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Ethnic differences in breast cancer outcomes in Aotearoa New Zealand

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery, The University of Auckland, 2015.

Abstract

Background:

Indigenous Māori women experience significantly worse breast cancer outcomes compared with European women in New Zealand. Underlying reasons for this disparity are complex, and inadequately explained in the existing literature. This study was aimed at estimating the Māori-NZ European breast cancer survival disparity, and to identify and quantify impacts of various factors contributing to this disparity.

Methods:

Data for all women with newly diagnosed invasive breast cancer in the Waikato District Health Board area between 01/01/1999 and 31/12/2012 were obtained from the Waikato Breast Cancer Register, and through a retrospective patient clinical notes review. Patient, tumour and treatment characteristics of Māori and NZ European women were compared in adjusted multivariable models. Cancer specific survivals were compared using Kaplan-Meier survival curves, while contributions of different factors towards the survival disparity were quantified with Cox proportional hazard modelling.

Results:

Of the total of 2791 women included, 2260 (80.1%) were NZ European and 419 (15%) were Māori. Compared with NZ European women, Māori were significantly more likely to be diagnosed with more advanced breast cancer, to have comorbidities and to experience longer treatment delays. Māori were significantly less likely to be diagnosed through screening, to receive adjuvant radiotherapy and endocrine therapy based on recommended guidelines, and to be optimally adherent with endocrine therapy.

Compared with NZ European women, Māori had a significantly higher age adjusted cancer specific mortality (HR=2.02, 95% CI, 1.59-2.58) with significantly lower 5-year (86.8% vs. 76.1%, p<0.001) and 10-year (79.9% vs. 66.9%, p<0.001%) crude cancer-specific survival rates. Stage at diagnosis explained approximately 40% of the survival disparity while

screening, treatment and patient factors (i.e. comorbidity, obesity and smoking) contributed by approximately 15% each. The final model accounted for almost all the cancer survival disparity between Māori and NZ European women (HR=1.07, 95% CI, 0.80-1.44).

Conclusions:

Māori women with breast cancer are twice as likely as NZ European women to die from their cancer. Lower screening coverage, delay in diagnosis, inferior quality of treatment and greater patient comorbidity were largely responsible for this survival disparity. Improving healthcare access and provision of an equitable cancer care for Māori needs greater attention.

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List of Publications

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2. Seneviratne S, Campbell I, Scott N, Lawrenson R, Shirley R, Elwood M (2015) Risk factors associated with mortality from breast cancer in Waikato, New Zealand: A case control study – *Public Health* (epub ahead of print)
3. Seneviratne S, Campbell I, Scott N, Shirley R, Lawrenson R (2015) Impact of mammographic screening on ethnic and socioeconomic inequities in breast cancer stage at diagnosis and survival in New Zealand: a cohort study. *BMC Public Health* 15: 46.
4. Seneviratne S, Scott N, Shirley R, Kim B, Lawrenson R, Campbell I (2015) Breast cancer biology and ethnic disparities in breast cancer mortality in New Zealand: a cohort study – *PLOS ONE* (In press)
5. Seneviratne S, Campbell I, Scott N, Coles C, Lawrenson R (2015) Treatment delay for Māori women with breast cancer in New Zealand. *Ethnicity and Health* 20: 178-193.
6. Seneviratne S, Campbell I, Scott N, Kuper-Hommel M, Round G, Lawrenson R (2014) Ethnic differences in timely adjuvant chemotherapy and radiation therapy for breast cancer in New Zealand: a cohort study. *BMC Cancer* 14: 839.
7. Seneviratne S, Campbell I, Scott N, Lawrenson R. Ethnic differences in use of adjuvant therapy for breast cancer in New Zealand. Submitted for publication in *Australian and New Zealand Journal of Public health*
8. Seneviratne S, Campbell I, Scott N, Kuper-Hommel M, Kim B, Lawrenson R (2015) Adherence to adjuvant endocrine therapy: Is it a factor for ethnic differences in breast cancer outcomes in New Zealand? *The Breast* 24: 62-67.
9. Seneviratne S, Scott N, Lawrenson R, Campbell I (2015) Ethnic, socio-demographic and socioeconomic differences in surgical treatment of breast cancer in New Zealand, *ANZ Journal of Surgery* (epub ahead of print)
10. Seneviratne S, Campbell I, Scott N, Shirley R, Peni T, Lawrenson R. Ethnic differences in breast cancer survival in New Zealand: Contributions of differences in screening, treatment, tumour biology, demographics and comorbidities, Submitted for publication in *Cancer Causes & Control*

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Chapter - Results

Paper title : Accuracy and completeness of the New Zealand Cancer Registry for staging of invasive breast cancer

Nature of contribution by PhD candidate	Candidate developed the concept, designed the study, developed the methodology, collected data, performed the analysis and wrote up the initial version of the manuscript
Extent of contribution by PhD candidate (%)	90%

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Certification by Co-Authors

The undersigned hereby certify that:

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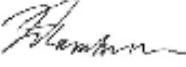
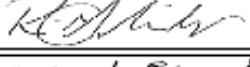
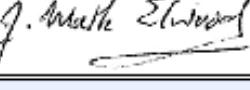
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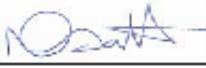
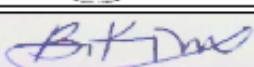
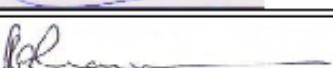
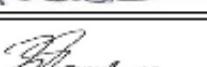
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Nina Scott	Advised on study design and provided comments on the manuscript
Clare Coles	Provided comments on the manuscript
Ross Lawrenson	Advised on study design and methodology and provided comments on the manuscript

Certification by Co-Authors

The undersigned hereby certify that:

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Chapter - Results

Paper title : Ethnic differences in use of adjuvant therapy for breast cancer in New Zealand

Nature of contribution by PhD candidate	Candidate developed the concept, designed the study, developed the methodology, collected data, performed the analysis and wrote up the initial version of the manuscript
Extent of contribution by PhD candidate (%)	95%

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Chapter - Results

Paper title : Ethnic differences in timely adjuvant chemotherapy and radiation therapy for breast cancer in New Zealand: A cohort study

Nature of contribution by PhD candidate	Candidate developed the concept, designed the study, developed the methodology, collected data, performed the analysis and wrote up the initial version of the manuscript
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Chapter - Results

Paper title : Adherence to adjuvant endocrine therapy: Is it a factor for differences in breast cancer outcomes by ethnicity in New Zealand?

Nature of contribution by PhD candidate	Candidate developed the concept, designed the study, developed the methodology, collected data, performed the analysis and wrote up the initial version of the manuscript
Extent of contribution by PhD candidate (%)	90%

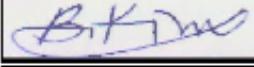
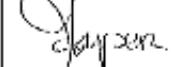
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Chapter - Results

Paper title : Are there ethnic differences in the quality of surgical care provided for breast cancer?

Nature of contribution by PhD candidate	Candidate developed the concept, designed the study, developed the methodology, collected data, performed the analysis and wrote up the initial version of the manuscript
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Chapter - Results

Paper title : Ethnic differences in breast cancer survival in New Zealand: Contributions of differences in screening, treatment, tumour biology, demographics and comorbidities

Nature of contribution by PhD candidate	Candidate developed the concept, designed the study, developed the methodology, collected data, performed the analysis and wrote up the initial version of the manuscript
Extent of contribution by PhD candidate (%)	90%

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Abbreviations

- AI – Aromatase inhibitors
ALND – Axillary lymph node dissection
BCS – Breast Conserving Surgery
BCSM- Breast cancer specific mortality
BMI – Body mass index
BSA – BreastScreen Aotearoa
CCC- Cancer care coordinator
CI – Confidence interval
DHB – District Health Board
ER – Oestrogen receptor
FNAC – Fine needle aspiration cytology
FSA- First specialist assessment
HCP - Health Care Provider
HER-2 – Human epidermal growth factor receptor – type 2
HR – Hazard ratio
LN – Lymph node
LVI – Lympho-vascular invasion
MDT – Multidisciplinary team
MPR – Medication possession ratio
MRI – Magnetic resonance imaging
NHI – National Health Index
NMDS – National Minimum Dataset
NZCR – New Zealand Cancer Registry
OR – Odds ratio
PR – Progesterone receptor
SD – Standard deviation
SEER – Surveillance Epidemiology and End Results
SNB – Sentinel lymph node biopsy
TNM – Tumour, Node, Metastasis
US scan – Ultrasound scan
WBCR – Waikato Breast Cancer Register
WHO – World Health Organization

Chapter 1. Introduction

Approximately 3,000 New Zealand women are diagnosed with breast cancer and more than 600 women die each year (1). New Zealand has the seventh highest age standardized mortality rate from breast cancer in the world; a rate which is 20% higher than Australia (2, 3).

Māori, the Indigenous New Zealand population has the highest known breast cancer incidence of any population group in the world, and this incidence is 28% higher compared to NZ European women (117.2 vs. 90.6 per 100,000 population) (1). Māori women have experienced an increase in breast cancer incidence over the last 20 years compared to a decline in incidence among NZ European women (1). Māori women have a lower survival rate from breast cancer which together with the higher incidence translates into a 60% higher breast cancer mortality compared to NZ European women (31.8 vs. 17.9 per 100,000 population) (4, 5). While there has been an improvement in breast cancer survival for both Māori and NZ European over last two decades, a significant gap in survival persists (6).

Factors that contribute toward inequities in breast cancer survival in New Zealand may include; health service and patient factors including stage at diagnosis, access, timeliness and quality of cancer treatment and tumour factors including biological behaviour (5, 7-9). Delay in diagnosis in Māori leading to more advanced breast cancer at diagnosis has repeatedly been shown to be a major factor for lower survival rates in Māori women (4). However, Māori women have been shown to have a 32% higher stage adjusted mortality compared to non-Māori, hence factors other than stage at diagnosis make an important contribution to mortality inequity (4).

Irrespective of their origins or basis of formations, different ethnic groups in different countries have been shown to have substantially different diagnosis rates, treatment, and outcomes for a variety of diseases, including cancer (4, 10, 11). Explaining these differences has inherent value, in that the understanding and treatment of all patients with breast cancer may be improved. A clear understanding of the relative contributions of each of the contributing factors toward breast cancer disparities between Māori and NZ European women will inform future research and guide strategies to address breast cancer inequities.

Achieving equity along cancer care pathways could result in large and rapid gains for cancer control, especially when compared to developing new treatments or reducing incidence and help improve outcomes for all.

Reducing inequities in cancer mortality using quality improvement measures could theoretically result in about a 50% reduction in breast cancer mortality inequities seen between Māori and NZ European women (12). Research is needed to identify where inequities in access, timeliness and quality of care occur. Such information could inform the development of quality improvement initiatives to achieve equity along the breast cancer care pathway between Māori and NZ European women.

Most data for New Zealand research into breast cancer inequities have been from National Datasets (13, 14). Although the New Zealand National Cancer Registry is a valuable resource for population based research into cancer, it has significant limitations for researching causes of inequities due to inconsistent recording of disease stage at diagnosis and limited data on treatment (15, 16). Currently available data alone have been insufficient to fully understand ethnic inequities in breast cancer outcomes in New Zealand and its underlying causes.

This thesis examines differences in socio-demographic, tumour and treatment characteristics and their impacts on breast cancer survival disparity between Māori and NZ European women. It also seeks to explore possible reasons for why these factors may differ between Māori and NZ European women. Data for this thesis come from a cohort of women diagnosed with breast cancer in the Waikato, New Zealand between 1999 and 2012. It also draws on published literature on cancer inequities in general, and on breast cancer inequities in specific, which have provided the platform for the current research.

Cancer is a complex illness; its management even more complex. Cancer control covers the spectrum from cancer prevention through screening, diagnosis, treatment, rehabilitation to provision of palliative care. Due to the nature of the data availability, this thesis has restricted the analyses to elements within secondary and tertiary care; that is from the point of first specialist assessment onwards. Where feasible, data prior to the first specialist assessment, including breast cancer screening data have also been included. As the focus of this thesis is breast cancer outcomes in relation to mortality and recurrence, rehabilitative and palliative care services are not examined.

The specific objectives of this thesis are as follows:

1. To determine differences in access to care factors (i.e., breast cancer screening, socioeconomic status, ethnicity and residence) on stage at diagnosis
2. To determine the association of age, residence, ethnicity, public/private treatment and screen/non-screen presentation on delay and/or quality of care (i.e., delay in primary surgery, type of surgical treatment, usage and delay in adjuvant therapy and adherence with adjuvant therapy)
3. To determine ethnic differences in cancer biological characteristics (i.e., histology, tumour grade, lympho-vascular invasion, oestrogen/progesterone receptor [ER/PR] status, HER-2 status)
4. To determine ethnic differences in breast cancer outcomes and factors contributing to such differences
 - To determine the magnitude of breast cancer specific survival disparity between Māori and NZ European women, stratified by stage at diagnosis.
 - To determine differences in survival for different treatment groups and different biological markers
 - To determine the quantitative impact of these factors on the overall ethnic disparity

Chapters of this thesis and their purposes are as follows:

Chapter 1- Introduction: Provides an introduction to the topic of the thesis and defines the specific objectives. It also clarifies the focus of this thesis.

Chapter 2 – Background: This chapter provides an insight into the context in which breast cancer disparities between Māori and NZ European populations are generated. It includes a history of New Zealand, political and health system changes leading to the current political landscape and healthcare system. The last section of this chapter includes a brief description of breast cancer and its basic management principles.

Chapter 3 - Literature Review: This chapter is aimed at reviewing available literature on cancer disparities, and underlying causes, both locally and internationally. It attempts to critically analyse literature to identify existing gaps, to build a platform and create a niche for this research project. It also attempts to analyse different theories on ethnic disparities to identify key drivers and finally attempts to build a conceptual framework on which the study analyses are based upon.

Chapter 4 - Design and Methods: This chapter includes a detailed description on how the study was conducted including study sample selection, data collection, data definitions and data analyses.

Chapter 5 – Results: This chapter is set out in ten sections; each a separate study aimed at clarifying a specific area in relation to breast cancer ethnic disparity. Each study is set up with a brief introduction, specific methods used for the study, results and a focussed discussion of findings.

Chapter 6 – Discussion: This chapter is kept relatively brief as most of the study results and their specific meanings and implications are discussed under each section in Results. The discussion attempts to bring together and summarize all of the study findings and then attempts to fill the gaps identified during the literature review to create a clearer picture on why ethnic disparities might occur and what strategies are available to tackle these disparities. This chapter will also critically analyse strengths and limitations of the study, and finishes with a conclusions section which summarizes the whole thesis.

Chapter 2. Background – People and health services in Aotearoa New Zealand and the Waikato region

2.1. People of New Zealand:

Māori are the Indigenous people of New Zealand. They are Polynesian people who settled in New Zealand about 1000 years ago. Subsequent immigrations, initially by Europeans starting from 1800's and later by Pacific Islanders and Asians, have created the present day dynamic multicultural society of New Zealand. According to the latest population census in 2013, NZ Europeans (Pākehā) make the numeric majority (74%), while Māori comprise approximately 15% of the population. Asian (11.8%) and Pacific (7.4%) comprise the other two main ethnic groups (17).

Māori were the sole inhabitants of Aotearoa New Zealand for several hundred years until the arrival of the British and subsequent colonization which started in the early 1800s. Through a combination of colonization, the Treaty of Waitangi and military suppression of Māori resistance, the British settlers managed to make New Zealand a part of the British Empire (18).

Although the Treaty granted Māori equal rights, acquisition of Māori land by the British led to the New Zealand land wars in 1860's. Following these wars, over 100,000 hectares of Māori land was confiscated by the government under the New Zealand Settlements Act in 1863, purportedly as punishment for Māori rebellion. Loss of land, illnesses and after effects of tribal wars led to a rapid decline in the Māori population with many scientists and politicians predicting an imminent extinction in the late 1800s (19).

A major resurgence in the Māori population was observed after the Second World War. Many Māori migrated to larger towns and cities during the depression and post-world war periods in search of employment, leaving rural communities depleted and disconnecting many urban Māori from their traditional ways of life (20). While standards of living improved among Māori during this time, they continued to lag behind Pākehā in areas such as health, income, skilled employment and access to higher education. Māori leaders and government policymakers alike have struggled to deal with social issues stemming from increased urban migration, including a shortage of housing and jobs, and a rise in crime, poverty and health problems.

2.2. Indigenous Māori, British colonization, the Treaty and evolution into present day New Zealand

2.2.1 Māori

Māori are the Indigenous people in NZ and are considered *tangata whenua* –people of the land. They are descendants of Polynesians who had arrived approximately 1000 years ago (18, 21).

Iwi (tribes) formed the largest social groups of Māori who trace their ancestry to original Polynesian migrants. Each iwi comprised of a structure for ruling and leadership was based on a system of chieftainship. Important units of pre-European Māori society were the whānau or extended family, and the hapū or group of whānau. After these came the iwi or tribe, consisting of groups of hapū. Traditional Māori society preserved history orally through narratives, songs, and chants; skilled experts could recite the tribal genealogies (whakapapa) back for hundreds of years.

Traditional Māori belief systems, such as views about reliance on the whānau, individual mana (prestige), death and dying, and practices associated with tapu (sacred), continue to influence health behaviour. These views may influence preferences for care, individual help-seeking behaviour and responses to health care providers (22).

2.2.2 British colonization

The first significant contact between Māori and Europeans occurred in 1769, at the time of James Cook's expedition to New Zealand from Britain (23). Subsequently, by early 1800s many Europeans traders, missionaries, convicts escaped from Australia, and deserting seamen began to settle in the country.

From about 1800 to about 1830, the Europeans lived in New Zealand on Māori sufferance. During this period a rapid decline in Māori population was observed partly because thousands were killed in their musket wars in the 1820s and 1830s, but mainly because the Europeans brought a battery of new germs and viruses. Measles, some forms of influenza, typhoid, small pox and other diseases reduced the Māori population from perhaps 200,000 in 1769, when James Cook arrived, to less than 40,000 by 1870.

With the growing British population in New Zealand and due to the threat from the French, the British Crown intended to annex New Zealand into the British Empire. The authority of New Zealand was taken by the British Crown through the signing of the Treaty of Waitangi in 1840 (24).

2.2.3 Treaty of Waitangi (Te Tiriti o Waitangi)

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 chiefs (24). This is considered as the foundational document of New Zealand as a modern state. The Treaty exists in both Māori and English texts with important differences between the two (25).

Māori and colonial British had different expectations of the Treaty in accordance with the language, worldview and political agenda of each. Māori chiefs expected to retain self-governance at tribal level largely unaltered with the Treaty (26). However, the British regarded the Treaty as a mechanism through which to create a relationship where “the Crown as sovereign and the Māori as subject” (24, 25). The Crown’s interpretation of the Treaty prevailed despite the objections of Māori chiefs who signed the Treaty (24, 25).

It is estimated that the Māori population numbered approximately 80,000 at the time of signing the Treaty, along with a population of about 2,000 settlers. Signing of the Waitangi treaty facilitated a large-scale influx of British migrants. Rapid influx of settler Europeans and a decline in Māori resulted in a major change in country’s demographics. By 1901, the settler population of 770,000 outnumbered the Māori population by 16.5:1 (23).

Majority of the Māori regarded the Treaty as the basis for their relationship with the British Crown and sought to have their rights as the Indigenous people addressed (27). The British Crown considered the content of the Treaty to be largely irrelevant and considered it only as a document through which the British established its ‘ownership’ of New Zealand (27).

Since the 1970s, public awareness of the Treaty of Waitangi has continued to increase, primarily as a result of growing Māori aspirations for self-determination. In recent government health documents, the Indigenous status of Māori has been recognized, and the Treaty of Waitangi has been acknowledged as a fundamental component of the relationship between Māori and the government (28, 29). However, the Treaty has never been included in social

policy legislation, and there is a clear gap between acceptance of the Treaty and translation of its aims into actual health gains for Māori (30).

The Treaty's primary intention was to protect and maintain the well-being of all citizens, although many of its components were not implemented by the colonial government. The Treaty has relevance for health care services and how these should address needs of Māori communities to have equitable care (31). Further, the Treaty supports the principle of tino rangatiratanga (self-determination) that encourages the development of Māori providers where Māori deliver health care for Māori. (32). Despite the provisions in the Treaty and subsequent policies supporting equitable care, Māori continue to experience poor health compared with Pākehā populations (31).

2.2.4 Present day New Zealand

The present day New Zealand landscape reflects the relationships and interactions of Māori and European settlers over 200 years. Māori continue to be disadvantaged with poor educational achievements, high rates of unemployment and poor health compared with NZ Europeans (33-35). Implementation of several policies specifically aimed at improving education, employment and health among Māori have seen gradual improvements that have narrowed the disparity between Māori and Europeans. Still, lack of an organized, integrated approach towards correcting these differences seems to be deficient.

Several new policies were implemented especially over the last two decades with increased government spending on Māori specific programmes (36). These efforts have seen some improvements in health and education for Māori, although some of these efforts have been criticised for lack of benefit in relation to the amount of money spent, due to poor planning and implementation. Absence of a broad, integrated approach for Māori development and implementation of programmes which were piecemeal or sector specific are also believed to be responsible for not achieving expected results out of these programmes.

2.3. Health care system in New Zealand

The healthcare system of New Zealand has been primarily a public funded system since introduction of the Social Security Act in 1938. It has undergone significant structural changes throughout past several decades (37). The Labour Government introduced the Social Security Act in 1938 with the objective of providing free and universally available healthcare for all. However, the British Medical Association (i.e., the organisation of doctors) campaigned against a salaried system, as it interfered in the relationship between doctors and their patients. The Government compromised by instituting a General Medical Services benefit, but doctors reserved the right to set their fees and to charge an additional fee. Hence, ‘private practice’ survived the 1938 reforms.

