast cancer survival in New Zealand (chapter six) found low SEP remained a strong predictor of poor survival, even after adjustment for other known prognostic factors (chapter four). Results showed that the two most deprived groups both have a 50% excess mortality compared to the affluent women. Only a small proportion of the observed differences were explained by ethnicity, highlighting the fact that these differences are independent of any ethnic differences in survival previously described. Variables which measured timely access to care accounted for more of the remaining survival disparity than breast cancer subtype variables.

Collectively, these results suggest early detection and diagnosis is an effective point of intervention to reduce survival disparities for women with breast cancer. It is evident from these studies that, while SEP explains a sizeable proportion of ethnic inequalities in breast cancer survival, there are also other factors involved. The largest contributors to ethnic inequalities appear to be factors associated with access to timely health care. There are considerable SEP inequalities in breast cancer survival, which are independent of ethnicity. A large proportion of the observed deprivation gap in breast cancer survival can be accounted for by early detection. Therefore efforts to eliminate inequalities in breast cancer should focus on increasing attendance at breast screening for women of lower socioeconomic position. Screening programmes can increase disparities if differential uptake between social groups occurs; thus, it is vital that focussed and comprehensive screening coverage be prioritised to ensure inclusion of disadvantaged or underserved groups. Additionally, efforts should also be made to

ensure equal access through the secondary care system to address the attenuated survival inequalities evident even among screen-detected women with breast cancer. Differences in tumour biology that we investigated are ER, PR and HER2, which are currently used as markers of breast cancer subtypes. These do not appear to explain survival inequalities among women of different ethnicity or among women of different SEP.

Limitations

The specific limitations of the individual studies have already been addressed in their corresponding chapters. However, there are commonalities in these limitations, particularly relating to bias and residual confounding, which are discussed in more detail below.

Bias can be split into two main categories: selection and information. Selection bias occurs when there is systematic error in the way participants are selected for a study. Information bias occurs when there is systematic error in the collection or categorisation of study data. Bias is a consequence of faults in study design or incomplete data collection and cannot be adjusted for, even if the general impact and direction of the bias can be described. Confounding however, is unrelated to study design; it is intrinsic to the structure of data in the real world. Confounding occurs when the effect of an exposure is mixed, or confused, with the effect of another variable, which can also distort estimates of association. [227,228] Unlike bias, confounding can be adjusted for in the analyses, if the relevant data have been collected and the data structure is well understood.

Selection bias was not a concern for these studies as they utilised registrations from well established cancer registries with high coverage. There are concerns regarding the collection and accuracy of ethnicity information in New Zealand registries. However bias would only be introduced if the misclassification of ethnicity was related to tumour characteristics (chapter four). Since ethnicity data are collected independently of the tumour data, it is highly unlikely that the misclassification of ethnicity could be differential with respect to the tumour markers investigated. Therefore, any misclassification of ethnicity would be non-differential, thus diluting the observed differences rather than producing spurious results. The accuracy of ethnicity recording in registries is likely to differ by ethnic group. Specifically, high rates of misclassification have been reported for Hispanic, Asian, and Pacific Island ethnicities in the United States. [103-106] Unpublished data from the NZCR indicates very good agreement (kappa = 85%) in the comparison of ethnicity among Māori, Pacific and non-Māori/non-Pacific women with breast cancer, although the accuracy of Māori ethnicity was lower than for Pacific and non-Māori/non-Pacific women, with 15% of women coded as Māori on the NZCR actually identifying as non-Māori/non-Pacific.

The effect of adjusting ethnic inequalities in health for SEP is strongly affected by the choice of SEP measure, and health inequalities between different ethnic groups respond in different ways to this adjustment. [115] Therefore, the aggregation of different ethnic groups, (e.g., the grouping ‘‘Asian/Pacific Islander’’ in the United States and ‘‘South Asian’’ in the United Kingdom) could be diluting or masking the real effect that various individual-level measures of SEP would have on ethnic inequalities in survival.