By 1970s the rapid growth in health costs resulted in a series of changes being introduced to improve efficiency and health outcomes. Although the public health system, especially the hospital side had developed rapidly, there was still a strong private sector especially for surgical interventions.

2.3.1 Health care structure, organization and delivery

The health care system in New Zealand comprises an interlinking system of primary, secondary and tertiary health services. From its establishment in 1930’s the evolution of the health system has resulted in various changes.

The health system that was established based on the 1938 reforms included minimal regard to needs or aspirations of the Māori society. Nonetheless, universal coverage remained one of the prime goals of this health structure, which aimed to provide accessible healthcare for all citizens, including Māori. Primary care remained within the private sector though it was subsidized by the government (37). Some of the primary characteristics of this initially laid down health system remain in the present New Zealand health system including subsidization of primary health care and universal publicly funded hospital care (37).

In 1987, the Area Health Board Act created 14 Area Health Boards in place of Hospital Boards, which existed following the 1938 Social Security Act. Later, in 1993 the Health and Disability Services Act was introduced creating 23 Crown Health Authorities that functioned under four Regional Health Authorities. The current District Health Board (DHB) system was

introduced in 2001 creating 21 DHBs (reduced to 20 in 2010) to deliver public health care in New Zealand.

During the evolution of the health system, it was dominated by Pākehā needs and beliefs with minimal input or involvement of Māori. First Māori involvement in health care organization was reported in mid 1980s; even then it was more symbolic than with active participation in decision making (37). The more recent health service changes have seen a greater participation of Māori in health care organizations and health care decision making processes. Despite that, under-representation of Māori in health organisations, lack of focus on equity and health delivery processes remains a significant concern in addressing Māori health issues.

The majority of the burden for core healthcare system expenditure rests with government (approximately 77% in 2005). Private payment by individuals also plays an important role in the overall system, although the costs of these payments are comparatively minor. In 2009, New Zealand spent 10.3% of gross domestic product (GDP) on health care compared with 8.7% in Australia, 9.8% in the United Kingdom and 17.4% in the USA. However, per capita health expenditure in Australia (US \$ 4179) and USA (US \$ 7163) were much greater than that of New Zealand (US \$ 2917) (38).

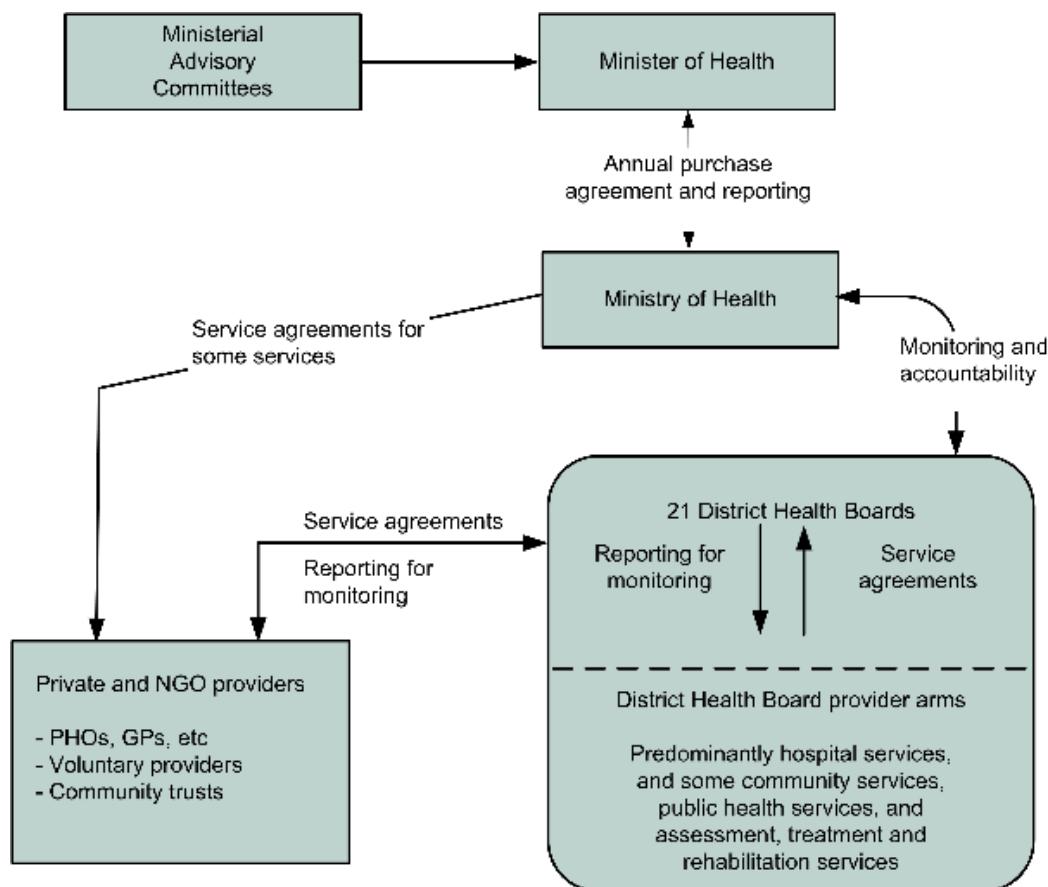
The current structure of the health system has a greater devolution of service planning and funding and, greater emphasis on primary health care services (Figure 1). Twenty DHB's are responsible for funding and provision of services at a local level. All public hospitals come under the care of DHBs, who are responsible for providing secondary and tertiary health care. Primary health care (provided by general practitioners) and community based services are also funded by DHBs, but are delivered by independent providers (36).

The current health system places more emphasis on Māori health compared with previous manifestations (36). DHBs are required to have at least two Māori members which need to be increased based on population structure of the DHB area. DHBs are specifically required to work towards reducing health disparities by improving health outcomes for Māori and other disadvantaged population groups. Further, they are required to establish and maintain processes to enable Māori to participate in and contribute to strategies for Māori health improvement.

Private sector health care in New Zealand is mostly provided at secondary care level. These institutions are focused on providing specialist elective services which include elective surgical and other invasive procedures. Patients are referred to private hospitals or to

appropriate specialist consultants by general practitioners. All surgical procedures for breast cancer including major breast reconstructions are provided through private hospitals. However the provision of oncology services is limited in the private sector. Although specialist outpatient care is freely available, private parenteral chemotherapy facilities are available only in a few areas such as Auckland and Palmerston North. Radiotherapy facilities have been recently started in the private sector in Auckland.

Figure 1: The structure of the New Zealand health system in 2008 (*Source - Ministry of Health*)



National Cancer Control Strategy

The National Cancer Control Strategy was initiated in 2003 with the two key objectives of reducing the incidence and impact of cancer, and reducing inequalities with respect to cancer (21). As with many government documents, the National Cancer Control Strategy also refers to three principles derived from the Treaty of Waitangi; partnership (between Māori and Crown agencies), participation (of Māori in service planning and delivery) and protection (of Māori health and health equity with non-Māori). Through its action plan the Cancer control

Strategy has put forward an intervention framework to improve health outcomes and reduce inequalities (21). It specifically targets to reduce the burden of cancer by making structural changes in the society through economic and social policy changes, and by improving access and care pathways in health and disability services.

BreastScreen Aotearoa

BreastScreen Aotearoa (BSA) is the New Zealand National Breast Screening Programme, a free mammographic breast screening service available for all screening age women. Since it was established in 1999, the BSA has provided free biennial mammographic screening for all women aged between 50 to 64 years, and this age range was extended to include women aged 45 to 49 and 65 to 69 years from July 2004.

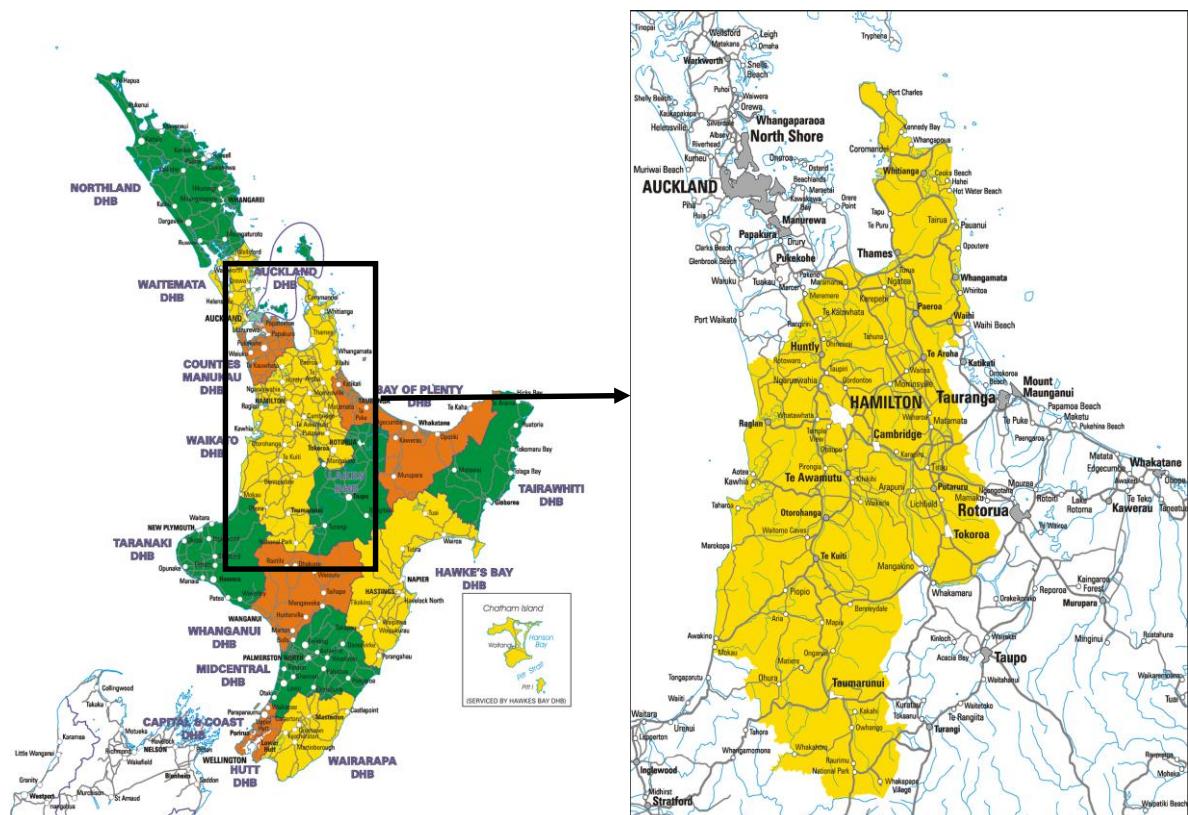
Mammographic screening coverage in New Zealand has gradually picked up over the last decade and has achieved the target biennial coverage of 70% for NZ European women since 2010 (39). However, poor screening coverage has remained a significant issue for Māori women for whom the coverage was only 62.7% in 2012 (39). There was a large variability in screening coverage rate for Māori by region, which ranged from 54% to 79% across the country in 2012 (40). There is close monitoring of coverage by region and by ethnicity, and targets are set yearly with screening providers to improve these rates.

2.4. Waikato Region and the Waikato District Health Board

The Waikato region which is situated in the central part of North Island of New Zealand, is based on the catchment of the Waikato River and includes Lake Taupo and Rotorua regions. This is similar to the catchment area of the Waikato Hospital Board formed in 1938. The Waikato Area Health Board (formed in 1989) was based on a smaller area, excluding Taupo and Rotorua. Boundaries of the Waikato Area Health Board have largely remained unchanged during the creation of Waikato Crown Health Authority in 1993 and more recently the Waikato District Health Board in 2001 (Figure 2).

With a population of 365,000 Waikato District Health Board (DHB) is the fourth largest in New Zealand. The Waikato DHB covers an area of 21,220 square kilometres and stretches from northern Coromandel to close to Mount Ruapehu in the south and from Raglan on the west coast to Waihi on the east. It has a major urban centre (i.e., Hamilton), a significant rural population and a Māori population of more than 76,000 (21% of the Waikato DHB population) which is the second highest in New Zealand. Waikato Māori comprise 13.5% of the total New Zealand Māori population (41).

Figure 2 - Map of the Waikato District Health Board catchment area



Breast cancer services in the Waikato DHB area are provided in the public sector through specialist services located at the tertiary hospital in Hamilton. In addition, surgical treatment is also provided through several well equipped private hospitals. Radiation therapy services for the Waikato region are provided exclusively through a radiation facility at the tertiary hospital in Hamilton, while chemotherapy facilities are provided through a satellite site (i.e., Thames) in addition to the tertiary hospital in Hamilton.

2.5. Breast Cancer

The following section provides a brief overview of breast cancer and basic principles of management.

2.5.1 Breast cancer

Breast cancer primarily includes malignant tumours arising from epithelial cells of ducts and lobules of the breast. Other types of breast cancers include sarcomas and phyllodes tumours which originate, behave and are treated differently, and hence have been excluded from this study.

Breast cancer is the commonest cancer among women in the world with 1.7 million new breast cancers diagnosed in 2012, which represents about 12% of all new cancer cases and 25% of all cancers in women (42). Incidence of breast cancer is substantially higher in developed countries compared with less developed countries. New Zealand, with an age standardised incidence of 93.3 per 100,000 population in 2008, was ranked 7th highest in the world (43).

2.5.2 Management of breast cancer

Most early breast cancers are curable while metastatic breast cancer is considered incurable. Surgery is considered as the primary treatment modality for all early breast cancers. Adjuvant therapy is recommended based on future risk of local and/or systemic failure. Advanced breast cancers (non-metastatic) are managed with neo-adjuvant therapy followed by surgery while metastatic cancer is managed mostly with primary systemic therapy.

Investigations and diagnosis

Breast cancers are diagnosed through two main methods; through mammographic breast cancer screening and through non-screen (symptomatic) presentations. In New Zealand, approximately a third of breast cancers overall, and approximately two thirds of cancers within screening age are diagnosed through mammographic screening.

A breast lump is the most common (>80%) presenting symptom for symptomatic breast cancer. Other symptoms include breast pain, nipple discharge, axillary or neck lump/s or symptoms of metastatic disease. A woman with symptoms suspicious of a breast cancer is initially assessed by a primary care physician / general practitioner and is referred to a specialist breast care unit for further management.

Triple assessment forms the cornerstone of breast cancer diagnosis. This includes clinical, radiological and pathological assessment aimed to diagnose or exclude cancer in all women presenting with symptoms suggestive or suspicious of a breast cancer. Standard imaging includes mammogram and ultra sound scan (US scan) of the breast while Magnetic Resonance Imaging (MRI) is reserved for situations including assessment for multi-focality in lobular cancer or for women with mammographically dense breasts.

Once clinical and imaging assessments are completed, a pathological examination is done to complete the triple assessment. Traditionally fine needle aspiration cytology (FNAC) was used, but this has gradually been replaced with core biopsy as the preferred modality. Core biopsy has a higher sensitivity and provides better histologic detail which helps in decisions, including for neo-adjuvant therapy. The majority of core biopsies are performed under image guidance (US or stereotactic) further increasing the diagnostic yield of a core biopsy. Other pathological techniques for diagnosis include punch biopsy (when the cancer involves the skin) or open excisional biopsy that is performed in situations where triple assessment fails to exclude or confirm a cancer.

Following confirmation of the diagnosis of breast cancer, further management depends on several of patient and tumour characteristics. Clinical tumour stage which encompasses both clinical and image findings and patient fitness for treatment are the most important of these factors. If the patient is relatively young and fit, cancer stage (early or advanced) alone governs further treatment. In general terms, early breast cancers (stages I & II) are treated with primary surgery while advanced cancers (stage III) are treated with neo-adjuvant therapy (chemotherapy or endocrine therapy) which is aimed at down-staging the cancer and to make it operable. Metastatic cancers are managed with the objectives of controlling the disease to prolong life and to manage symptoms, as these are deemed incurable.

Surgery

Early breast cancers are treated with primary surgery if the patient is fit to undergo surgery. Primary surgery is aimed at completely removing the primary tumour and removing involved axillary nodes or staging the axilla. Mastectomy (removal of the whole breast) and breast conserving surgery (BCS) are the two main surgical options for the breast. Axilla is treated with axillary lymph node dissection (ALND) if there is clinical evidence of node involvement. If the axilla is clinically normal, it is managed based on a sentinel node biopsy (SNB). SNB

attempts to identify the first node/s draining the axilla and if it is positive for tumour cells on a frozen section, an ALND is done. If SNB is free of tumour, no further surgery is performed on the axilla. Reconstruction of the ipsilateral breast (after mastectomy) using either autologous tissue or an implant or a combination, constitutes the final step in surgical treatment.

Radiation therapy

Radiotherapy forms another loco-regional treatment modality which is aimed at reducing the risk of local recurrence of breast cancer in the preserved breast after BCS or in the chest wall after mastectomy. All women after a BCS are required to receive radiation therapy while after a mastectomy the need depends on the risk of local recurrence. For instance, New Zealand breast cancer guidelines recommend radiation therapy for all women if ≥ 4 lymph nodes are involved or if the primary tumour diameter is $\geq 50\text{mm}$ (44). External beam radiation is provided through a linear accelerator and a woman is given 40-50Gy of radiation delivered over 15 to 25 fractions.

Chemotherapy

Chemotherapy is one of the systemic breast cancer treatments, and together with endocrine therapy has been responsible for the major reduction in breast cancer mortality observed over the last two to three decades. Chemotherapy is aimed at targeting and killing any residual tumour cells remaining after primary surgery. Chemotherapy is highly toxic to rapidly dividing cells that include cancer cells. Due to its toxicity, side effects and lack of action on slow growing cancers, chemotherapy is generally reserved only for aggressive or advanced cancers which are generally associated with poor outcomes. However, selection of women who would get a significant survival benefit (generally considered as $>5\%$) is complicated. Although several algorithms and software programmes (e.g. Adjuvant online!, Predict) help in this decision (45, 46), still they lack the necessary precision. Newer tumour genome based tests including OncotypeDX® and Mammaprint® have improved this precision to predict which women would benefit from chemotherapy (47, 48), but for a significant minority the dilemma of chemotherapy remains, even with these tests.

More effective chemotherapy regimens have replaced the traditional CMF (cyclophosphamide, methotrexate and 5-fluorouracil) regimen and now include doxorubicin and cyclophosphamide followed by a taxane (e.g., docetaxel).

Hormonal / Endocrine therapy

A majority of breast cancers are dependent on female hormones (i.e. oestrogen and progesterone) for their growth and sustenance. Blockage or removal of this hormonal stimulation is a highly effective strategy of treating breast cancer in women whose cancers are hormone receptor positive. Traditionally, tamoxifen, a selective oestrogen receptor modulator (SERM) has been used, but has largely been replaced by aromatase inhibitors for post-menopausal women (49). Still, tamoxifen is the preferred agent for pre-menopausal women. Traditionally, hormonal therapy was prescribed for five years. However, recent trials have shown additional mortality benefit of longer term tamoxifen up to 10 years as compared with the conventional 5-year therapy (50, 51).

Biological therapy

Amplification of human epidermal growth factor receptor type-2 (HER-2) in breast cancer is associated with aggressive cancer behaviour and poor outcomes. Blockage of HER-2 with trastuzumab (brand name - *Herceptin®*) has helped to significantly reduce the risk of breast cancer mortality in these women.

2.5.3 Management guidelines

Guidelines for the management of early breast cancer were first published in New Zealand in 2009 (44). Prior to this, management of breast cancer in New Zealand was based on guidelines published in other countries including Australia and the United Kingdom (52-54).

Staging

All breast cancer patients are expected undergo clinical staging at the time of diagnosis which include assessment of clinical tumour size, loco-regional node involvement and a general

physical examination along with a history to check for possible symptoms of distant disease (55). Several staging investigations may also be used, including chest X-ray, bone scintigraphy, liver imaging, computerised tomography (CT), positron emission tomography (PET), and serum biomarkers (e.g. CA 15-3).

Staging investigations are generally reserved for women with features suggestive of advanced breast cancer or specific symptoms that may indicate presence of metastatic disease (44).

Staging investigations are generally performed prior to surgery, however may also be performed after primary surgery in situations where a woman is found to have more advanced disease than expected after pathological assessment of the resected specimen.

Multidisciplinary care

Breast cancer care provided through a multidisciplinary breast team (MDT) has been shown to be an effective means of establishing a correct diagnosis in women referred with breast symptoms and has also been established to be an efficient, cost-effective way to care for women with breast cancer (56). MDTs also provide the opportunity for useful second opinions. Cases of all New Zealand women diagnosed with breast cancer are expected to be discussed at least once at a MDT, that should comprise of Surgeons, Pathologists, Radiologists and Oncologists (Medical and Radiation) (55). However, this is not compulsory and hence cases of some women with breast cancer diagnosed and managed at secondary care institutions and private sector are not routinely discussed at MDTs.

Timeliness of treatment

Guidelines on timeliness of diagnosis and treatment were available for women diagnosed through the BSA programme since 1999 (57) . However, no guidelines on timeliness were available in New Zealand for women with symptomatic breast cancer until the Faster Cancer Treatment Indicators and the standards of service provision for women with breast cancer were published in 2012 and 2014, respectively (58, 59). Based on current guidelines, women with high risk of breast cancer are expected to have their first specialist assessment (FSA) within 14 days and receive first treatment within 31 days of confirming diagnosis (Table 1) (58, 59).

Table 1: Guidelines for timeliness of breast cancer care (*Adapted from: Faster Cancer Treatment Guidelines 2012 and Standards of Service Provision for Breast Cancer Patients 2014*)

Timely access – referral

- Women referred urgently with a high suspicion of breast cancer - FSA within 14 days
- Women referred with a moderate suspicion of breast cancer - FSA within 30 days
- Women referred with a low suspicion of breast cancer - FSA within 90 days

Timely access – primary treatment

- Women referred urgently with a high suspicion of breast cancer - first cancer treatment within 62 days
- Women with a confirmed diagnosis of breast cancer - first cancer treatment within 31 days of the decision to treat

Timely access – systemic treatment

- Women recommended adjuvant systemic therapy by an MDT and fit to receive it - commence treatment within six weeks of surgery for breast cancer

Timely access – radiation treatment

- Women with breast cancer referred for radiation oncology assessment - FSA with a radiation oncologist within two weeks of receipt of referral (where chemotherapy is not part of the management)
- Women consenting to radiation therapy after surgery - commence treatment once the surgical site has healed and within six weeks of surgery (where chemotherapy is not part of management)

FSA – First Specialist Assessment

Follow up

Follow up after treatment of breast cancer is aimed at early detection of tumour recurrences or development of new breast cancer. In addition this provides an opportunity for detection and management of therapy related complications and to provide psychological support for these

women (59, 60). In New Zealand setup, an annual clinical examination and mammography are provided through a specialist breast service for 10 years for all women treated with breast cancer who are in good health (44).

Changes in management guidelines

Although the general principles of management of breast cancer have remained largely unchanged, significant changes in specific aspects of management are observed over last 10–15 years.

In relation to surgical treatment, a major change has been the management of the axilla. All women with invasive cancer were uniformly treated with an axillary lymph node dissection up to late 1990s. However, early 2000's a significant change was observed where more and more women were offered sentinel lymph node biopsy (SNB) based management for the axilla. Currently, all women who have early breast cancer with clinically node negative axillae are offered SNB based management (44, 59).

Other major changes were observed in systemic therapy for breast cancer. Traditional CMF chemotherapy was gradually replaced with AC (doxorubicin and cyclophosphamide) chemotherapy in late 1990s, and over last 10 years has seen further changes with the addition of taxanes (44). Further, trastuzumab became available in early 2000's, and was made available through the public health care system in New Zealand for HER-2 amplified early breast cancer from 2007 (61).

Significant changes in endocrine therapy include the use of aromatase inhibitors as the preferred endocrine therapy for post-menopausal women in place of traditional tamoxifen and prolongation of endocrine therapy from conventional five years for up to 10 years (62).

Another major advancement in cancer treatment and especially in treatment of breast cancer has been the gradual incorporation of personalized cancer treatment. As of now, personalized treatment for cancer is only beginning, with a small number of validated drug-test companion products available. Currently, personalized treatment is most advanced for breast cancer, and tests such as ER, HER-2, Oncotype DX, and MammaPrint are available to personalize treatment decisions. Although the evolution of personalized treatment is likely to be slow personalized treatment for every patient with breast cancer is likely to be available in the near future.

Chapter 3. Literature review

This chapter describes and discusses evidence on Indigenous non-Indigenous and ethnic inequalities in breast cancer, breast cancer care and outcomes. This review is aimed at informing these questions based on current evidence what is the extent of ethnic disparity in breast cancer survival in New Zealand, and why ethnic disparities in breast cancer outcomes might occur. The review was performed by combining a formal literature review with a search of references and bibliographies from a range of books and documents, without applying any specific inclusion or exclusion criteria.

This chapter starts with a discussion on Indigenous and ethnic disparities in cancer with a special emphasis on breast cancer, and is followed by a discussion on underlying causes and theories for these disparities. The chapter concludes with a conceptual framework that is aimed at understanding the key factors contributing to ethnic disparities in breast cancer.

3.1. Ethnic inequalities in breast cancer and breast cancer survival

Ethnic and geographic differences in cancer including breast cancer are extremely variable, and are believed to be due to a multiplicity of factors. For instance, geographically, women from Europe, North America and Oceania have experienced significantly higher incidences of breast cancer compared with women from Asian and African countries (3, 43). Similar disparities in breast cancer incidence are observed among different ethnic groups in many multi-ethnic countries, including the USA, Australia, Canada and New Zealand (63).

Historically, many Indigenous and ethnic minority populations have had low incidences of cancer compared with majority or non-Indigenous populations of their respective countries (63). The extent of these differences have been observed to become smaller over successive generations, as the Indigenous and minority populations have taken up cancer-promoting environmental exposures, at rates similar to or higher than that of majority/settler populations. In contrast, many of these Indigenous and minority ethnic groups have continued to experience far worse cancer survival rates than the majority/non-Indigenous populations of respective countries. Poorer cancer survival rates combined with increasing cancer incidences have resulted in a rapidly worsening cancer burden among Indigenous and minority populations (63).

Ethnic differences in breast cancer outcomes in Aotearoa New Zealand

The following section first analyses ethnic disparity in breast cancer and breast cancer survival in New Zealand. Then a comparison is performed with ethnic disparities in breast cancer from other countries.

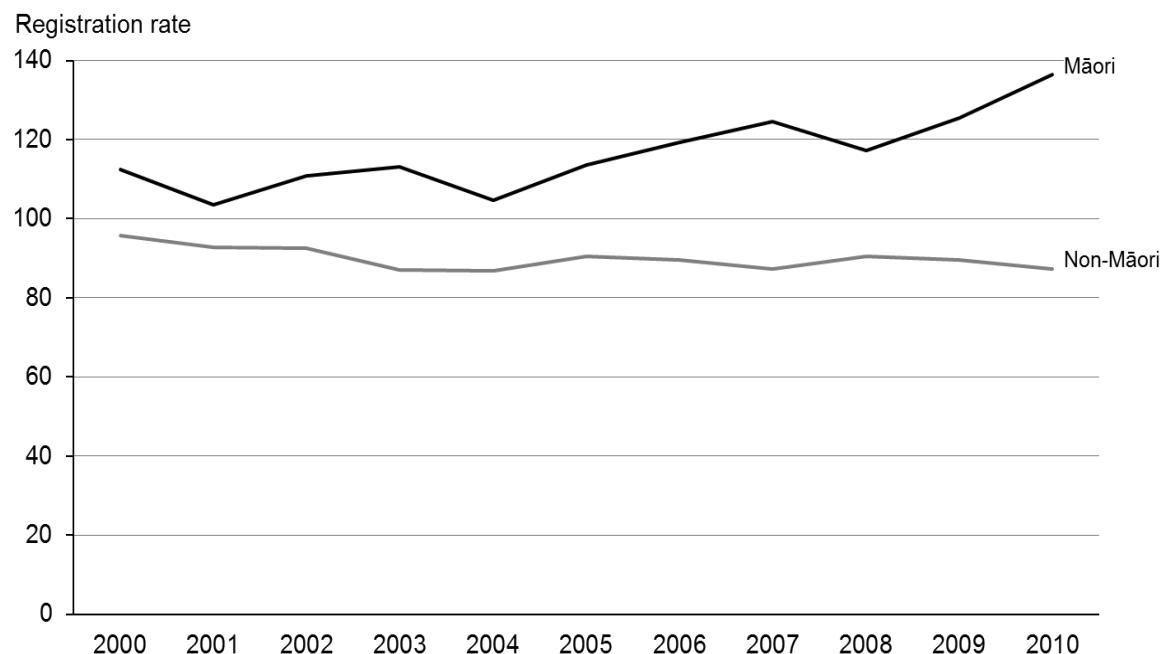
3.1.1 Ethnic inequalities in breast cancer and breast cancer survival in New Zealand

Major ethnic disparities in cancer incidence and outcomes are documented in New Zealand.

Poorer cancer outcomes for Māori compared with non-Māori have been well known for over three decades (64-66). In 2008, overall cancer incidence in Indigenous Māori was 19% higher compared with non-Māori (220 vs. 185 per 100,000 age standardized population) (4). The extent of this disparity is quadrupled for cancer mortality as the mortality rate in Māori was 78% higher compared with non-Māori (112 vs. 63 per 100,000 population) (67).

Approximately a quarter of the Māori non-Māori cancer survival disparity has been shown to be due to breast cancer (4).

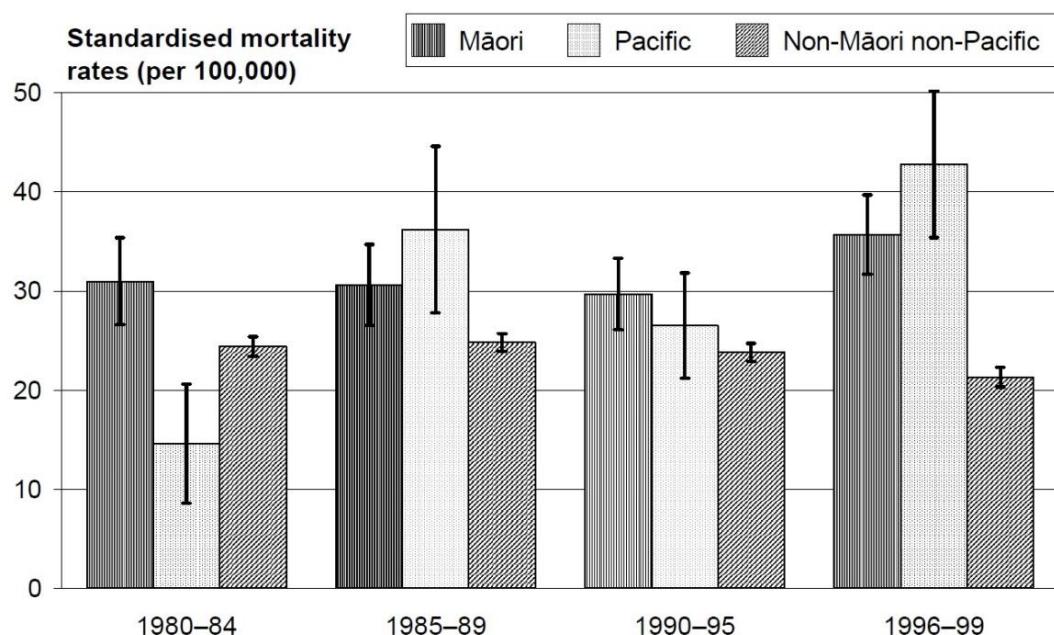
Figure 3: Registration rates for female breast cancer in New Zealand, by ethnicity, 2000–2010 (*Source – New Zealand Cancer Registry*)



Note: The rate shown is the age-standardised rate per 100,000 female population, standardised to the WHO world standard population.

Māori women have one of the highest incidences of breast cancer in the world (42). The incidence of breast cancer in Māori is approximately 30% higher compared with non-Māori (117.2 vs. 90.6 per 100,000 age standardized population) and appears to be increasing further, while the incidence in non-Māori is on the decline (1). This has created a rapidly widening gap in incidence between Māori and non-Māori women (Figure 3). For instance, over the period between 2000 and 2010, breast cancer incidence in non-Māori has declined by about 5% while the incidence in Māori has risen by 10-15% (1). The increase in breast cancer incidence in Māori is largely unexplained at present. Increasing rates of obesity, alcohol consumption and changes in reproductive behaviours all contribute to the increase, but not fully account for it (33).

Figure 4: Age standardised breast cancer mortality rates in New Zealand by ethnicity (for ages 1–74 years) (68)



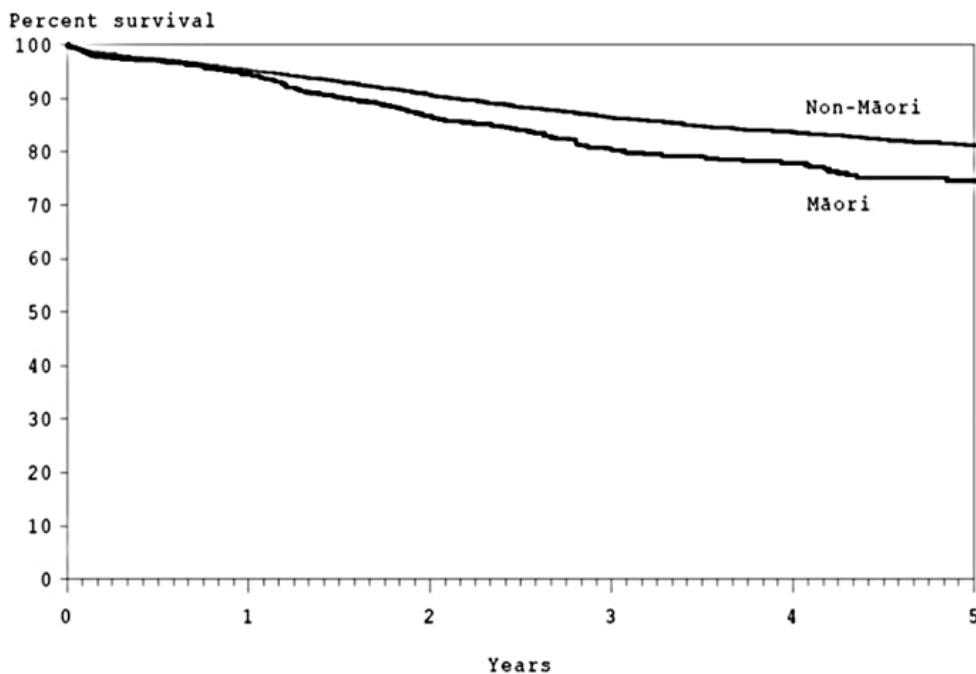
A similar trend is observed for breast cancer mortality where the rates have been gradually increasing for Māori while a gradual reduction is seen for non-Māori women (Figure 4). Many factors are believed to be contributing to this inequality in breast cancer mortality between Māori and non-Māori women (7, 13). Several authors have attempted to identify these factors, and to quantify the contribution of each of these factors towards Māori non-Māori breast cancer survival disparity. Almost all such studies to date have used routinely collected administrative data from the NZCR. Although this approach has provided large numbers of breast cancers for these studies, high percentages of missing data and possible biases including

miscoding and misclassification of the NZCR data have significantly restricted the validity of these studies (4, 6, 13). Furthermore, absence of data in the NZCR on some of the important aspects of breast cancer inequalities including cancer treatment and comorbidities has prevented a complete analysis of factors contributing to ethnic disparities in breast cancer outcomes in New Zealand. For instance, based on the NZCR data, Māori women with breast cancer have been shown to be diagnosed with more advanced staged breast cancer compared with NZ European women (Figure 2). However, after adjusting for stage, breast cancer mortality rate is still about 40% higher in Māori which indicates a major contributions of other factors, including treatment differences, towards this disparity (4).

The *Unequal Impact* report published in 2006 has analysed New Zealand cancer data by ethnicity for the period from 1996 to 2001 (69). Its second edition *Unequal Impact-II* included cancers diagnosed between 2002 and 2006, and overall disparities are reported for the 11 year period from 1996-2006 (4). Both these reports are based on data from the NZCR and have included more than 1,000 and 2,000 Māori and more than 10,000 and 20,000 non-Māori breast cancers in *Unequal Impact* and *Unequal Impact-II*, respectively.

Both *Unequal Impact* reports reported significantly higher incidences and lower breast cancer survival rates for Māori compared with non-Māori women (Figure 5). Age standardized rate ratios for breast cancer incidence and mortality have shown marginal increases from the first to second reports. The incidence ratio has increased from 1.21 (1.14-1.28) to 1.28 (1.20-1.37) while the morality hazard ratio has increased from 1.68 (1.54-1.88) to 1.73 (1.55-1.94). An increase in mortality hazard ratio was observed for distant (HR increase from 1.34 to 1.51) stage cancer, while a substantial reduction in mortality hazard was reported for localized breast cancer (HR from 1.87 to 0.74) in Māori compared with non-Māori women from the first to second reports. Despite these variations, the overall stage adjusted breast cancer mortality hazard ratio has shown only a marginal reduction from the first to second report (HR from 1.48 to 1.44). According to these reports, advanced stage at diagnosis has contributed by approximately a third to the observed mortality disparity, with only minimal change overtime. The high proportion of unstaged cancer included in *Unequal Impact* and *Unequal Impact-II* reports (17% and 15% respectively) has impacted on the accuracy of these quantifications, especially as Māori were over-represented in the unstaged breast cancer category. Despite these limitations, *Unequal Impact* reports provide useful information on the extent of Māori non-Māori breast cancer disparity, and trends in breast cancer incidence and mortality disparity between Māori and non-Māori women over time.

Figure 5: Cancer specific survival from breast cancer in Māori and non-Māori, 1996–2001 (unadjusted) (Source – *Unequal Impact – II*)



The fourth version of the *Hauora - Māori Standards of Health* has also performed an analysis, similar to the *Unequal impact* using the NZCR data, but only included women diagnosed over a five-year period between 2000 and 2004 (31). Incidence and mortality hazard ratios published in this report are much similar to *Unequal Impact* reports with an incidence rate ratio of 1.14 and a mortality hazard ratio of 1.71 for Māori compared with non-Māori women.

In 2005, Jeffreys and colleagues published relative 5-year breast cancer survival by ethnicity using data from the NZCR, for women diagnosed between 1991 and 2004 (9). This study included a total of over 16,000 breast cancers, and included over a thousand of Māori breast cancers. Age adjusted 5-year survival rates were 76% and 82% for Māori and non-Māori non-Pacific women, respectively. Adjusting for stage at diagnosis resulted in almost equal 5-year relative survival rates of 81% and 82 % for Māori and non-Māori non-Pacific women, respectively in their analysis. These findings are quite contradictory to *Unequal Impact*, where only a third of the survival disparity was observed to be due to stage at diagnosis, despite using data from the same source. Methodological differences and differences in statistical methods used in these two studies may have contributed to these variations. For example, the

Unequal Impact report has used Cox proportional hazard modelling while the Jefferys study has used relative survival for comparison of survival between Māori and non-Māori women.

The *Cancer Trends in New Zealand for 1991-2004* report compiled by Soeberg and colleagues analysed relative survival trends for Māori and non-Māori cancer including breast cancer, adjusting for socioeconomic and income status (6). According to models used in this report, over the 15-year period from 1991 to 2004, breast cancer mortality for Māori and non-Māori declined significantly, with a greater decline for Māori than for non-Māori. Although the excess mortality in Māori compared with non-Māori has declined by approximately 50% over each 10-year period, even in 2004, mortality rate in Māori was about 20% higher than for non-Māori women. Similar substantial reductions in mortality for socioeconomic and income categories were documented in this report. However, in contrast to ethnicity, the mortality gap between the lowest and the highest socioeconomic groups have remained essentially unchanged over the 15-year study period.

McKenzie and colleagues have performed a series of studies with the aim of quantifying the impact of cancer stage, healthcare access and tumour characteristics on breast cancer survival disparity between Māori and non-Māori women (12, 13, 70). Similar to studies described previously, these studies also used the NZCR data, but included additional data including socioeconomic status and tumour biological characteristics in their analyses. Their first study, which used data for women diagnosed over a 2-year period from April 2005 to April 2007 from the NZCR, reported an unadjusted breast cancer mortality hazard ratio of 1.73 for Māori compared with non-Māori women (13). Adjusting for age, socioeconomic and tumour characteristics, completely explained the survival disparity, with a final adjusted hazard ratio for Māori of 1.03. However, several important characteristics in this study needs clarification. First, this study included very high percentages of missing data which were over 60% for some key variables. Data imputation has been used to overcome this issue, but this potentially has added further bias. For instance, the authors have considered missing data as missing at random (which it was not, with higher percentages of data missing for Māori and for women with poor survivals) and have performed a simple multiple imputation (71). A different imputation method such as multiple imputation combined with either chained equations or modelling could have been used, which might have helped to overcome the issue of non-random missing data and provide more accurate estimates (72). The same study has reported an adjusted hazard ratio of 1.43 for Māori compared with non-Māori, who had complete data, which differs substantially from final analysis based on data imputation.

Further, this study has reported that there were significant differences in breast cancer biological characteristics between Māori and non-Māori women. However these differences in biology were not found to be contributing to breast cancer mortality disparity. Limitations of the study analysis, as discussed above, are likely to have limited the validity of these findings.

Pacific women have a lower breast cancer incidence than Māori and European women in New Zealand (73). However, a rapid rise in breast cancer incidence among Pacific women has been observed over last three decades. Compared to NZ European women, Pacific women are more likely to be younger at diagnosis, present with more advanced disease and have prognostic phenotypes associated with poor survival (70, 74). Pacific women have a breast cancer survival rate which is worse than Māori women. A rapidly rising incidence combined with a lower survival has resulted in a threefold increase in breast cancer mortality among Pacific women over a two decade period (7). Literature on breast cancer for Pacific women are sparse.

Overall, based on existing literature, there is conclusive evidence on breast cancer incidence and mortality disparity between Māori and non-Māori women, where Māori have about 20-30% and 60-70% higher age standardized rates of incidence and mortality, respectively compared with non-Māori women. Some studies have shown a substantial reduction in mortality disparity over last 10-20 years while others have shown only a marginal decrease. Advanced stage at diagnosis in Māori appeared to be the biggest contributor to this disparity with a reported contribution of approximately 30-40%, although some have reported this to be close to 100%. Although differences in socioeconomic status and cancer biological characteristics appeared to be contributing to the survival disparity, its quantitative impact is unclear at present. None of the studies to date has provided any data on possible inequalities in treatment or its contribution towards mortality disparity.