The use of an area level index of SEP would have resulted in misclassification of some women due to the heterogeneity of geographic areas. However, this kind of measurement error would be non-differential, providing equal chance of

misclassification for all women, screened and other. Non-differential measurement error would only attenuate, rather than create inequalities, and therefore under-estimate the observed deprivation gap. However, the smallest geographic unit available was used, which is markedly smaller than those used in other countries. [4,163] Therefore, it is likely that the results are affected to a smaller degree than studies based on larger, more heterogeneous, areas. [97]

Misclassification of tumour characteristics may have affected results through residual confounding. However the NZCR has been audited in relation to other cancer sites and found to have similar accuracy as other comparable registries.[218] Extent of disease is the most difficult data for registries to collect accurately and a NZCR lung cancer audit found this was recorded accurately for 77% of cases,[219] while a colon cancer audit found 80% accuracy [218] and noted that this is continuing to improve. Tumour stage or extent of disease is extracted from pathology reports where staging information is frequently done in a clinical staging system (TNM).[229] The NZCR uses the SEER summary staging system,[230] which is specifically designed for use by cancer registry coders. The TNM system is designed for clinical prognostic use and therefore does not map directly to the SEER system, which may cause discrepancies in the extent if disease coding. There is also likely to be residual confounding due to misclassification of confounding variables which will be discussed in greater detail in the subsequent confounding section.

An important limitation to this body of work is missing data, which was a concern throughout this research. There were large amounts of missing data in the NZCR, most notably in the grade, hormone receptors and HER2 variables (prognostic paper, chapter four). Importantly, the proportion of missing data for these variables differed systematically across deprivation categories, with higher proportions of missing data

seen in women living in more deprived areas. Therefore, we cannot exclude the possibility that the results which we found for deprivation were biased, and this would affect the reliability of our results. There was also a large degree of missing screening data in the South West Cancer Registry (chapter three). This may have affected our results and, after internal investigations at the registry, it appears likely that the missing/unknown screening status category would have largely comprised women with interval cancers.

For the ethnicity and SEP papers (chapters five and six), rather than restricting analyses to those with only complete information available, where possible, missing variables were imputed to obtain more reliable and unbiased estimates. Imputation has been recommended for use with incomplete cancer registry data to estimate relative survival. [215] The process involves 'filling in' the gaps of information to produce a complete dataset to use for analyses. Multiple imputation (MI) deals with the uncertainty of the missing data by constructing different plausible data sets and then combining results from each. The true values of missing data will never be known; however, MI uses a Bayesian approach to predict distributions based on the known data. Each of the imputed data sets is used to estimate associations, which are pooled together to give overall estimates. Effect estimates obtained from MI are valid, as this approach accounts for the potential variance of the missing data. [216] Analyses that only utilise records with complete information would provide biased results unless the causes of missing information are not associated with other variables of interest, i.e. that they are missing completely at random (MCAR). As missing cancer information has been reported to vary with social factors,[192] it is unlikely to be MCAR. Information is assumed to be missing at random (MAR) for imputation to be a valid approach, although this can not be directly validated,[215] including as many predictive factors as possible in the model will ensure the missing information is more likely to be MAR.

[216,217] Analysing only complete cases is simple and is an option if incomplete cases comprise only a small fraction of the data. However, it does not compensate for the sampling bias due to the loss of cases. Furthermore, if there is a loss of substantial data, there will be a loss of statistical power.