3.1.2 Ethnic inequalities in breast cancer and breast cancer survival in other countries

Ethnic disparities in breast cancer and breast cancer outcomes have been reported from many countries including the USA, Australia, Canada and the UK.

Breast cancer disparities in the USA

Breast cancer disparities in the USA are mostly reported in relation to disparities between White European and African American women, and less frequently including Hispanic and

Asian women. Comparatively, limited data are available on breast cancer disparities between settler White American women and Indigenous populations in the USA which include American Indians and Alaskan Natives.

African Americans

In the USA, African American women bear a greater burden of breast cancer, similar to Māori in New Zealand. Breast cancer mortality rate is about 40% higher in African American than in White women, despite a 10-20% lower breast cancer incidence (75).

The disparity in breast cancer mortality between African American and White American women has been known for almost half a century (76). A disparity in stage adjusted breast cancer survival between African American and White women was first reported in the 1980's, from a study based on US national breast cancer statistics (77), which changed the earlier notion that poorer outcome among African Americans were solely due to advanced stage at presentation (78). Since then several studies have shown more aggressive tumour biology, higher rates of comorbidity and inferior quality of breast cancer care being factors contributing to poorer outcomes in African American compared with White American women in the USA (79-81).

A large number of studies have examined breast cancer outcome differences between African American women and White American women, and underlying causes for these differences, especially over the last decade. Findings from some of the larger studies and meta-analyses are discussed below.

Newman and colleagues published a meta-analysis of 20 studies published between 1980 and 2005 on ethnic inequalities in breast cancer outcomes in the USA (82). They reported that African American ethnicity to be an independent predictor for worse overall mortality (HR=1.27, 95% CI 1.18-1.38) and breast cancer mortality (HR=1.19, 95% CI 1.10-1.29) compared with White American women, after adjusting for cancer stage, age and socioeconomic status. This analysis confirmed findings of several previous studies, which have demonstrated more aggressive cancer biology and inferior quality cancer treatment for African American compared with White American women as major contributors for breast cancer survival disparity in the USA (80).

Curtis and colleagues attempted to identify and quantify the impact of different factors contributing to ethnic disparity in breast cancer survival in the USA, with a sample of over 40,000 women over the age of 68 years, diagnosed with breast cancer between 1994 and 1999

(83). In this study, the unadjusted breast cancer mortality rate for African American women was 63% higher compared with White American women. Adjusting for screening status, stage at diagnosis, comorbidity, tumour biology and treatment almost completely explained the survival disparity with a final adjusted hazard ratio of 1.08. Lowest unadjusted and adjusted breast cancer mortality hazards were observed for Asian and Pacific Island women (HR=0.59 and 0.61, respectively).

Silber and colleagues also investigated reasons for ethnic disparity in breast cancer survival in the USA by comparing a cohort of African American women with breast cancer over the age of 65 years with three matched cohorts of White American women, diagnosed during 1991-2005 (81). The 5-year survival rate for African American women was 12.9% lower than for White women, and approximately two-thirds of this disparity was due to more advanced stage at diagnosis in African American women. Most of the residual disparity was explained by comorbidity and differences in tumour biology. Although significant differences in treatment including longer delays and lower use of chemotherapy was observed in African American women, these differences apparently contributed to <1% of the survival disparity. However, these results are substantially different from several other published studies including a meta-analysis published by Blackman and colleagues (80, 84). This analysis has reported that disparities in breast cancer treatment as a substantial and significant contributor towards the final survival disparity between African and White American women.

Overall, based on published studies, advanced stage at diagnosis appears to be contributing to approximately a third to a half of the mortality disparity between African American and White women in the USA, while the rest seems to be distributed among cancer biology, treatment differences and patient comorbidity.

American Indians and Alaskan Natives

The incidence of breast cancer among Indigenous populations in the USA are substantially lower compared with White American women (58 vs. 141 per 100,000 age standardized population in 2000) (85). Comparatively, a much narrower mortality gap (14.9 vs. 27.2 per 100,000 age standardized population in 2000) is observed between Indigenous and White women due to substantially lower survival rates in Indigenous women. Similar with African American women, delay in diagnosis, high rate of comorbidity and inferior quality of treatment are the likely major causes for poor survival in Indigenous women. However, unlike for African American women, cancer biology has not been shown to be a factor for lower survival among Indigenous women (86).

Breast cancer disparities in Australia

Indigenous Australians including the Aborigines and Torres Straight Islanders have been documented to have significantly poor health outcomes, including from cancer, compared with settler European population (87-89). Bramley and colleagues published a comparison of survival disparities between Indigenous and settler populations in the USA, Canada, Australia and New Zealand (63). Of these countries, the greatest absolute and relative survival disparity between Indigenous and settler populations was observed in Australia.

The incidence of breast cancer among Indigenous populations is about half of that of European women in Australia (89), which is similar to Indigenous American Indians in the USA (85).

Similarly, Aborigines were reported to have worse survival from cancer, as shown in a matched cohort study of Indigenous and non-Indigenous Australians with cancer by Valery and colleagues (88). Aboriginal patients were found to be diagnosed with more advanced cancer, were more likely to have comorbidities and were less likely to receive surgery, chemotherapy and radiotherapy for treatment of cancer. The worse hazard ratio for mortality persisted even after adjusting for stage, comorbidity and treatment differences indicating impacts of other confounders including level of education, health literacy, and cultural and religious differences interfering with optimum cancer care for these Indigenous patients.

Breast cancer disparities in the United Kingdom

Compared with the USA, data from the UK on ethnic disparities in breast cancer are relatively sparse (90-92). A recent study published with data from over 35,000 women with breast cancer from South London reported that all minority ethnic groups in the UK have lower breast cancer incidences compared with White European women (90). However, compared with White European women, mortality hazard ratios were worse for women of all ethnic minority groups, except Chinese. Adjusting for stage at diagnosis, treatment and socioeconomic status almost completely explained these ethnic disparities in breast cancer survival. Another study investigating breast cancer survival between South Asian and non-South Asian women in the UK has reported South Asian women to have better 10-year survival rates, which persisted after adjusting for age, stage and cancer treatment (92). Overall, ethnic disparity in breast cancer outcomes in the UK appear to be much smaller compared with both Australia and the USA, though they seem to follow a similar pattern.

3.2. Reasons for ethnic disparities in breast cancer outcomes

Several different explanations have been proposed to describe reasons for poor breast cancer survival among Indigenous and ethnic minority populations. These explanations include more advanced cancer stage at diagnosis due to delay in diagnosis and lower screening coverage, more aggressive tumour biology, high rates of comorbidity and inferior quality of breast cancer treatment. Most studies have analysed the impact of one or more of these factors separately, and only a few studies have taken a holistic approach incorporating all these factors included within contextual factors.

The following section explores the impacts of individual patient level factors, tumour factors and healthcare service related factors on ethnic disparities in breast cancer mortality in New Zealand and in other countries where similar disparities are encountered. Although I have used this classification for ease of explanation, significant overlap among these categories for some of the characteristics should be emphasized. For instance cancer stage at diagnosis will depend on a combination of patient recognition of symptoms and presenting to a healthcare facility (patient level), growth rate of the tumour (tumour level) and provision of an accessible and equitable health service (healthcare service level) for patients (Figure 6).

3.2.1 Patient level factors

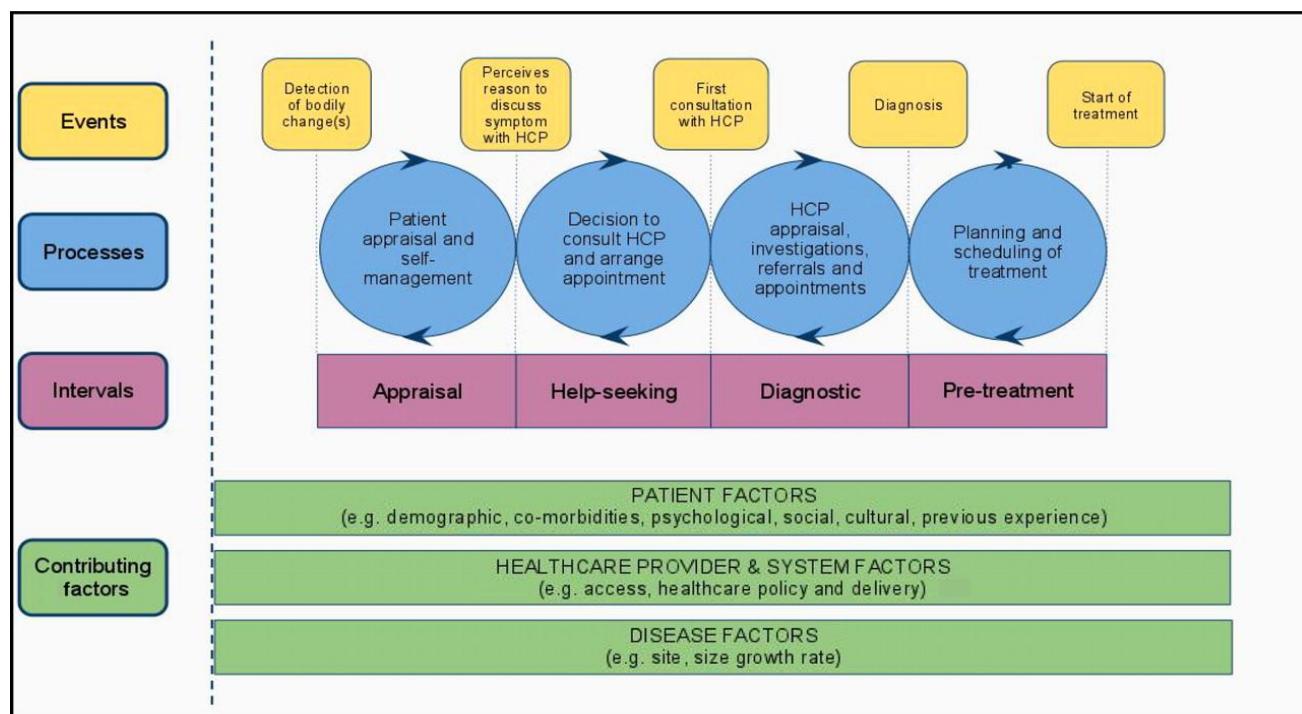
Patient level factors including cancer stage at presentation, comorbidity, socioeconomic status and urban/ rural residency have been shown to have major impacts on cancer stage at diagnosis and outcomes. As described above, some of these factors (i.e. stage at diagnosis) will have an influence from tumour biology and healthcare service, while some other factors (i.e. socioeconomic status, urban/rural residency) will influence accessibility of healthcare services and treatment.

Stage at diagnosis

Stage at diagnosis (tumour size, nodal involvement and metastasis) is the strongest predictor of breast cancer mortality (11). Compared to localized breast cancer with a 5-year survival of over 90%, metastatic breast cancer remains largely incurable with a 5-year survival of approximately 20% (93).

More advanced cancer stage at diagnosis in Māori compared with non-Māori is well known (4, 9, 69). All studies to date have shown that Māori were more likely to be diagnosed with more advanced staged breast cancer compared with non-Māori women (Figure 7). This difference in stage at diagnosis seems to have declined only marginally over last two decades (4). As discussed previously, advanced stage at diagnosis is the biggest contributor to mortality disparity, which is likely between a third and a half of the overall disparity. However, all previous studies have used data from the NZCR, which includes a high proportion of unstaged breast cancer (approximately 15%) complicating these estimations (15). A higher proportion of Māori having an ‘unknown’ stage combined with possible inaccuracies in cancer staging in the NZCR (94) may have resulted in an under estimation of the impact of advanced stage on survival disparity between Māori and non-Māori women.

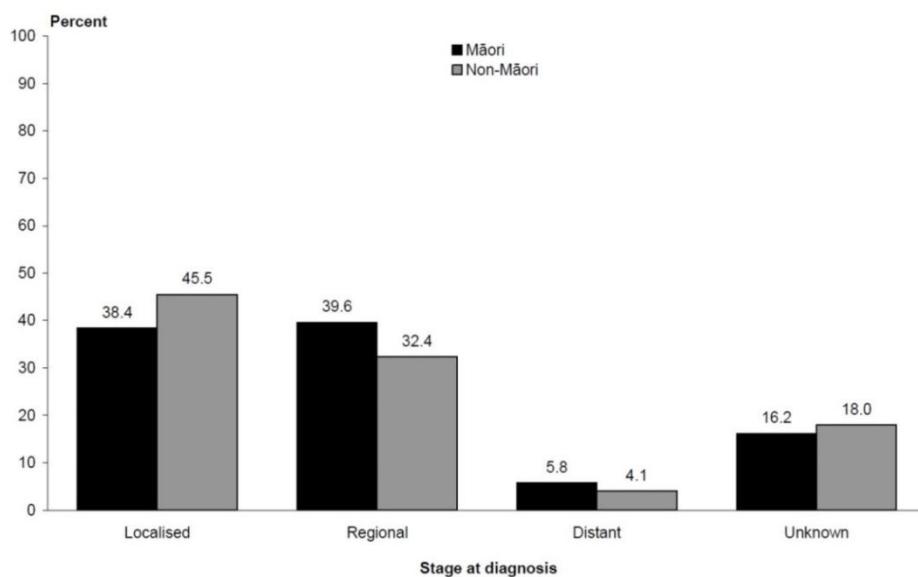
Figure 6: Model of pathways to cancer treatment (95)



HCP - Health Care Provider

The stage at diagnosis of a breast cancer is dependent on several of patient, tumour and health care system factors (Figure 6), although the degree of impact of these factors for each woman may vary substantially. This section discusses factors contributing to stage at presentation with a greater emphasis on patient related factors, which include delay in presentation and associated factors. Tumour and health system factors contributing to stage disparity are discussed under respective topics.

Figure 7: Distribution of stage at diagnosis for breast cancer in New Zealand, 1996-2001 (Source – *Unequal impact – II*) (69)



Barriers to access care

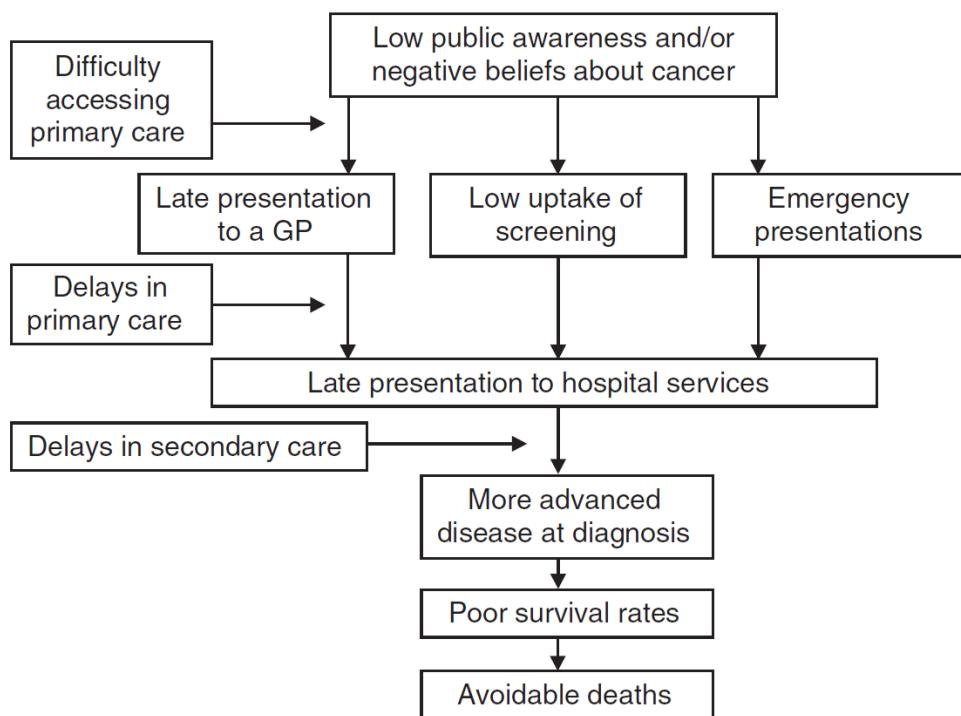
Differences in access to health care (defined as timely use of personal health services to achieve the best possible health outcomes) is believed to be a major reason for ethnic and socioeconomic inequities in breast cancer outcomes (96). Barriers to access may occur at health system, health care process or patient level. Several international and local studies have identified older age, minority ethnicity and socioeconomic status to be major barriers to access optimum healthcare (96).

Disparities in access to healthcare for Māori compared to non-Māori have been demonstrated across the New Zealand health care sector. Differences have been observed in terms of gaining entry into services and differential experience of services including poorer quality of care and a higher risk of adverse events and complications (35, 97-99).

Access to primary care has also been found to be poorer for Māori women with breast cancer. Māori belief systems, such as views about reliance on the whānau (family), individual mana (freedom or spiritual power), death and dying, and practices associated with tapu/noa (sacred or holy), continue to influence health behaviour. These views may influence, for example, preferences for care, individual help-seeking behaviour and responses to health care providers. Previous qualitative research has identified cost of care, communication difficulties due to factors such as low health literacy, structural barriers such as distance to travel and wait times, previous negative experiences (e.g., institutional racism) and lack of ‘cultural fit’ in health care services as barriers to access healthcare among Māori (100-102).

Level of education and health literacy are important factors associated with early diagnosis, through promoting screening participation and minimizing delays in presenting to a primary healthcare service for cancer related symptoms (Figure 8). Health literacy is defined as “the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions” (103). The exchange of health information is a complex process involving service configuration, the health professional and the recipient (104). Key components of health literacy include individual skills, health tasks undertaken, health materials used, skills of providers (including the ‘oral exchange’), and the physical and social environment (105). Three out of four Māori females have poor health literacy skills, which is approximately 50% higher than NZ European women (106). It is likely that levels of education and health literacy are possible confounders contributing to ethnic disparity in breast cancer outcomes not only through delay in diagnosis, but also through interfering with optimum breast cancer treatment or through poor compliance with treatment.

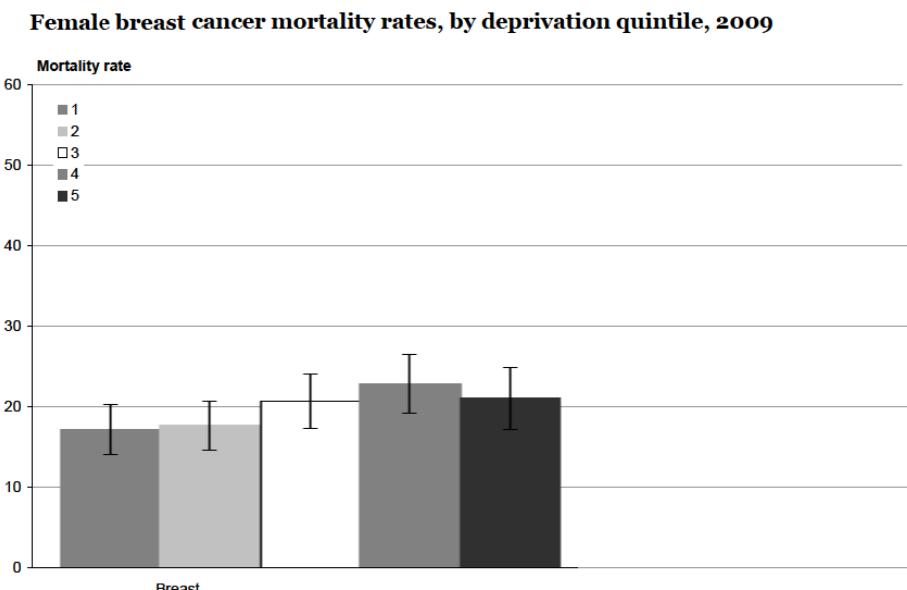
Figure 8: Cancer detection pathway (*Source: The National Awareness and Early Diagnosis Initiative, UK*)(107)



Socioeconomic status

Several studies have shown that women of lower socioeconomic groups have lower survival (Figure 9) and higher recurrence rates from breast cancer (108, 109). The higher breast cancer mortality rate observed among patients of lower compared with higher socioeconomic groups have essentially remained unchanged in New Zealand over the last two decades (6, 7). A significantly greater proportion of Māori live in socioeconomically deprived circumstances compared with NZ Europeans (Figure 10). Therefore it is believed that some of the observed survival disparity between Māori and NZ European women is contributed by these socioeconomic differences.

Figure 9: Age standardized mortality rates for breast cancer in New Zealand by deprivation quintiles
(Source – Ministry of Health)



Source: New Zealand Cancer Registry

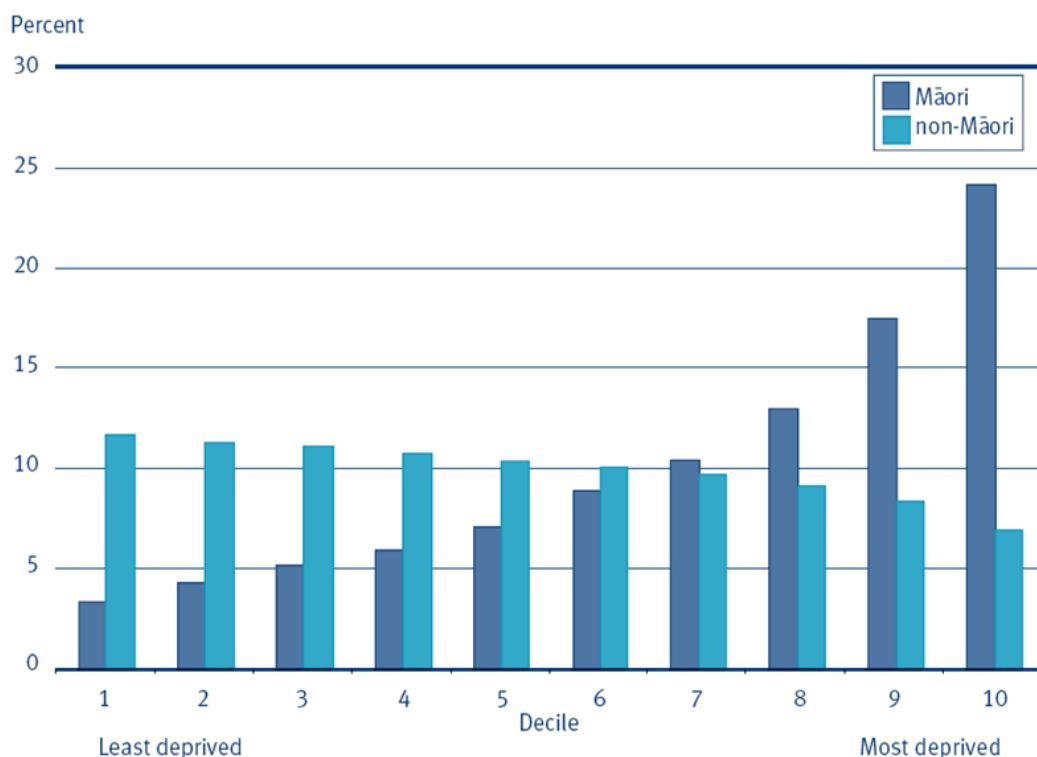
Note: The rate shown is the age-standardised rate per 100,000 population, standardised to the WHO world standard population; 95% confidence intervals.

Lower socioeconomic status has been shown to influence poor cancer outcomes through late presentation, lower screening uptake, delays in treatment and poor compliance (110). Some of the excess mortality observed among low socioeconomic patients could be explained by differential access to healthcare services, although other associated factors including level of education, health literacy, language and cultural differences also play a role (12). Similar differences in breast cancer outcomes among different socioeconomic groups are observed in

Ethnic differences in breast cancer outcomes in Aotearoa New Zealand

countries with different health systems including the USA, the UK, Australia, Sweden and New Zealand (111-115). Lower socioeconomic status which is more commonly seen among Indigenous/ethnic minority women contributes, but does not fully explain the breast cancer survival disparity (116).

Figure 10: Neighbourhood socioeconomic deprivation (NZDep2006) for Māori and non-Māori 2010
(Source: *Tatau Kahukura, Māori Health Chart book 2010*)



In the USA, lack of private insurance has been shown to be an independent predictor of advanced stage at diagnosis and higher mortality, which has contributed to ethnic inequities in breast cancer outcomes (117). Similarly, treatment provided in private sector which is accessible to patients of higher socioeconomic status and/or with a private health insurance, has also been shown to be associated with a shorter treatment delays and better long term outcomes from breast cancer (118).

From a study conducted among women with breast cancer in New Zealand, McKenzie et al demonstrated that the lowest socioeconomic group had a 50% higher breast cancer mortality rate compared to the most affluent group, even after adjusting for ethnicity, tumour and socio-demographic characteristics (12). Furthermore, the same authors in a later publication found

that the breast cancer survival disparity between Māori and non-Māori women was completely attributable to social deprivation and differential access to health care, without any significant contributions from cancer biology or treatment differences (13). However, other similar studies from New Zealand suggest a much smaller impact from socioeconomic status, and have demonstrated a significant residual ethnic disparity after adjustment for socioeconomic status (7, 14). A study combining socio-demographic, tumour and treatment factors to clarify and quantify the contribution of socioeconomic status towards the ethnic disparity has not been done to date.

Urban / Rural residency

Residence in a rural compared to an urban area has been shown to negatively influence the outcomes of cancer patients in different countries including the USA, Australia, France, Canada and New Zealand (119-122). This disparity is mostly due to the advanced stage at diagnosis in patients from rural areas, and this risk seems to increase proportionately to the distance from residence to cancer centre, as reported by Campbell and colleagues from Scotland (123).

International evidence on urban rural disparity in the stage at diagnosis and survival of breast cancer is somewhat similar with most studies to date reporting rural patients to present with advanced stage disease (124, 125). Rural women also experience poor breast cancer outcomes even after adjusting for stage (126, 127). In contrary, a New Zealand study based on the NZCR data for 1994-2004 period has reported that women residing in remote areas with cancers of breast, colon and melanoma to be diagnosed with relatively early staged disease compared with women residing in main urban areas (122). Despite that, this study has shown significantly worse stage adjusted survival rates for rural women compared with urban women, with a hazard ratio of 1.24 for most remote compared with urban women. Findings from several other New Zealand studies have not supported those findings, as these studies have failed to show significant differences in breast cancer stage at diagnosis or survival between urban and rural dwelling women (15, 128, 129). Based on current evidence, it appears that rural compared with urban residence is not associated with more advanced breast cancer stage at presentation in New Zealand; however the impact of residential status on breast cancer survival remains unclear.

Breast cancer screening

Mammographic screenings for early detection of breast cancer has shown to significantly reduce mortality in women aged 50-69 years (130). Regular two-yearly breast screening has shown to reduce the population risk of dying from a breast cancer by about 30% (131). A recent review conducted by the Independent UK Panel on Breast Screening estimated the relative mortality risk reduction to be 20% (95% CI 11%-27%) among women invited for screening compared with women who were not invited (130). They further estimated that one breast cancer death would be prevented for every 180 women screened (130).

Screening coverage of BSA has grown steadily since it was established in 1999. However, still there are wide variations in the levels of coverage by different age groups, geographic areas and ethnic populations. BSA achieved its target biennial coverage of 70% for NZ European women in 2010 (132). However, for women aged 45 – 49 years it was 64.1% and for Māori 54.9%, both of which were well below the target 70% level (132). Further, there were large variability in screening coverage rates for Māori by region, which ranged from 54% to 79% across the country in 2012 (40). Lower screening coverage for Māori is a likely contributor for more advanced disease, which in turn is the major contributor for lower breast cancer survival in Māori (133).

Similar ethnic disparities in breast cancer screening participation rates have been reported from the USA, the UK and Australia, with lower rates been observed in African Americans in the USA and the UK, and Aborigines in Australia, compared with White women (134). Lower breast cancer screening coverage has been shown to be responsible for approximately 10-25% of the ethnic disparity in breast cancer mortality in the USA based on different statistical models (83, 135).

Difficulty or barriers to access mammographic screening has shown to be a more important factor for lower screening participation in Indigenous/ethnic minority women and in women from low socioeconomic groups (136-139). In addition, uneasiness with the health care system due to mistrust, perceived discrimination or perceived lack of quality have also shown to impact on screening participation in ethnic minority women in minority African American and Latina women in the USA (140, 141).

McNoe and colleagues studied reasons for non-participation in breast cancer screening during the pilot phase of New Zealand national breast screening programme in 1996 (142). Practical difficulties in attending screening including time, cost and transport, and negative attitude

towards screening among Māori including fear of the procedure or of a diagnosis of cancer were some of the more common reasons for non-participation in Māori. Thomson et al, published a retrospective process evaluation which evaluated the impact of several strategies which were aimed at improving mammographic screening participation in a rural, predominantly Māori population (143). Several community and practice-based strategies were implemented with existing health resources through participation of Māori health providers aimed at improving access, communication and community participation. These interventions resulted in an increase in the rate of screening participation from 45% to 98% over a two year period, which was observed to be maintained two years later. This study has demonstrated some of reasons for screening non-participation in Māori and perhaps more importantly, possibility of improving participation, with simple but well-planned strategic interventions.

Comorbidity

Comorbidity is the co-existence of diseases or disorders in addition to a primary disease of interest. Comorbidity has many detrimental effects on cancer survival, the degree varies by cancer site (144-146). These detrimental effects include lower use of primary and adjuvant therapy, treatment delays and higher rate of treatment associated complications (147).

Breast cancer treatment is multimodal; for a majority of women it includes adjuvant systemic therapy and/or radiotherapy in addition to surgery. Patient's general health status and comorbid illnesses may reduce tolerability and increase complications of primary and/or adjuvant treatments, and may force to use a lower dose or a shorter duration of treatment or in worst scenarios, a complete discontinuation of treatment.

Numerous studies have shown that comorbidities to be an independent predictor of worse overall and cancer specific survival in women with breast cancer (148, 149). From a cohort study of women with breast cancer with a 10-year follow up, Tammemagi and colleagues showed that approximately 50% of the observed survival disparity among African Americans and white women, to be due to differential distribution of comorbidities (146). However, other similar studies from the USA have quoted much smaller contributions from comorbidities at less than 25% (150, 151). Another US study by West and colleagues, failed to show any significant impact of co-morbidities on survival disparity between African American and White women despite the strong correlation observed between the comorbidity index score (Charlson index) and mortality rate (152, 153).

A recently published New Zealand study has shown the impacts of different comorbidities on cancer mortality including for breast cancer (154). This study which has used data from the NZCR and the National Minimum Dataset (NMDS) has shown a direct relationship between comorbidity and, poor overall and cancer specific survival. The impact of comorbidity on mortality has been shown to be greater for cancers with a generally good prognoses including for breast cancer compared with cancers with a relatively poor prognosis, for example for cancers of liver and stomach (154).

Māori generally have a higher prevalence of comorbidities compared with non-Māori (33). Comorbid illnesses such as cardiovascular diseases, chronic respiratory illnesses and diabetes have been shown to be significantly higher among Māori, in comparison to non-Māori women (68). This difference may be influenced by higher prevalence rates of modifiable risk factors such as smoking, alcohol use and obesity in Māori compared with non-Māori women. Comorbidity has been shown to be a significant factor for poor overall and cancer specific survival for cancers including bowel and cervical cancer in Māori (67, 154-157). Although it is clear that comorbidity is a likely contributor to ethnic disparity in breast cancer outcomes, its proportional contribution is unclear at present.

Body mass index (BMI)

Obesity has a complicated relationship with risk of developing breast cancer and with clinical behaviour of established disease. It has been shown that obesity is associated with both an increase in risk of developing breast cancer and a worse prognosis (158-160). It has also been shown that the magnitude of difference for cancer recurrence in obese women versus lean women to be comparable to the difference achieved by use of systemic hormonal and chemotherapy (161).

Obesity is increasing at alarming rates in almost all countries in the world and has rapidly become a major global health problem (162). It is believed that increasing obesity rates are partly responsible for increasing post-menopausal breast cancer, especially in developing countries. Obesity is one of the few modifiable risk factors that influence both development and prognosis of breast cancer. It is suggested that reducing population prevalence of obesity could reduce the number of cases of breast cancer by a tenth in Europe (163).

Rates of obesity have rapidly risen in New Zealand with one in every three adults being obese currently (33), which is worse among socioeconomically deprived and ethnic minority

populations. In 2010, adult obesity rates were 48% and 68% respectively, for Māori and Pacific compared with 30% for NZ Europeans (33). A recently published multi-ethnic case-control study from New Zealand, has failed to demonstrate a differential impact of obesity on breast cancer incidence disparity among Māori, Pacific and non-Māori non-Pacific women (164). However, significant selection bias was documented for this study where response rates for Māori and non-Māori women were 38.1% vs. 56.8%, respectively. This selection bias may have impacted on the study results and its conclusions. No New Zealand study to date has assessed the link between BMI and its impact of breast cancer mortality disparity in Māori (and Pacific) women due to unavailability of BMI data from routine breast cancer datasets including the NZCR or other regional breast cancer registries.

3.2.2 Tumour factors

Breast cancer is a heterogeneous disease; some are slow growing with an excellent prognosis, while some have a grave prognosis irrespective of aggressive therapy. Measures of cancer biology include;

- Histological type
- Tumour grade
- Lympho-vascular invasion (LVI)
- Oestrogen (ER) and Progesterone receptor (PR) status
- HER-2 (Human Epidermal Growth Factor Receptor type 2) status

Histology, tumour grade and LVI

Differences in breast cancer biological characteristics by ethnicity are observed in many countries, and between many ethnic groups. For example, African American women with breast cancer in both the USA and the UK are known to have higher grade, ER/PR negative and triple negative breast cancers than their European American counterparts (11, 165-167). Further, these differences are known to be major contributors for excess breast cancer mortality in African American women (11, 166). Some of the biological differences in breast cancer between African American and White women have been attributed to lower socioeconomic status, which is more common among African American women. Differences in cancer biology between African American and White women appear to persist after

adjusting for age and socioeconomic status (168), which supports an independent association between ethnicity and cancer biology.

Although several New Zealand studies have compared the ethnic differences among Māori and non-Māori on tumour grade, no published study to date has compared the distribution of histological varieties between the two ethnic groups.

A study carried out in Christchurch, New Zealand (total of 337 patients) showed a significant difference in tumour grade between Māori and non-Māori, with more Māori women having lower grade tumours (169). These findings contradicted a study published by the Auckland Breast Cancer Study Group with a larger sample of 1577 women, where they found Māori women to have significantly more, higher grade tumours (74). Further, they postulated that this difference in the grade being a contributor to the higher mortality from breast cancer observed among Māori women. These findings were further supported by McKenzie et al who published data from 2968 patients, where Māori women had significantly more, higher grade tumours compared to non-Māori (13). However, tumour grade was not observed to have a significant effect on the mortality disparity between Māori and non-Māori, when adjusted for other tumour variables including tumour size and extent of spread.

Very few studies to date have compared the impact of LVI in breast cancer outcome among different races/ethnicities in the world. Chavez-MacGregor and colleagues compared the rates of LVI among ethnicities during their study on breast cancer response to neo-adjuvant chemotherapy (170). Their data showed that there was no significant difference in rates of LVI among African Americans, Hispanics and White women. Weston study based the Auckland Breast cancer Register, reported that there was no difference in the rates of LVI among Māori, Pacific and non-Māori, non-Pacific populations (74).

ER/PR and HER-2 status

Women with ER and PR negative tumours have approximately a 10-15% lower 5-year disease free survival rate than women with ER/PR positive cancers (171-173), while HER-2 amplified tumours (not treated with trastuzumab) have been shown to be associated with approximately a 5-10% lower 5-year survival compared with HER-2 non-amplified cancers (172). A US study using Surveillance, Epidemiology and End Results (SEER) data from over 70,000 patients' demonstrated significant differences in tumour histology and receptor status by ethnicity which were also observed to be linked strongly with breast cancer mortality (86).

These findings were supported by several other studies including the Women's Health Initiative (WHI) study and Carolina Breast Cancer Study from the USA, which demonstrated significantly higher proportions of ER/PR negative (including triple negative breast cancer) in African American women (11, 165, 166). Further, a recent publication has shown a 50% higher incidence of triple negative cancer in African American compared with White American women, while no differences in HER-2 status were observed among different ethnic groups (174).

ER/PR status has been measured routinely in New Zealand since early 1990's, but no major differences in ER/PR status has been observed among ethnic groups (13, 74, 169). However, some of these studies were too small to detect a statistically significant difference, if one existed and others based on the NZCR might have been influenced by a high proportion of missing data.

HER-2 receptor status has only been routine in breast cancer pathology reporting in New Zealand over the last 7-8 years. Analysis of data from the NZCR has shown a higher rate of HER-2 positive cancers among Māori and Pacific compared to non-Māori, non-Pacific women (13). However, HER-2 status has not been shown to be associated with breast cancer mortality disparity (13). A high proportion of missing data (38%) in this study has weakened the accuracy of these conclusions.

Overall, present evidence suggests significant differences in breast cancer biological characteristics by ethnicity in New Zealand. These appear to be dissimilar to biological differences reported from the USA. It is unclear at present, whether these biological differences are a factor contributing to mortality disparity, similar to the contribution seen for African American women in the USA.

3.2.3 Healthcare service factors

Relatively few published papers have directly analysed ethnic disparities in healthcare access or utilization in New Zealand. The studies that have been published have reported significant disparities in care between Māori and non-Māori patients for diabetes (102, 175), cardiac interventions (176-178), surgery (179, 180) and for cancer treatment (181, 182).

In 2002, the National Diabetes Working Group conducted a literature review to investigate barriers to access care for Māori with diabetes (102). This review identified cost of care, low

numbers of Māori among health staff, and lack of understanding among mainstream health workers concerning the context in which Māori patients live their lives as major barriers for optimum care for Māori. A study from South Auckland included in the previously mentioned review, has reported that lack of community based services and lack of perceived benefit from treatment as common factors for poor compliance among Māori and Pacific patients (175).

Several studies have investigated and reported on the lower rate of cardiac interventions in Māori who have a much higher rate of ischaemic heart disease and cardiac deaths compared with non-Māori (176, 177). For instance, during the 10-year period between 1990 and 1999, rate ratios for coronary artery bypass grafting and percutaneous coronary angioplasty for Māori compared with non-Māori non-Pacific were 0.40 and 0.29, respectively (183).

However, these disparities seem to have improved substantially, especially over last 5-10 years as reported by Kerr and colleagues (178). This study has not shown a significant difference in rates of cardiac intervention by ethnicity during 2007-2012, once adjusted for other disease characteristics.

Reported ethnic disparities in cancer care in New Zealand include care for colon and lung cancers. Stevens and colleagues have reported on fewer curative resections and longer treatment delays for surgery for lung cancer experienced by Māori compared with non-Māori patients in Auckland and Northland regions (182). A more detailed analysis of disparities in colon cancer care in New Zealand has been done by Hill and colleagues. They conducted a nationwide cohort study of colon cancer disparities using a case note review, and reported that Māori patients to have received substantially poorer quality of cancer care compared with non-Māori patients (67, 181, 184). These included lower likelihood of undergoing a curative resection for operable cancer, higher likelihood of undergoing emergency surgery and higher likelihood of undergoing a palliative resection compared with non-Māori. Further, eligible Māori were less likely to be offered chemotherapy and were more likely to experience longer delays to receive chemotherapy compared with non-Māori patients. This study concluded that disparities in cancer care have been responsible for approximately a third of colon cancer disparity between Māori and non-Māori patients.

These findings are further supported by data mostly from the USA on ethnic disparities in cancer treatment and its impact on outcome disparities. Several researchers in the USA have studied ethnic differences in surgical treatment of cancer, which included surgery for cancers of lung, oesophagus, prostate, liver, endometrium and colon (185-190). These studies have reported statistically significant differences in rates of surgical treatment for respective cancers

between African American and White American patients. Perhaps more importantly, these studies have shown minimal or no survival difference between patients from these two ethnic groups with similar staged disease who underwent surgery.

To assess the ethnic disparities in breast cancer treatment in the USA, Li and colleagues carried out a study with 124,934 patient data from SEER database covering 11 regional breast cancer registries over a 7-year period (80). They found that patients with breast cancer from ethnic minorities were more likely to receive surgical or radiation therapy not meeting national standards. The authors have concluded that these differences were more likely to be due to socioeconomic and cultural backgrounds of these patients, rather than due to discrimination by health care providers. However, whether these differences in care represent differences in patient preference, provider decisions, poor patient-provider communication or a deficiency of the healthcare structure has not been studied adequately in context of cancer surgery.

Shavers and Brown published a review of literature on ethnic disparities in cancer treatment in the USA (191). Their review has reported significant ethnic differences in cancer treatment, and has identified several structural barriers as well as physician and patient related factors contributing to ethnic differences in treatment. General observations following their study of 23 publications on ethnic disparities in breast cancer treatment in the USA were that, ethnic minority women to have a lesser chance of receiving breast conservation surgery (BCS) and radiotherapy following BCS, a lesser chance of receiving adjuvant chemotherapy or hormonal therapy and a higher likelihood of receiving chemotherapy and hormonal therapy for a shorter duration not keeping in with recommended guidelines compared with Caucasian women (192, 193). However, all the studies were not in agreement and there were several studies that contradict above general observations, which have demonstrated absence of any significant differences among different ethnicities in rates of BCS, radiotherapy, chemotherapy and hormonal therapy (194, 195). Differences in study methodology, smaller sample sizes and possible regional variations in cancer care might have contributed to these variations.

Quality of treatment

Early detection through screening mammography or through general practitioners and timely, optimal treatment provided through a multi-disciplinary team (MDT) is believed to be the ideal method for achieving best long term outcomes from breast cancer (196).

Major advances in treatment of cancer have been made over past few decades. These advances have resulted in significant survival improvements for most cancers. Breast cancer survival also has shown a marked improvement, mainly for localized cancer which is over 90% at five years in the developed world (93). However, there are clear differences in survival improvement among different ethnicities in many countries, indicating unequal distribution of advances in cancer therapy. Many a research has looked into the impact of possible ethnic disparities in the administration of cancer treatment and provider delays as contributors to this disparity.

Possible areas of lower access or inferior quality of care for Māori compared with non-Māori include; delays in diagnosis and treatment (including primary and adjuvant therapy), inferior quality or inadequate use of appropriate treatment (due to lower referral rates, comorbidities, patient declining treatment) and a lesser proportion of patients being managed through MDTs.