Many of the results from the studies presented in this thesis could be due to residual confounding. Reproductive and lifestyle variables (for which no information was available), together with menopausal status, may be important confounders in these studies, but no data on these variables were available from the routinely collected sources that we were using. There is no data available to indicate whether age at menopause differs by ethnicity in New Zealand. Factors which influence menopause including parity, obesity, and smoking, differ by social groups, which suggest that there may be differences in menopausal age for ethnic and socioeconomic groups. Obesity could also be a confounding factor (chapters three, five and six). Obesity affects hormone levels and may play a role in the observed social group differences in tumour prognostic factors, and survival. Tumours in overweight women have been found to be larger and more likely to have markers of high cellular proliferation than their thinner counterparts.[72] Other factors such as an elevated waist-to-hip ratio (as a marker for insulin resistance) have been found to be a predictor of breast cancer mortality, with menopausal and ER status at diagnosis being important modifiers of that relation.[231]

Comorbidity as a potential confounding factor cannot be ruled out (chapters three, five and six). Comorbidities may be higher among different population groups[232] of women. Deprivation-specific life tables in the analysis will have taken the effect of comorbidities on underlying mortality into account, though again there may be residual confounding due to treatment limitations. The results could also be confounded by screening

attendance, which may differ by ethnicity[35] and SEP in New Zealand, factors on which we had no information to allow adjustment in the analysis.

Implications of this work

One of the key strengths of this work is the investigation of the separate, but entwined influences of ethnicity and SEP in relation to breast cancer survival. It is difficult to separate the influence of ethnicity from the influence of deprivation on health outcomes in New Zealand. Māori and Pacific peoples are over represented in the highest deprivation areas, and correspondingly, under represented in the most affluent areas of New Zealand. Ethnic and socioeconomic (dis)advantage interact and accumulate across the lifespan,[13] which can make social mobility more difficult. Furthermore, discrimination and prejudice can be directed towards both disadvantaged ethnic and socioeconomic groups. Nevertheless, it is apparent from this body of work that there are more than socioeconomic differentials influencing ethnic disparities in survival.

Based on this work, it is clear that timely access to care, which may be influenced at the patient level, the provider level, and the system level, [33,233] is a key contributor to the observed disparities. 'Access' to care can be viewed as a multidimensional and multilevel process, which involves gaining entry into and through health services.[33,233] Importantly, access also encompasses timeliness, quality and outcomes as core components.[41] In New Zealand, disparities in health care access are increasingly recognised as having an important impact at all levels of health care, particularly for Māori and Pacific peoples and for those in the lower SEP groups.[234-239] Health care can involve multiple care pathways and is provided by a range of individuals, organisations, and services, and this is particularly so in cancer care.[33]

Central barriers to cancer service access have been identified as low socioeconomic class and minority status alongside other inter-related factors such as cost, transportation, accommodation, and travel requirements.[240] Issues concerning trust and continuity of care at the provider level were found to be important for low-income women in their decision to participate in cancer screening.[241] Class-related and race-related attitudes that are manifest in clinician interactions with patients are important determinants of access to cancer care[240], with provider biases and discrimination certainly acting as contributory factors to healthcare disparities.

Māori health providers have played a crucial role in facilitating access to services for Māori, from the provision of Māori-specific health services through to advocacy within mainstream service.[33] Little work to date has been undertaken to examine access to care specifically for Māori with cancer, although a few small studies have identified features of importance to be: integration of primary and secondary cancer care; enhancement of mainstream services; provision of culturally safe cancer services; relevant information provision; recognition of the role of caregiver support and; advocacy and navigator roles as being central to facilitating the negotiation of complex and dispersed cancer services.[242-244] These findings are consistent with similar work being undertaken in other indigenous populations.[245-247]

The findings from the current work identify early detection and diagnosis as being pivotal to addressing breast cancer survival disparities. There has been very little research on differences in screening uptake among New Zealand women.[248] One report of New Zealand adults' awareness of the primary prevention of common cancers found that knowledge of breast cancer risk factors was low, [249] but knowledge of screening programmes or women's views on the uptake of and access to these services was not investigated. The attitudes of women that have been identified in the

international literature as important include factors at the patient level, the carer level, and the system level. Studies conducted amongst indigenous Australian, [175] English [250] and Swedish [251] women found physical access, embarrassment, and cultural safety all to be important determinants of whether a woman would attend screening or not. In smaller communities, such as among Pacific women in New Zealand, fear of breach of confidentiality is likely to be an important barrier. [252] The need for community and family involvement in providing information about screening programmes has also been highlighted internationally [253] as well as in both Māori and Pacific communities in New Zealand. [254]

Māori providers have advocated for improved access to early detection services[33] following reports that national screening programmes are not achieving adequate or equitable coverage for Māori women.[255] Early detection, outside of screening programmes, is most likely to occur within primary care; thus, access to quality primary care and a focus on early detection for Māori women must be prioritised. Māori provider services are in a key position to undertake part of this work; however, improvements to both the provision of mainstream primary care services and the breast screening programme is critical.