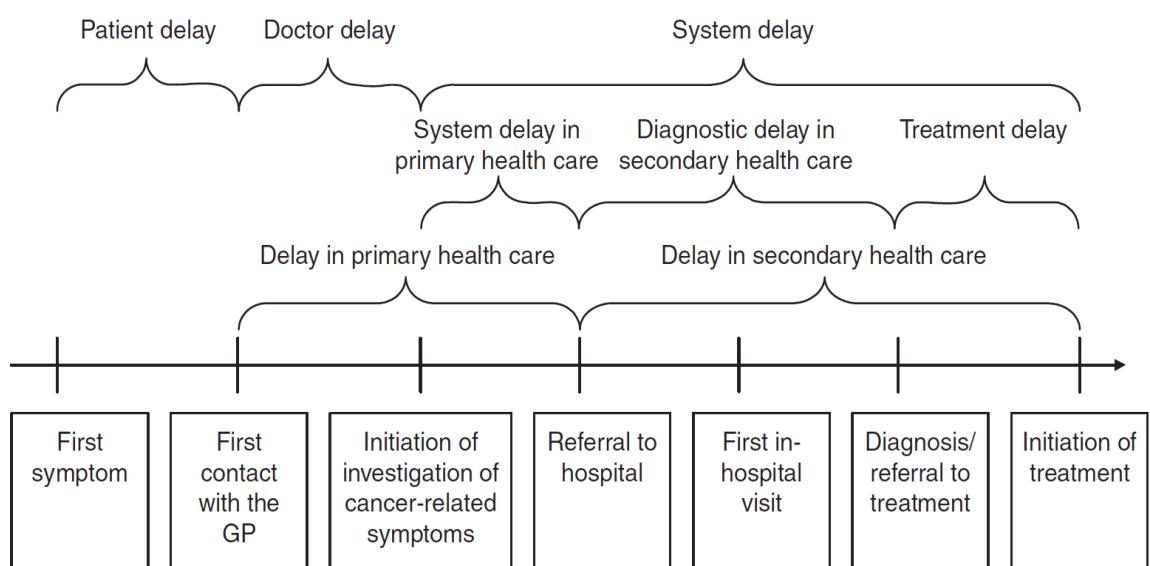
In New Zealand, BreastScreen Aotearoa (BSA) Independent Monitoring Reports and Māori Independent Monitoring Reports have published data on treatment differences for screen detected breast cancer by ethnicity, and to date are the only reports to have published such data (40, 197). BSA Independent Māori Monitoring Reports were commissioned to provide an analysis of Māori data, and inequities between Māori and non-Māori for quality and timeliness of assessment and treatment for women diagnosed with screen detected breast cancer (197). These reports have documented significant inequities in breast cancer treatment between Māori and non-Māori women. For example, Māori women were 20% less likely to receive their first treatment surgery within 20 working days than non-Māori women.

Overall inequities along the screen detected breast cancer treatment pathway between Māori and non-Māori women appear to be minimal, especially in comparison with what is known of non-screen cancer treatment pathway (181). It is possible that inequities have been minimised due to intensive quality control measures along the screen detected breast cancer treatment pathway, including monitoring against key quality indicators, audit and independent review. For non-screen detected cancers the disparities are likely to be greater, but we lack this information, which is a major deficiency.

Delay

A delay in presentation with symptoms of breast cancer is known to reduce the rate of survival from breast cancer (198). A total delay, which is a combination of patient and provider delay (Figure 11) of more than three months from the time of detection of symptoms to initiation of treatment has been shown to be associated with significantly higher rates of mortality and cancer recurrences (199). In the only published New Zealand study to date looking at delay in relation to breast cancer, Meechan and colleagues reported that 13% women presented with a delay of longer than three months. However, the authors have not assessed the differences in delay among different ethnicities in their study population (200).

Figure 11: An illustration of the overall milestones and time intervals in the route from first symptom until start of treatment (201)



Several international researchers have studied ethnic differences in delay in breast cancer, mainly focusing on patient delay. Facione and colleagues performed a critical review of literature on ethnicity and delay in breast cancer presentation in the USA using 12 published studies (202). They concluded that there is a consistent and significant longer delay among African Americans and Hispanics compared with White women across all studies. However, possible reasons behind these delays were less clear, but possibly included lower level of education, poor socioeconomic status and lack of ready access to health care. Other researchers have investigated provider delay in cancer therapy, among different ethnicities in

the USA. These studies have shown that there are longer provider delays in treatment for African Americans and Hispanic breast cancers, compared with White Caucasian women (203, 204).

In a meta-analysis published in the Lancet in 1999, Richards and colleagues confirmed the relationship between delay in treatment and poor breast cancer survival (198, 205). In this meta-analysis, a delay of more than three months from the onset of symptoms to initiation of treatment was associated with a 12% lower 5-year survival compared with a delay of less than three months, after adjusting for lead time bias. A recent study published by McLaughlin and colleagues have shown that a much shorter delay of 2-months was associated with significantly higher mortality rates for advanced breast cancers and for cancers associated with adverse prognostic characteristics including higher grade, HER-2 positivity and triple negative cancers (206).

According to BSA quality standards, at least 90% women should receive their first surgical treatment within 20 working days of receiving their final diagnostic result (132). However, figures from BSA in 2008 indicate that only 57.7% Māori and 71.2% non-Māori women achieved these targets. Given the lack of standards and audit for management of symptomatic non-screen detected cancers, disparities are likely to be greater, although we lack data on this currently.

Timeliness of instituting adjuvant treatment has also been shown to be crucial for the maximum potential benefit from these treatments. Two recent meta-analyses have shown a 6% and 15% increase in relative mortality rate with each 4-week delay in initiating adjuvant chemotherapy for breast cancer (207, 208). Delays longer than 3 months for adjuvant radiation therapy has been shown to be associated with higher risks of local recurrence and mortality (209). Although timeline thresholds given in treatment guidelines are sometimes arbitrary and controversial, longer delays for surgery, chemotherapy and radiation therapy have all been proven to be associated with poorer breast cancer outcomes including higher risks of recurrence and mortality (198, 207-210).

Several New Zealand researchers have looked into possible provider delays, leading to worse cancer outcomes in Māori. In two such studies on treatment differences for lung and colon cancers, authors have concluded that Māori were more likely to experience significantly longer delays for treatment compared to non-Māori patients (181, 182). They have also highlighted the higher frequency of defaulted appointments and delays in consent for treatment by Māori, contributing to observed provider delay. However in a publication in the

Lancet in 2006, Harris et al claimed that ethnic discrimination in New Zealand public health institutions, as a major reason for such defaulted appointments and delays in consent by Māori, which adds up towards the ethnic disparity in outcomes for major diseases including cancer (35). This is further supported by two previous studies on asthma and diabetes which have shown that either conscious or unconscious attitudes of healthcare workers have contributed to delay in seeking medical care among Māori (175, 211).

In an effort to reduce delays in cancer treatment the Ministry of Health introduced Faster Cancer Treatment Indicators as targets for timeliness of cancer treatment for all District Health Boards in 2012 (58). According to these indicators cancer treatment is expected to be initiated within 62 days of initial referral and within 31 days from the day a decision to treat the cancer is discussed with the patient. Whether this initiative could reduce overall delays in cancer treatment and ethnic disparities in delay is yet to be seen.

Adherence with treatment and other patient related factors influencing treatment

Completion of cancer treatment including adjuvant therapy and a proper follow up after initial treatment plays an important role in improving overall breast cancer outcome. Evidence from population based studies indicates that poor compliance with adjuvant therapy and missed follow up appointments are important factors negatively influencing breast cancer survival (212). The reasons for differences in compliance among ethnic groups are complicated and it depends on a multiplicity of patient, physician and system related factors (213, 214).

Indigenous populations from different parts of the world have varying views on diseases including cancer that sometimes significantly differ from the western beliefs. Similarly, Māori also have a different view on diseases and treatment, which is based on their culture and beliefs (214). When a Māori woman with breast cancer has to obtain allopathic treatment from a non-Māori provider it has the potential for a conflict with their beliefs and culture, which could result in poor compliance with prescribed treatment. Several studies from New Zealand support this theory, as they have shown poor compliance among Māori with treatment for several chronic illnesses including cancer (157, 215).

One example of importance is adherence for adjuvant endocrine therapy for hormone receptor positive breast cancer. Endocrine therapy has been shown to reduce risks of cancer recurrence for early breast cancer by approximately a half and breast cancer mortality by approximately a third (216). However many women do not get the maximum potential benefit either due to

non-prescription or due to discontinuation of treatment prematurely or due to not maintaining an optimum level of adherence over the duration of treatment, which result in higher recurrences and lower survival rates (217).

Data from the National Breast Cancer Audit of the Royal Australasian College of Surgeons showed that only 81% of NZ women with oestrogen receptor (ER) positive invasive breast cancer to have been prescribed with endocrine therapy in 2008 (218).

Non-adherence with endocrine therapy is common (25-35%) and, is one of the most important areas of sub-optimal breast cancer care (219). Side effects of endocrine therapy, lack of understanding of its benefits which is related to poor health literacy, comorbidities and cost are known barriers to adherence (220). Lower adherence to endocrine therapy has been observed more often among women from ethnic minority groups and lower socio-economic groups in the USA (221). Further, improving adherence to endocrine therapy is an area where substantial cost effective gains are achievable. Several studies have proven the effectiveness of measures to improve adherence with endocrine therapy such as increased patient awareness of its benefits, regular reinforcement of advice and providing supportive care to manage side effects (222).

Multi-disciplinary Team care (MDT care) and Cancer Care Coordinators (CCC's)

Providing breast cancer treatment through a dedicated multi-disciplinary breast cancer care team has been shown to increase the overall quality of care and survival from breast cancer (196, 223). In keeping with this, the Ministry of Health has implemented several initiatives targeted at increasing the proportion of cancers provided with care through MDTs including for colo-rectal, breast and lung cancer.

Recent introduction of identification and flagging of patients at risk for poorer outcome (e.g. due to low socioeconomic status, ethnicity, poor family/social support) through MDTs has met with some success for colo-rectal cancer patients. This strategy is aimed at proactive identification of at risk patients during early part of cancer management and providing them with support to achieve optimal outcomes. However, this requires a comprehensive knowledge of factors associated with poorer outcomes especially those factors which can be most easily improved by healthcare service interventions.

Improved patient navigation through dedicated cancer care coordinators (CCC) has been shown to help reduce delays, especially for women who are at-risk for longer delays which include women of minority ethnicity and low socioeconomic groups (224). These nurses act as a single point of contact for cancer patients. CCCs help to coordinate care, providing continuity of care and support from diagnosis through the course of cancer care. Personalised coordinated care programmes for cancer patients have been shown to improve timeliness of care (225, 226), and patient satisfaction with the level of care and support (227). CCC's have also been shown to reduce inequity in access to care by reducing barriers relating to cultural, language, educational, socioeconomic and geographical factors (228) and thereby to improve quality of the delivery of nursing care.

The Waikato DHB has two full-time CCC's providing support for women with breast cancer since 2009. The Ministry of Health has identified CCC's as a key strategy to increase quality and reduce inequalities in cancer care, and since 2012 has provided funding for all District Health Boards to employ CCC's for management of common cancers in New Zealand (229).

Institutional discrimination

Discrimination based on patient ethnicity, socioeconomic status or residence could impact significantly on these patients who are anyway at risk of worse cancer outcomes. Following a population based study in New Zealand, Harris and colleagues reported that previous experiences of ethnic discrimination in public health setup as an important factor leading to lack of participation of Māori women in cervical and breast screening programmes (230). Despite the absence of further studies to support their claims, the authors have raised an important issue that many have ignored in investigating reasons for ethnic disparities in breast cancer outcome in New Zealand. This issue and its possible impacts are discussed further in next section.

3.3. Understanding key drivers behind ethnic inequities in breast cancer outcomes

Ethnic inequities in breast cancer outcomes in New Zealand appear to be a direct or indirect result of differences in healthcare access and quality of treatment received by Māori compared with NZ European women. This raises the issue as to why Māori women experience greater barriers to access healthcare and once gained access, a quality of care which possibly is inferior to NZ European women. New Zealand has a publicly funded health care system that provides free hospital and specialist care for all citizens with the aim of providing equitable healthcare for all patients irrespective of ethnicity or income. Yet, Māori appear to experience a poorer quality health service compared with NZ Europeans.

Inequities in cancer care are generated within the healthcare system both due to its structural organization as well as due to the way in which healthcare services are delivered. For instance geographical location or segregation of healthcare services could result in longer travel distances or preferential access to some patient groups over others. Further, health insurance status, type of the hospital where care is received and regional variations in quality of care also could contribute to inequities in treatment as a consequence of structural organization of health services (191). Treatment recommendations for a woman diagnosed with a breast cancer would be based upon cancer stage, biological characteristics, comorbidities and patient preference. However, physician perceptions and physician bias also could influence these decisions. Further, patient perceptions, beliefs and expectations, and social and socioeconomic circumstances may influence the treatment process directly or through interactions with physicians and healthcare institutions (191).

Several authors have attempted to disentangle underlying causes for ethnic inequities in cancer care and have proposed different frameworks and theories. Of these, two reviews by Shavers et al and Mandelblatt et al and a report published by Smedley et al standout (96, 191, 231). These two reviews have used similar frameworks to categorise factors into healthcare system factors, factors influencing physician decision process and patient factors, while the report by Smedley et al has categorized factors into system, provider and patient factors (Table 2).

Table 2: Potential barriers interfering with optimal cancer treatment

Category	Specific factors
Healthcare structure (System level)	<ul style="list-style-type: none"> • Geographical location and type of institution • Healthcare funding
Physician level factors (Provider level)	<ul style="list-style-type: none"> • Physician perceptions / Biases • Communication and cultural safety
Patient level factors	<ul style="list-style-type: none"> • Clinical factors • Patient preference / Choice • Social and socioeconomic circumstances

The following section discusses and explores mechanisms contributing to ethnic inequities in access and quality of treatment under broader topics of healthcare structure, physician and patient related factors while acknowledging their significant overlaps and mutual interactions.

3.3.1 Healthcare structure (System level)

The structure of a healthcare organization should be designed in a way to maximally facilitate the provision of care needed for patients, including for cancer. However, organizations of many healthcare systems induce potential barriers to optimum level of care, and include organizational and structural factors, funding and financial forces and regional factors.

Shavers et al, in their review of ethnic disparities in cancer care have identified health insurance as a major system level determinant of ethnic disparities in receipt of healthcare in the US setup, which lacks a proper publicly funded healthcare system (191). A greater proportion of minority Black Africans compared with White in the USA, either lack health insurance or do not have an adequate health insurance policy, which significantly hinders access and to receive quality healthcare. In a fee levying health system, as in the USA, these healthcare access disparities are greater for conditions such as cancer, where the costs are generally greater (232). Other system level factors identified in the USA include provider resourcing, cultural focus of healthcare services and segregation of healthcare services (231).

Access to Cancer Services for Māori, a report compiled by the Ministry of Health has documented several healthcare system level factors creating difficult access and inferior quality of cancer care for Māori (97). This report has identified four main areas contributing to these disparities and includes location of cancer services, cost of cancer care, focus of cancer services, and the composition of the cancer service workforce. These findings are similar to the findings reported by Baxter and colleagues for diabetes care in New Zealand where provision of a health service that does not cater to cultural and societal needs of patients was found to be a major factor (102).

Geographical location

Healthcare service institutions are generally located or concentrated in urban areas which have a high population density. New Zealand in general and to a greater degree in the Waikato, includes large proportions of rural and remote areas. For instance, the Waikato DHB covers an area of over 20,000 square kilometres, yet has only a single major city, Hamilton, where the tertiary hospital providing specialist cancer services is located. This means that some remote dwelling patients in the Waikato have to travel up to 200 kilometres to access specialist cancer care. Differential urban rural distribution of Māori and NZ European populations in New Zealand and in the Waikato means that this invariably contributes to healthcare access inequity between Māori and NZ European patients.

In 1990s, many changes to the health care structure were instituted in New Zealand, and included downgrading or closure of many rural hospitals and centralization of specialist cancer services to larger metropolitan hospitals (233). Although the impact of these changes on access and quality of healthcare for rural and remote populations have not been studied, they obviously have increased travel times and costs, and perhaps longer wait times to access centralized cancer care.

Many healthcare practitioners have identified geographical location or service location as significant issues influencing healthcare service access for Māori as reported in *Access for Cancer Services for Māori* (97). Lack of or inadequate locally accessible healthcare services probably have affected Māori more than NZ Europeans as this has created a barrier for whānau-based care, which is the expectation among many traditional Māori patients.

Healthcare provision based on ethnic segregation of communities is seen prominently in the USA, and is believed to be a factor contributing to ethnic inequalities in cancer care. Although

official segregation of care does not exist anymore, in reality, clear differences in the quality of care provided to Black compared with White communities are observed in the USA (234). Such differences in care are driven mostly by differences in healthcare insurance, which has resulted in better hospitals being located within rich White communities who have better health insurance, while low quality hospitals are being located within Black communities, who are covered mostly by government provided medical insurance.

However, little is known about the impact of health insurance on quality of healthcare or whether there is a difference in quality of service provided by private hospitals which provide care for patients with health insurance, compared with the public system. One such study comes from neighbouring Australia which has reported on relatively poorer quality of healthcare received by public compared with private patients for lung and breast cancer, which was associated with poor long term cancer outcomes (118). Despite the lack of evidence from New Zealand, presence of disparities based on private public private care in Australia, which has a healthcare service similar to New Zealand, strongly indicate the existence of similar disparities in New Zealand. As fewer Māori are known to possess a health insurance policy compared with NZ Europeans (235), this may have created another avenue through which disparities in care are induced, contributing to cancer outcome disparities between Māori and NZ Europeans.

Provision of healthcare through greater Māori provider participation for predominantly Māori communities is considered as a possible way of improving accessibility and providing a better quality service for Māori patients. A similar approach has been reported to be highly successful in improving mammographic screening participation for Māori (143). However, provision of healthcare through Māori providers represent only a small proportion of healthcare delivery presently which is limited almost exclusively to primary health care services (36).

Healthcare funding

Hospital and healthcare expenditure have sky-rocketed especially over the last two decades. Reasons for this increase include increased man-power costs, use of advanced technological equipment, and use of newer more costly treatment. Expanding population, especially the elderly population, with added healthcare needs have further exacerbated the healthcare costs. In the USA, this has resulted in closure or restructuring of many hospitals to maintain financial

viability (236). In New Zealand, as a greater portion of healthcare delivery rests with the public system which is government funded, the implications of cost have been different from the USA. Healthcare reforms in 1990s were introduced to absorb some of these financial strains by reducing cost of healthcare, but have resulted in some major and significant quality issues. For instance, major shortages in provision and delays in radiotherapy for cancer was observed in early 2000s where over 40% of patients experienced delays longer than recommended guidelines (237). Although wait times for cancer care seems to have improved over the last decade, some of the centralized cancer treatment units still experience significant staff and equipment shortages resulting in longer wait times for cancer care.

The primary health care system in New Zealand is highly subsidized, but patient co-payment is also substantial. A visit to a general practitioner may cost between \$20 and \$50 for an adult, and for cancer patients requiring repeated visits this may create a major financial constrain. Cost of primary care has been shown to be the major reason for not visiting a general practitioner when required and has been shown to affect Māori more than NZ European patients (34). While some of this disparity is due to higher proportions of Māori within lower socioeconomic categories, lower rates are seen for Māori even within the same socioeconomic decile, indicating the presence of further barriers to primary care for Māori. Costs of primary care is likely to further exacerbate financial constraints of cancer patients, due to additional costs of cancer care including travel for cancer treatment, at a time when income may be lost due to being away from work.

3.3.2 Physician level factors (Provider level)

Healthcare service expectations of Māori may significantly differ from beliefs and attitudes of a non-Māori physicians providing care in a European/Western designed healthcare institution. Poor communication due to cultural differences, knowledge, attitudes and behaviours may further exacerbate this discordance, ultimately resulting in a quality of care which falls well below patient expectations and perhaps, recommended standards. These factors may create an impression in Māori that they are being subjected to discrimination, and rates of self-reported discrimination in Māori which is about ten times higher than NZ European patients, support this premise (238). Perceived discrimination among Māori patients is also likely to be transferred to other members within the community creating a general reluctance to seek care from mainstream public healthcare institutions.

Physician belief and attitudes

Health care providers play a pivotal role in ensuring access to and quality of cancer care for their patient populations, and provider recommendations are one of the most consistent predictors of receipt of early detection and other cancer services (239). Findings from several studies from the USA suggest that a physician's perception of patients may be influenced by non-clinical characteristics including ethnicity, religion and socioeconomic status (240, 241), which may then be manifested in differences in patient referral patterns and treatment recommendations (241, 242). In a survey of physicians from the USA, it was reported that physicians were more likely to have negative perceptions of African Americans and persons of low or middle socioeconomic status than of Whites and persons of high socioeconomic status, respectively (240). Differences in attitudes of physicians towards patients may impact on patient care, and these perceptions are likely to contribute to ethnic disparities in cancer treatment and resulting differences in cancer outcomes.

Physician beliefs could influence his/her decision making process through two main mechanisms. First, the physician may believe that a particular group of patients (ethnic or socioeconomic) are non-compliant, late-presenting and defaulting clinic visit type of patients due to stereotyping (243). Barriers to access care including cost, travel, time off work and caring for dependants would explain most of such behaviours, but unfortunately creates a prejudice among some physicians due to lack of understanding of these circumstances. On the other hand some other physicians may make decisions for these patients genuinely believing that they are making the best decision for that particular patient group, but due to lack of understanding of their values and culture, makes a decision that is either not optimal or not acceptable to the patient. Whatever the mechanism that is involved it finally ends up creating a process that leads to sub-optimal quality of care for these patients.

Communication and cultural safety

Physician-patient communication is another key domain in determining access to care. The quality of communication on cancer care has been noted to vary by physician gender, by patient race or ethnicity, and by patient's socioeconomic status (244-246). For example, in the USA physicians discuss mammography less often with their Hispanic patients than with their non-Hispanic patients, and Black patients are less likely to receive advice about cancer screening in general than Whites who see the same physician (247).

In New Zealand, similar quality issues in relation to communication between Māori patients and health care providers have been reported. For instance, at primary care level, general practitioners on average have shorter consultations with Māori and have lower levels of rapport with Māori compared with NZ European patients (99). This contradicts with expectations of Māori patients which include desire for careful listening, personal engagement and face-to-face communication with health professionals (248). Further, Māori patients have an expectation for them to be identified as Māori which enable them to participate in health decision making and service engagement while maintaining their cultural and ethnic identity (249).

Ensuring cultural safety provides the essential foundation that creates a suitable background for effective communication. A commonly accepted definition of cultural safety is ‘an environment which is safe for people; where there is no assault, challenge or denial of their identity, of who they are and what they need’. It is about shared respect, shared meaning, shared knowledge and experience, of learning together with dignity, and truly listening (250). For Indigenous people including Māori, cultural safety is essentially a basic right recognised at international and local levels (251). Lack of recognition and emphasis placed on this important issue, however, appeared to have interfered with effective communication with Māori patients within the mainstream healthcare system.

3.3.3 Patient level factors

Clinical factors

Patient clinical factors including comorbidity, obesity and smoking are known to influence cancer treatment decisions mostly due to reduced tolerability of treatment or due to risk of significant complications. Indigenous and ethnic minority patients are more likely to have higher levels of comorbidity, obesity and smoking and hence are at a greater risk of not receiving optimum cancer treatment (31). Studies have shown that Indigenous and ethnic minority patients including Māori, with these risk factors to have received sub-optimal care which is not adequately explained by presence of these conditions (67). Comorbidity and obesity in many occasions are not contraindications for primary or adjuvant breast cancer treatment, although change in regimens may be required (252). It appears that presence of these risk factors has influenced treatment decision process, with a greater preference for not to use optimum therapy, especially for Indigenous and ethnic minority patients.

Patient choice

Health beliefs and attitudes influence health-care behaviour (253). On the other hand, health beliefs and attitudes are influenced by culture, education and health literacy of patients. For example, the prevalence of fatalistic and nihilistic attitudes towards cancer have been shown to be higher among ethnic minority populations than White populations in the USA (254). A proportion of the higher treatment refusal rates reported among ethnic minorities in the USA has been demonstrated to be due to differences attitudes towards treatment among these populations (255). Treatment refusal however, may also be influenced by number of other factors including poor provider-patient communication, lack of trust, provider patient differences in beliefs and expectations and due to competing priorities.

Several New Zealand studies have reported on higher rates of cancer treatment refusal in Māori compared with non-Māori patients (4, 182). However, as noted in the *Unequal Impact – II* report, patient choice is only a minor contributor for treatment differences and is an unlikely cause for cancer survival disparities in New Zealand (4).

Social and socioeconomic circumstances

Lower socioeconomic has a direct correlation with poorer cancer survival for many cancers including breast cancer (191). Poor cancer outcomes among Māori is known to be influenced to an extent by the higher prevalence of lower socioeconomic status among Māori compared with NZ Europeans.

Lower social or socioeconomic circumstances are known to interfere with proper access to healthcare services and are believed to be a major reason for poorer cancer outcomes in these patients (4, 34). In the USA, socioeconomic status is closely correlated with health insurance which determines access and choice of healthcare services (84, 118). Lack of time off work, travel time, cost or lack of transport and lack of social support to care for dependants are some of the common reasons influencing patients of lower socioeconomic states not to seek medical care or delay seeking medical care. Although specialist care in public sector is provided free of charge in New Zealand, co-payments involved with primary care and payments required for specialist care in private are some of the other reasons, which may influence Māori patients to receive an inferior quality of care compared with NZ European patients (31).

3.4. Conceptual framework

The discussion presented up to this point suggests that a considerable number of potential causal explanations for inequities in breast cancer outcomes between Māori and NZ European women. Drawing from the literature, a conceptual framework for Māori - NZ European breast cancer inequities was developed and is presented in Figure 12. It is evident from the literature that ethnicity and socioeconomic status are intermingled in their effect on stage at diagnosis and survival/mortality; as such the conceptual framework illustrates the pathways in which these two variables influence stage and survival outcomes.

Ethnicity and socioeconomic status could be considered to be influencing stage at diagnosis and survival/mortality through three main mechanisms; patient characteristics, cancer biology and the healthcare system/treatment.

This thesis aims to bring together all these characteristics in an attempt to provide explanations for observed breast cancer inequity between Māori and NZ European women. Most of these factors could be influenced by access to the social determinants of health, including racism, and access, timeliness and quality of health care which can be influenced by health services inequities. Initially, the impacts of ethnicity and socioeconomic status on cancer stage at diagnosis, screening participation, cancer biological characteristics and treatment differences are explored in detail to identify inequities in these key areas. The final analysis attempts to bring together all findings from previous analyses into a single model to describe and quantify the impacts of each of these factors towards the observed survival inequity between Māori and NZ European women.

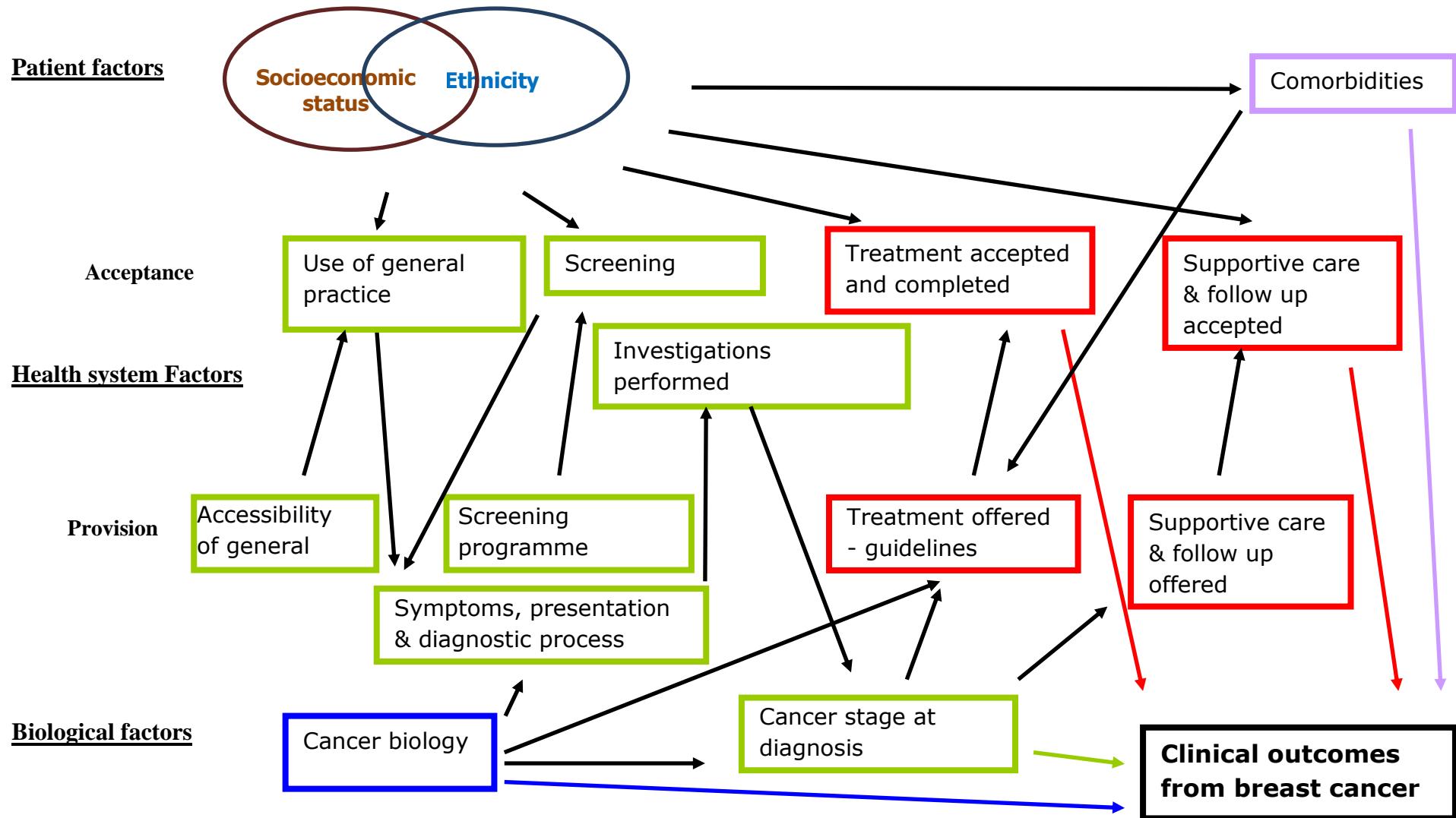


Figure 12: Conceptual framework depicting complex interaction of patient, health system and cancer related factors influencing clinical outcomes from breast cancer

Chapter 4. Design and Methods

4.1. Study population

The target population for this study comprised of all newly diagnosed women with primary incidental breast cancer while being a resident within the Waikato District Health Board (DHB) area during a 14-year period from 01/01/1999 to 31/12/2012. Date of diagnosis was defined as the first date of obtaining tissue/cells from the primary tumour or its secondary deposits for confirmation of diagnosis of the index breast cancer.

Target population of women were primarily identified from breast cancer records for the Waikato DHB area included in the New Zealand Cancer Registry (NZCR), for the period from 01/01/1999 to 31/12/2012. Additionally clinic records, operation records, multi-disciplinary meeting records, oncology, palliative care and other private and public hospital records were accessed to supplement the NZCR list and also to confirm eligibility of each woman to be included in this study.

Study eligibility criteria:

1. Newly diagnosed women with primary in-situ or invasive breast cancer between 01/01/1999 and 31/12/2012 (ICD-9 diagnosis codes 174.0 to 174.9, ICD-10 diagnosis codes 50.0 to 50.9).
2. Morphology consistent with or specific to primary breast cancer originating from the epithelium of ducts or lobules of the breast. Other varieties of cancer originating from supporting connecting tissues (i.e., phyllodes tumours and sarcomas) were excluded.
3. Absence of a breast cancer diagnosis prior to 1999 (including the contralateral breast).
4. At the time of the diagnosis, patient residing within the Waikato DHB area or within the current geographical limits defined by the Waikato DHB
5. Diagnosis of breast cancer made prior to death/ post-mortem

(Note: women who had primary surgery and/or follow up outside Waikato DHB area were included if all the above criteria were fulfilled)

4.2. Data sources:

Data for this study were primarily derived through two sources and were supplemented by data from several other sources.

For women diagnosed after 01/01/2005, the WBCR was the main data source. For women diagnosed between 01/01/1999 and 31/12/2004, a retrospective notes review was the main data source. This review included electronic and hard copy clinical notes from both private and public hospitals.

4.2.1 The Waikato Breast Cancer Register (WBCR):

The WBCR is a prospectively maintained database that includes all invasive breast cancers in women who were residents of the Waikato District Health Board area at the time of diagnosis. The WBCR was established in 2005 and included a process of individual patient consent. The requirement for patient consent was waived off in 2012. Eligible women with newly diagnosed breast cancer for the WBCR are identified through clinic records, operation records, multi-disciplinary meeting records, oncology, palliative care and other private and public hospital records.

4.2.2 Retrospective data collection:

All women with newly diagnosed cancer between 01/01/1999 and 31/12/2004 were identified from the NZCR and by accessing clinic records, operation records, multi-disciplinary meeting records, oncology and palliative care records. All clinical records (i.e., hard copy and electronic) for these women were accessed and relevant information was extracted into a data collection form similar to the one used for the WBCR data collection. Subsequently, this information was transferred into the WBCR database. Further, data for women who were diagnosed after 2005, but were not included in the WBCR initially, either due to lack of individual consent (i.e., patient deceased prior to consent) or declined consent were also collected retrospectively. At the end of this process, a complete dataset of women with newly diagnosed primary breast cancer between 01/01/1999 to 31/12/2012 was assembled.

4.2.3 Other data sources:

New Zealand Cancer Registry (NZCR):

The NZCR is the national population based cancer registry that records all primary cancers (excluding non-melanoma skin cancers) in New Zealand. Under the Cancer Registry Act 1993(256), all newly diagnosed cancers are legally required to be reported to the NZCR by the person in charge of the reporting laboratory. Thus, a copy of the pathology report for each newly diagnosed cancer is sent electronically to the NZCR which is the major source for new cancer registrations. Other sources of new cancer registrations include discharge reports from publicly funded and private hospitals, death certificates and autopsy reports. These non-histological sources account for less than 10% of all cancer registrations. The Ministry of Health is responsible for funding and maintaining the NZCR. The NZCR includes a quality assurance process which is through cross-referencing with data from other population registers such as the National Minimum Data Set, Mortality Register and other national collections.

Mortality records:

Mortality data were obtained from the National Mortality Database (also known as the Mortality Collection). The mortality database is maintained by the Ministry of Health and collects information on all deaths recorded in New Zealand (257). The underlying cause of death is recorded according to the International Classification of Diseases (ICD) and WHO Rules and Guidelines for Mortality Coding (109).

Death records with cause specific data were available in the Mortality Collection up to the end of 2013. For deaths during 1999, cause of death was coded according to the ninth revision of the International coding of diseases (ICD-9) and for deaths from 2000 onwards, ICD-10 system was used (258).

Pathology Records:

Pathology reports for confirmation of diagnosis and for excised primary tumours was obtained from patient clinical records, reporting laboratory, or if not available from these two sources, from the NZCR. For over 98% cancers, a pathology report (i.e., a copy of the authorized pathology report issued by a pathologist) was available from patient clinical records or from the reporting laboratory.

National Pharmaceutical Database:

Data records for endocrine therapy prescriptions were obtained from the National Pharmaceutical database for analyses of adherence/compliance with endocrine therapy. However, these records were found to be adequately complete (i.e., with a completion rate over 95%) only from 2005 onwards. Therefore these analyses were performed only for women diagnosed from 2005 onwards, and women who were diagnosed prior to 2005 were excluded. Although this substantially reduced the sample size and follow up duration, it was deemed to be the best option to minimize bias, and maximize the quality of the analysis.

National Breast Cancer Screening Database (*BreastScreen Aotearoa*):

The National Breast Cancer Screening Programme, BreastScreen Aoearoa (BSA) was established in 1999, and since has collected details of all screen detected and interval cancers (i.e., cancers diagnosed within 24 months from the last screening mammogram). These data were used to supplement and to confirm all cases of breast cancer included in the study as screen detected, interval or non-interval non-screen detected. Further, there were 110 women who were diagnosed through opportunistic screening mammograms arranged by physicians outside the BSA programme. These women were also included as screen detected cancers for analysis.

4.3. Data collection:

4.3.1 Ethics approval:

Ethical approval for this study was obtained from Northern ‘A’ Health and Disability Ethics Committee (Ethics Ref. 12/NTA/42) to collect breast cancer related information from all historical cases without individual patient informed consent. Additionally, approval was obtained from the Kaumatua Kaunihera Research Subcommittee of the Te Puna Oranga (Māori Health Service) of the Waikato District Health Board.

It was decided not to obtain individual patient consent for this study as we were analysing historical data from patients diagnosed with breast cancer which will have no influence on their disease outcomes. Furthermore, this was a large study of which many of the individuals have already died, but whose information was essential to avoid bias in the study. Practically, such consent would not be achievable for many and might also have caused significant difficulties to families of others.

4.3.2 The Waikato Breast Cancer Register (WBCR)

The WBCR has a standardized protocol for identification of eligible women, data collection and data entry. Eligible women are initially identified at the time of diagnosis from public and private hospitals in the region. Breast cancer data for these women are collected prospectively using data collection forms during each step of diagnostic, treatment and follow up pathways. In addition, all clinical and pathology reports for each eligible woman are accessed and relevant presenting, diagnostic, treatment (i.e., primary and adjuvant therapy) and follow up information are extracted into a structured format. Next this information is entered into the WBCR database which is maintained in a Microsoft Access® database by trained data entry personnel. Each woman is followed up prospectively through public and private clinic follow ups and, outcomes including cancer recurrence and death are recorded.

Validity and completeness of the WBCR records are compared annually with breast cancer records for the Waikato area from the NZCR. Further, data are validated with the Royal Australian College of Surgeons (RACS) breast section audit data base. Participation in this audit database and provision of data on breast cancers managed by each surgeon is compulsory for BSA surgeon accreditation.

Quality assurance of the WBCR is maintained through an audit process where at least one in ten entered records and all records for deceased women are audited by a breast surgeon. At present, the WBCR is the most complete regional breast cancer register in New Zealand with a data completion rate of over 98% (259, 260).

4.3.3 Retrospective data collection:

Once eligible women were identified as described above, a process similar to the WBCR was used to collect breast cancer data. Most of clinical data were extracted through patient medical notes review, which included pathology reports for all women. Abstracted data from medical notes review were recorded in a standardized data collection form that was in place for the WBCR prospective data collection and subsequently transferred into the WBCR database.

Retrospective data collection was performed during 2012 and 2013.

Of the 1131 eligible women identified for this period (1999-2004), breast cancer data for 31 (2.7%) women could not be traced and, hence were excluded from analysis.

4.3.4 Data preparation:

First, data from the retrospective data collection were combined with the WBCR data in its Microsoft Access database. Follow up information including death and cause of death, local or metastatic tumour recurrence and whether free of disease at last known follow up was also recorded. Next, all relevant data from this database were exported into a Microsoft Excel datasheet where data cleaning was undertaken. This procedure created a dataset with a single observation for each patient or for each cancer episode for women with metachronous cancer (i.e., second new breast cancer) during the study period. Additional linking of this completed dataset with data from the NZCR (for stage comparison and validation), National Pharmaceutical database (for adherence to endocrine therapy), BreastScreen Aotearoa (for comparison of differences in screen detected versus non-screen detected cancer) and National Minimum Dataset (for comorbidities) were done in Microsoft Excel datasheet using patient NHI and date of diagnosis.

Once cleaning, integration and data linkage were completed, the dataset was imported to SPSS Version 22 where all statistical analyses were performed (261).

4.4. Variables:

4.4.1 Exposure variable - Ethnicity:

Ethnicities (or Race) are constructed categories that may reflect history, geographic origin, cultural identity, socioeconomic status and sometimes genetics and biology, all in varying degrees. Human geneticists and anthropologists agree that pure human races do not exist (262). However, internal and external racial/ethnic identifications allow races/ethnicities to exist and sustain as social constructs (263). Irrespective of their origins or basis of formations, different racial/ethnic groups have substantially different rates of diagnosis, treatment, and outcome in a variety of diseases, including cancer in many different countries (4, 10, 11).

According to the definition used by New Zealand Statistics, ethnicity is the ethnic group or groups that people identify with or feel they belong to, which is a measure of cultural affiliation, as opposed to race, ancestry, nationality or citizenship. Using this definition, ethnicity is seen as self-perceived and people can belong to more than one ethnic group (264).

Although the terms race and ethnicity are sometimes used interchangeably, in many instances they have different meanings. In general, ethnicity refers to shared cultural practices, perspectives, and distinctions that set apart one group of people from another. However, the definition of ethnicity differs by country. For example, in neighbouring Australia ethnicity is defined as relating to or peculiar to a human population or group, especially one with a common ancestry, language, etc., or relating to the origin, classification, characteristics, etc., of such groups.

In New Zealand context, Māori and NZ European are recognized as two ethnic, but not racial groups. In fact many who identify themselves as Māori have a significant European inheritance. Therefore this thesis refers to Māori, European and other groups included in this study as ethnic and not as racial groups.

Up to the population census in 1981 Māori were defined as those with half or more Māori ancestry. But from the population census in 1986, the question relating to the ethnic origin allowed people to identify themselves using one or more of the following options: European, Māori, Pacific, Chinese, Indian or other ethnic origin irrespective of their ancestry.

Three approaches for assigning Māori ethnicity in health research are documented. First approach is to assign Māori ethnicity based on documented or self-identified ethnicity at a given point of time. This method has been shown to be associated with high risk of

misclassification leading to a significant undercounting for Māori. Second method, the ‘ever-Māori’ approach has the least likelihood of undercounting, but carries the risk of over-counting Māori especially for women who had multiple episodes of contact with health care system. This method has been shown to provide ethnicity distributions close to New Zealand Census Mortality Study (NZCMS) adjusted estimates for epidemiological studies, which is considered to be the gold standard (133). A third approach, that is ‘ever-Māori’ up to a given point in time balances biases of those two approaches as it minimizes risks for both over and under-counting.

Ethnicity was self-assigned by the patients for prospective data included in the WBCR; each woman was requested to fill the ethnicity field in the data collection form during consent process. For retrospective data collection (pre 2004) ethnicity data were obtained from patient clinical records maintained in electronic and hard copy formats, as per the Ministry of Health ethnicity data protocols (265).

For patients included in the prospective database, self-identified ethnicity was considered as the final ethnicity, while for retrospectively data collected women, Ever-Māori at a given point in time approach were used. With this approach, if any health service document has identified the woman of interest as Māori up to the point of diagnosis, she was assigned Māori ethnicity.

Ethnicity was recorded in the database using standard ethnicity codes from New Zealand Statistics. For patients with more than one recorded ethnicity, a prioritization system was used to assign ethnicity, giving highest priority to Māori followed by Pacific, Asian, Other (except NZ European) and NZ European, based on New Zealand Statistics ethnicity classification system. Subsequently, ethnicity was grouped by four categories for analysis; Māori, Pacific (including Samoan, Cook Island Māori, Tongan, Niuean, Tokelauan, Fijian and other pacific island), NZ European (European not further defined, NZ European, other European) and Other (Asian not further defined, South East Asian, Indian, Chinese, other Asian, Middle Eastern, Latin American / Hispanic, African and other).