Implications of this work beyond breast cancer

This body of work has demonstrated that ethnic differences are driven by more than socioeconomic markers; specifically, timely access to care is a key contributor to disparities. These key findings are likely to extend beyond this body of work. Nevertheless, caution should be exercised in generalising these results as they are all based specifically on breast cancer and cancer is an extremely heterogeneous disease. Breast cancer even has different risk factor profiles for different subtype groups.[256,257] Specifically breast cancer differs from most other cancer sites in as much

as it receives substantial media attention. There are widespread, well established breast screening programmes dedicated to early diagnosis and monitoring. Consequently, there are well developed procedures and protocols for diagnosis and treatment of breast cancer, which may not be the case for other, less scrutinised diseases. Cancers have very different aetiologies and prognoses and, just as there is variability in cancer inequalities, there is likely to be variability in causes of inequalities. Caution should also be used generalising to other populations as reasons for inequalities in breast cancer survival are likely to differ between countries and health systems.

Despite these issues, it is likely that some of the findings presented here could have direct implications for health service provision in New Zealand beyond the breast cancer remit. For example, it is clear that early diagnosis differs between ethnic groups, suggesting that access to diagnostic services needs to be addressed. To some degree, this is being addressed with the development of Primary Health Organisations (PHOs), which remove some of the direct costs associated with primary care provision. Another example of innovative ways used to address inequalities in access to care is the Marae based screening initiative by BreastScreen South.[258]

Māori providers are in a strong position to provide leadership in the area of advocating and working with Māori women to increase participation in national screening programmes. Their contribution in the primary cancer prevention and detection areas should be recognised and developed accordingly. Likewise, this could be extended to include Pacific provider organisations and even Union Health Centres, both of which provide primary health services specifically tailored to the needs of the socially diverse populations that they serve.

Policy implications

Identifying points along the pathway that are amenable to immediate change is the challenge for epidemiology, public health, and allied professionals. As noted in the WHO Report *Closing the Gap in a Generation* [259], ensuring heath equity is the responsibility of the highest level of government, which must be addressed through coherent, cross-policy agendas.

One of the two overall purposes of the New Zealand Cancer Control Strategy is to reduce cancer inequalities.[260] Cancer survival has been highlighted as one of the important determinants of differences in life expectancy between Māori and non-Māori [16] and these disparities need to be redressed.[27] This thesis is one of the first bodies of work in the area of cancer survival which has moved beyond the simple description of disparities to advance our understanding of the underlying causes for differences in survival. Further studies with similar aims will be required to develop the evidence base to inform health and other policy.

Primary care is the first level of contact and the entry point to the health system; the most obvious primary care involvement is through GP practices and PHOs. Campbell et al note that nearly all the priorities for cancer services are affected by actions in primary care – reducing the risk of cancer, early detection, faster access to specialist treatment, improved support for patients living with cancer (including good communication and palliative care), and reducing inequalities.[78] The impact of the patterns of primary care utilisation on screening and early detection among different ethnic and socioeconomic groups needs to be further investigated.[33]

Social, economic, and health inequalities are interrelated. As social and economic factors impact health, all policies in these areas can affect disparities in health. Social

and economic determinants of health inequalities include: income, education, employment, occupation, housing, and racism. Policies in these areas should take account of the impact that they will have on inequalities; the application of these policies should be monitored regularly to determine their specific effects on inequalities, keeping in mind that some policies which improve health overall may actually increase disparities.

There is a substantial body of research, in New Zealand and internationally, regarding inequalities and inequalities in health specifically. Furthermore in recent years much of this work has informed important and key policies affecting health and healthcare. Nevertheless, given how much we actually know about inequalities, it may not be considered sufficiently within these policies, and what is considered does not appear to be adequately translated into practice. The health system needs to be equally accessible for all population groups, regardless of ethnicity or socioeconomic background. However at present, there appear to be significant barriers to early access and detection for unprivileged women; this requires urgent attention.

There needs to be more synergy between agencies and stakeholders to truly have the effect needed to diminish social inequalities in health. It is not sufficient for one agency to affect a change in policy; this will not be enough. The wider picture needs to be taken into account and the influence of all the agencies and stakeholders that affect health, and the wider determinants of health, should be considered.

Further research

Disparities in breast cancer survival can be attributed to differences in timely access and detection rather than differences in breast cancer subtypes. However, further work

in this area is required before appropriate interventions can be designed. An ongoing study funded by the New Zealand Health Research Council is examining the role that access to care plays in explaining ethnic and SEP survival inequalities, through structured interviews with newly diagnosed women with breast cancer. This will examine the issues of patient and provider delay, [198,199] as well as barriers to accessing primary and secondary health services. [200-203]

Further research is also needed to elucidate ethnic disparities and the components of these which are not attributable to socioeconomic factors. Another new project funded by the New Zealand Health Research Council is going to be specifically examining the role of primary care for Māori with cancer; additional such studies will be required to elucidate these complex pathways.

Recommendations

It is beyond the scope of this thesis to be able to redress ethnic and socioeconomic inequalities in health; however, the following recommendations are made based on the findings from this body of work:

Cross-sector involvement

Collaboration between sectors is needed in order to further our understanding and to ensure development of interventions to address cancer disparities at a structural level. These need to take into account the inter-relationships among social, economic, and health inequalities. Specifically, the health sector needs to work with the education, employment, housing, Māori and social development sectors to ensure that policies decrease, rather than increase, the current ethnic and socioeconomic inequalities in health.

Specific tools such as Health Impact Assessment (HIA)[261] should be employed across all public sectors. HIA aims to predict the effects that implementation of policies will have on health, particularly for those most vulnerable. The Health Equity Assessment Tool (HEAT)[262] is an additional planning tool which can be employed to assess current and future impact of health initiatives on health inequalities.

Health service provision

There should be prioritisation of cancer control policies which focus on comprehensive screening coverage to ensure inclusion of disadvantaged or underserved groups. Access-enhancing interventions which address structural, economic and geographic barriers to screening, such as mobile vans and transportation services and flexible scheduling for appointments, which have been shown to be effective in addressing disparities in mammography uptake in different population groups of women, [263,264] need to be further developed, utilised, and standardised.

All primary care services need to identify barriers to access and urgently address these; this includes taking responsibility for access issues that are considered 'patient level factors' as well as barriers perpetuated by the services themselves. Strategies should be developed, implemented, and monitored to address those issues of concern. Regional and local services must be equally responsive to the service needs of all population groups.

There should be a convergence of activity nationwide with respect to access initiatives; a collaborative group to generate a more cohesive plan on improving access to primary care. Projects such as those funded through Services to Improve Access (SIA) [265] should be reviewed and widely disseminated.

Additionally, efforts should also be made to ensure equal access to and through the secondary care system for all population groups.

Research and surveillance

The social patterning of missing data on national registers is important evidence that there are disparities in the 'system' and this should be a priority area for future research and surveillance.

Further research should be supported to explore the extent to which delays in access to cancer services contribute to survival inequalities among different SEP groups and among different ethnic groups, with a particular focus on the provision of services in relation to primary prevention, screening, and early detection and diagnosis.

Further research should also be supported into those areas which were unable to be investigated in this study, such as treatment and possible mediators as shown in the conceptual model of pathways influencing ethnic and socioeconomic inequalities in breast cancer survival used in this thesis.

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