Table 3: Definitions of socio-demographic, tumour and treatment characteristics

Characteristic	Variable	Values	Comments / Definitions
Ethnicity	Ethnicity	Māori	For women diagnosed after 2005 - Self-identified ethnicity from the WBCR
		NZ European	
		Pacific	For women diagnosed during 1999-2004 - Self-identified ethnicity recorded in health service records up to the time of diagnosis using “Ever-Māori” approach
		Other	
Time origin	Date of diagnosis	From 01/01/1999 to 31/12/2012	Date of obtaining tissue (e.g. core biopsy)/cells (e.g. FNAC) from the primary tumour or secondary deposits that confirmed the diagnosis of breast cancer
Demographics	Age at diagnosis	20-99 years	Based on date of birth and date of diagnosis
	Year of diagnosis	1999-2012	Based on date of diagnosis
Tumour characteristics	Stage at diagnosis	TNM system – stages 0 and I to IV SEER– localized, regional & distant	
	Tumour size	0-210 mm	Maximum tumour diameter based on histopathology report
	Number of positive nodes	0-48	Total number of regional lymph nodes found to be invaded by tumour (macro or micro metastases, but excluding lymph nodes with only isolated tumour cells) based on histopathology report
	Tumour grade	Grade I-III	Based on the Elston and Ellis modified Scarff-Bloom-Richardson breast cancer grading system as reported in the histopathology report
	Histopathology type	Ductal, Lobular, Mixed, Other	Derived from histopathology report in accordance with World Health Organization Classification of tumours of the breast

Characteristic	Variable	Values	Comments / Definitions
Patient characteristics	Hormone receptor status - Oestrogen (ER) & Progesterone (PR)	Positive / Negative	Based on the results of immunohistochemistry tests as reported in histopathology report
	HER-2 status	Immunohistochemistry – Positive, Equivocal or negative Fluorescent in-situ hybridization – Positive or Negative	Based on Fluorescent In-Situ Hybridization (FISH) test or when this was not available, on immunohistochemistry
	Lympho-vascular invasion (LVI)	Positive or negative	Based on histopathology report
	Comorbidity score	0-8	According to the Charlson Comorbidity Index based on documented comorbidities at the time of diagnosis
Diagnosis	Body mass index (BMI)	1.8-59.9	Calculated using body weight and height where available
	Smoking status	Non, ex-smoker or current smoker	As documented at the time of diagnosis
	Mode of detection	Screen detected Non-screen detected Interval cancer	Screen - detected through a screening mammogram performed on an asymptomatic woman Non-screen - cancer diagnosis process initiated following symptoms directly or indirectly related to the breast cancer Interval - if diagnosis within 24 months from last screening mammogram
Health care access	Small area deprivation	1-10	Based on NZ Deprivation Index 2006. Deprivation deciles were aggregated to form quintiles (1 to 5) for analysis
	Residence	Urban, semi-urban, rural	Based on NZ Statistics Urban/Rural classification
	Distance from hospital	0-25, 25-50, 50-100, >100km	Distance from residence to tertiary hospital in Hamilton
	Facility type	Public or private	Facility type where primary cancer surgery was performed

Characteristic	Variable	Values	Comments / Definitions
Surgical treatment	Type of primary operation to the breast	Mastectomy, breast conserving surgery (BCS) or no primary surgery	Mastectomy - complete surgical removal of the ipsilateral breast, BCS - any operation for the breast cancer which was less than a mastectomy, No primary surgery - When no primary surgical excision done due to patient not fit for an operation, advanced nature of cancer or due to patient declining
	If primary mastectomy, decision taken by	patient / surgeon	Based on clinical records on decision making process for mastectomy. This information was clearly available for only 79.9% of women who underwent primary mastectomy
	Type of operation to the axilla	Sentinel node biopsy (SNB) based management, primary axillary node dissection (ALND), axillary sampling or no axillary surgery	SNB – if a radio isotope or blue dye or both have been used to ascertain nodes draining the breast/tumour. ALND – If standard level II or III dissection been done, Node sampling – where only enlarged discrete nodes were removed without a formal ALND
	Re-excision	Yes / No	When a secondary wider excisional surgery is performed on the ipsilateral breast following a BCS to clear any residual tumour and to achieve a cancer free margin
	Breast reconstruction	Yes / No	Major breast reconstruction (immediate or delayed) performed following a total mastectomy
	Timeliness of surgery	0-364	Time gap from the date patient informed of the diagnosis of breast cancer to the date of primary surgical operation
Adjuvant Chemotherapy	Received chemotherapy	Yes / No	If the patient received a single or more doses of chemotherapy prior to or after surgery
	Timeliness of chemotherapy	10-232 days	Time gap in days from most invasive surgery for cancer to initiation of chemotherapy

Characteristic	Variable	Values	Comments / Definitions
Adjuvant Radiation therapy	Received radiotherapy	Yes / No	If the patient received a single or more fractions of radiotherapy to the breast or chest wall prior to or after surgery
	Timeliness of radiotherapy	17-364 days	Time gap from most invasive surgery for women not receiving chemotherapy and for women receiving chemotherapy time gap from chemotherapy completion to radiotherapy
Adjuvant Endocrine therapy	Received endocrine therapy	Yes / No	If the patient has obtained endocrine therapy from a pharmacy after the date of diagnosis based on Pharmaceutical Database records
	Adherence to endocrine therapy	Good / Sub-optimal	Good – if medication possession ratio (adherence index) was $\geq 80\%$ over the follow up period up to 5-years or up to death, whichever was shorter. Sub-optimal – if medication possession ratio was $< 80\%$
Biological therapy	Received biological therapy	Yes / No	If a woman has received adjuvant biological therapy (Trastuzumab) for a HER-2 amplified cancer

4.4.2 Tumour characteristics

Stage at diagnosis

Many different staging systems exist for staging of breast cancer. Tumour, Node and Metastasis (TNM) system and the Surveillance Epidemiology and End Results (SEER) program cancer staging definitions are the commonly used of these systems (266, 267). This study primarily used the TNM staging system which is used by a majority of clinicians and was also used in many similar studies, which provided an opportunity for comparison. The SEER system was used in situations where comparisons were performed with the NZCR which primarily uses the SEER system.

Cancer stage was ascertained based on all available clinical, imaging (within four months before or after date of diagnosis) and pathology information from tumour excision.

TNM staging:

TNM system published by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) provides a universal approach to staging of cancer. The TNM system uses status of primary tumour (T), lymph node involvement (N) and metastatic deposits (M) to ascertain cancer stage. TNM summary stages (stages I to IV) are formed based on different TNM combinations (Table 4).

Table 4: TNM staging system for staging of breast cancer

TNM stage	Description
Tumour (T)	
Tis	Carcinoma in-situ
T1	Invasive tumour 20mm or less in greatest dimension
T2	Invasive tumour more than 20mm but less than 50mm in greatest dimension
T3	Invasive tumour more than 50mm in greatest dimension
T4	Invasive tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).

Nodes (N)

N0	Regional nodes not involved
	Micro-metastases or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
N1	
N2	Metastases in 4–9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the <i>absence</i> of axillary lymph node metastases
	Metastases in ten or more axillary lymph nodes; or in infra-clavicular (axillary level III) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the <i>presence</i> of one or more positive level I, II axillary lymph nodes; or in >3 axillary lymph nodes and in internal mammary lymph nodes with micro-metastases or macro-metastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
N3	

Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Stage grouping

Stage I	T1N0M0, T1N1micM0
Stage II	T1N1M0, T2N0M0, T2N1M0, T3N0M0
Stage III	T1-2N2-3M0, T3N1-3M0, T4N0-3M0
Stage IV	Any T, Any N, M1

The TNM staging is generally performed at two points for a majority of breast cancers. First is done (clinical TNM / cTNM) once the diagnosis is confirmed prior to treatment. Second or pathological TNM staging (pTNM) is done based on histopathology report from the primary tumour excision. Additionally in situations where a patient undergoes neo-adjuvant therapy (up-front chemotherapy or endocrine therapy prior to surgical excision) clinical staging is performed for a second time prior to surgery and is denoted as yTNM.

For this study, where ever it was available, pTNM stage was considered as the final tumour stage. In situations where pTNM was unavailable; for example in situations where primary surgery was not performed, or if a patient has received neo-adjuvant therapy, cTNM was considered as the final cancer stage. For prospective data collection AJCC/TNM 7th version was used and for retrospective data (pre 2004) 6th version was used.

SEER cancer stage (Extent of disease):

The SEER program cancer staging definitions (Table 5) are published by the United States National Cancer Institute and are preferred by many cancer registries for cancer stage recording including the NZCR, due to its simplicity (266). This system summarized cancers into localized, regional or distant.

The TNM and the SEER system are neither comparable nor interchangeable. For example, invasion into pectoralis major muscle is considered as regional disease in the SEER system while the TNM system does not acknowledge this fact in its classification.

The NZCR primarily uses the SEER program cancer staging definitions published by the National Cancer Institute of the USA (266). For each reported case of cancer to the NZCR, stage is manually determined by experienced cancer coders, primarily using pathology report from the primary tumour excision together with additional information from hospitalization records, death certificates and autopsy reports. Stage is assigned for each cancer based on staging data available at the end of the first course of therapy, or within four months of the date of diagnosis, whichever is earlier (268).

Table 5: SEER summary staging system for staging of invasive breast cancer

SEER summary stage	Description	Equivalent TNM stages
Localized	Invasive tumour confined to the breast	T1-4 N0 M0
Regional	Invasive tumour invading to adjacent tissue (i.e. skin or chest wall including pectoral muscle ^a) or regional lymph nodes	T4 N0 M0, Any T N1-3 M0
Distant	Tumour with distant metastasis	Any T, Any N, M1

^a Pectoral muscle invasion not recognized as local invasion in the TNM system

Cancer grade:

Invasive tumour grade was defined according to the Elston and Ellis modified Scarff-Bloom-Richardson breast cancer grading system (269). Tumour grades reported as; well, moderately or poorly differentiated were considered as corresponding to Scarff-Bloom-Richardson grades 1, 2, and 3 respectively. As tumour grading requires a histological specimen, women for whom the diagnosis was confirmed only on cytological features from a FNAC and has not had further biopsy, grading was unavailable. There were 201 (7.1%) women for whom the cancer grade was not available due to this reason. Significant proportions of these women had either advanced cancers or were deemed to be too ill for further investigations or treatment.

Histopathology:

Invasive or in-situ cancers arising from either ducts or lobules of the breast only were included and histologic types of the tumours were recorded in accordance with World Health Organization Classification of tumours of the breast. Histopathology was classified into ductal, lobular, mixed or other for analysis. Histopathology type was unavailable for women on whom the diagnosis was made based only on cytology (FNAC).

Hormone receptor status:

Oestrogen (ER) and progesterone (PR) receptor status was determined based on the results of immunohistochemistry tests and classified as positive or negative. ER status was missing from 60 (2.1%) and PR status was missing from 113 (4%) women with invasive cancer.

Human Epidermal Growth Factor Receptor type-2 (HER-2) status:

HER-2 status was based on Fluorescent In-Situ Hybridization (FISH) test or when this was not available, on immunohistochemistry (270). Immunohistochemistry results were available as positive, equivocal or negative while FISH reports which are more specific report as HER-2 positive or negative.

Trastuzumab (Herceptin) for adjuvant treatment of HER-2 amplified early breast cancer became fully funded through the public health system in New Zealand in 2007 (61), and assessment of HER-2 status has only been routine in New Zealand since then. This has resulted in a relatively high rate of missing HER-2 data in our study, especially among women

diagnosed with breast cancer prior to 2007. Although the overall missing HER-2 rate was 26.2%, missing rate was only 4.3% among women diagnosed after 2006.

Lympho-vascular invasion:

Lympho-vascular invasion (LVI) refers to invasion of lymphatic spaces, blood vessels, or both in the peri-tumoural area by tumour emboli which are critical steps in metastasis. LVI is routinely reported for all invasive cancers where tissue was available for histopathological analysis. Hence, similar to grade and histology type, this was missing for women for whom the diagnosis was made only on cytology from FNAC.

4.4.3 Patient characteristics:

Comorbidities:

Any significant coexisting medical conditions present or detected at the time of breast cancer diagnosis were considered as comorbid conditions. Comorbid conditions were identified from review of medical and anaesthetic records, multi-disciplinary team meeting records and from oncology records. This was further supplemented with comorbidity data from the National Minimum Dataset (NMDS) which include records of comorbid conditions documented during all public and private hospital inpatient episodes. Past conditions that have completely resolved and have no known significant long term consequences (e.g. appendectomy, cholecystectomy) were excluded.

The CCI uses 19 medical conditions, each allocated a weight of 1 to 6 depending on the adjusted relative risk of 1-year mortality, and added together to give an overall score. The CCI has been validated in a cohort of breast cancer patients with the 10-year mortality rate as an endpoint (152). The CCI score was categorized into 0, 1-2 and 3+ for analysis.

(A group of researchers led by Prof. Diana Sarfati at the University of Otago is conducting a nationwide study (C3 study) which is aimed at identifying the impact of comorbidity on ethnic disparities in cancer outcomes in New Zealand. The WBCR has also contributed its data to this study which will publish its final findings in the near future. In light of this large ongoing study, impact of comorbidities is not studied in great detail in this thesis, although comorbidity is considered as an important covariate and adjustments done accordingly.)

Smoking status:

Smoking status was denoted as non-smoker, ex-smoker or current smoker based on records from the WBCR (patient declared during consent process) or from medical notes review for retrospectively data collected women. Smoking data were missing for 217 (7.6%) women with invasive cancer.

For analysis including survival modelling, missing smoking status was considered as a separate categorical variable. A separate sensitivity analysis was also performed using imputed smoking data for these missing cases. Imputation was done using variables including age, ethnicity, residence status (urban/rural), deprivation and comorbidity. This analysis yielded results much similar to the first analysis where a separate missing category was used.

Survival analysis was repeated using only cases with complete data for all variables and the results of this analysis was also found to be almost similar to the full dataset.

Body mass index (BMI):

Weight and height data for each woman was documented as measured at or closest to the time of diagnosis. BMI was calculated by dividing weight in kilograms by square of height in meters. Both height and weight data were available only for 72.2% women with invasive breast cancer. Missing BMI was disproportionately higher for women not undergoing primary surgery (40.5%). For analysis, missing BMI status was considered as a separate categorical variable. However a selection bias is likely and hence caution is needed in interpreting these results.

4.4.4 Health care access

Health care access parameters were determined based on individual patient's address at the time of diagnosis. This was used to assign area level socioeconomic deprivation, urban/rural residential status and to determine distance from the health care facility.

Area level deprivation

Socioeconomic deprivation status of each woman was determined using the New Zealand Deprivation Index 2006 (NZDep06) (271). The NZDep06 measures deprivation level based on place of residence at the time of cancer diagnosis. This index uses nine variables (benefit income, employment, household income, communication, transport, support, qualifications, living space, and home ownership) as measured during the 2006 national census. The NZDep2006 has created small areas (mesh-blocks covering a population of approximately 100) in a geographical map, on a deprivation scale from 1 to 10; 10 represents the most deprived 10% of New Zealand areas, while 1 represents the least deprived 10% of areas.

Each patient's physical address at the time of diagnosis was used to assign each patient into an area of deprivation. For comparisons each two consecutive deciles were combined together to form five categories i.e. 1 and 2 – least deprived, 9 and 10 – most deprived.

A small number of area units are not included in the New Zealand Statistics concordance file. For women from these areas a deprivation decile was derived using the same method as used by the New Zealand Statistics. That is, for each census area in question, the population-weighted average NZDep score was calculated from all the mesh blocks that made up that area, and this NZDep score was then used to allocate the appropriate NZDep2006 decile.

Residential status:

Urban / rural residential status was determined based on individual residential address according to the Statistics New Zealand's urban rural classification system (Figure 13). This is a seven-level classification which allocates each census area based on both population size and mobility or access to urban amenities and services.

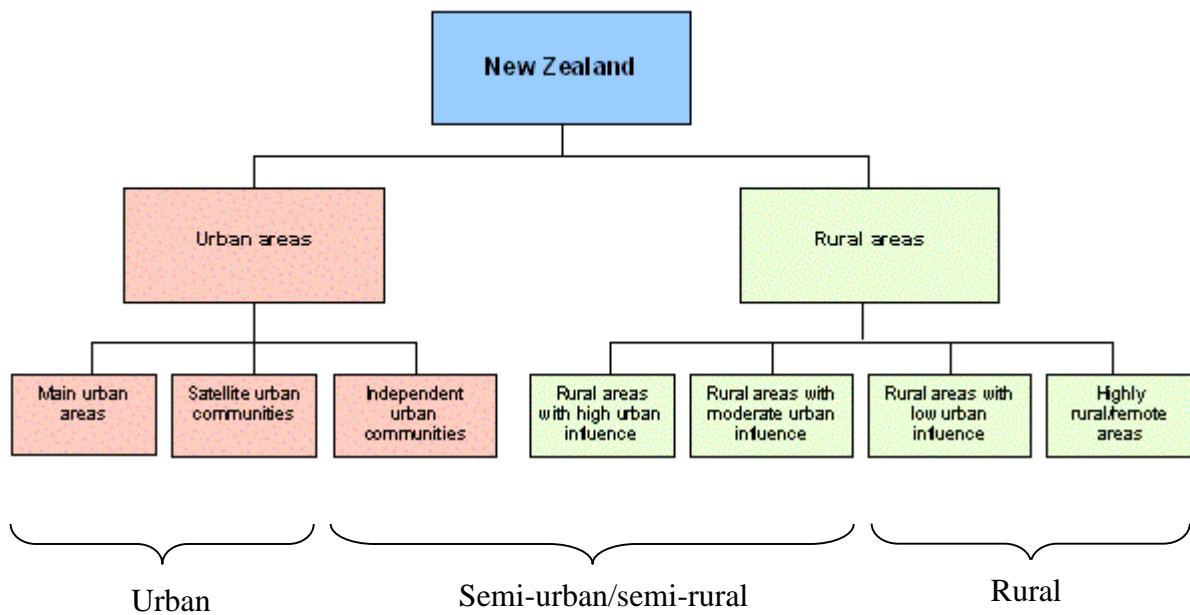
Main urban areas represent the most urbanised areas in New Zealand. Main urban areas are very large and centred on a city or main urban centre. They have a minimum population of

30,000. Population size is also used to define secondary and minor urban areas in the standard urban area classification. But population size alone cannot adequately describe the characteristics of different urban areas. Satellite urban category identifies towns and settlements with strong links to main urban centres and independent urban category identifies towns and settlements without significant dependence on main urban centres.

Rural areas are the other remaining areas of the country where the population does not exceed 999. Rural areas with a high urban influence category identify rural areas that form a transition between the main urban areas and rural areas, although mesh blocks are not necessarily contiguous with main urban centres. Rural areas with moderate urban influence category identify rural areas with a significant, but not exclusively, main urban area influence while areas with a strong rural focus are categorized as rural areas with low urban influence with majority of the population working within the same rural area. Highly rural or remote are rural areas where there is minimal dependence on urban areas in terms of employment, or where there is a very small employed population.

These seven levels were categorized into three levels; urban category included main and satellite urban communities. Semi-urban/semi-rural category included independent urban communities and rural areas with high or moderate urban influence. Rural category included rural areas with low urban influence and highly rural areas.

Figure 13: New Zealand Statistics – Urban/Rural Classification system (*Source NZ Statistics*)



Distance from treatment centre:

Distance from treatment centre was based upon individual patient address. As almost all women included in this study have received surgery, and adjuvant radiation and chemotherapy from the tertiary public hospital and/or private treatment facilities in Hamilton, distance was calculated from patient address to Hamilton city. Distances were categorized into <10km, 10-50km, 50-100km and >100km (129).

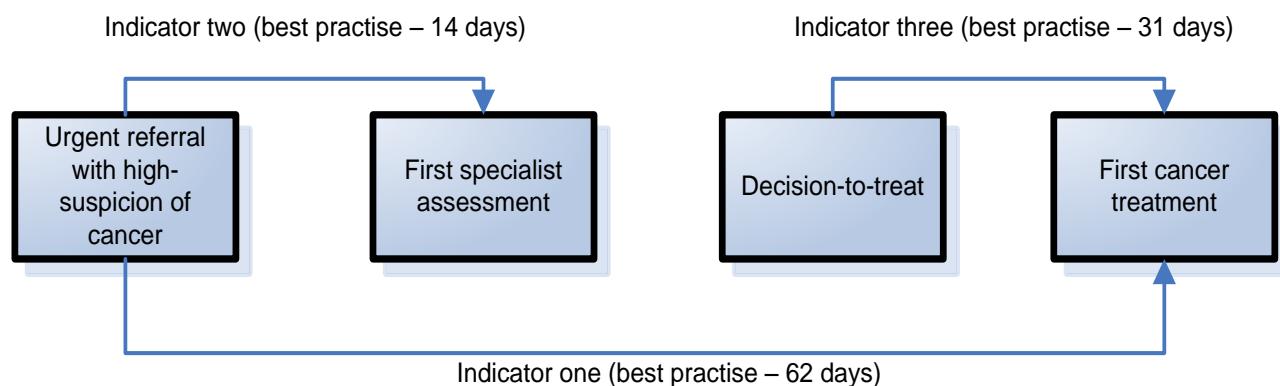
Treatment facility type:

Treatment facility type was categorized into public or private based on facility where patient underwent primary surgical treatment. As radiation therapy for all women and chemotherapy for almost all women (except for a few receiving chemotherapy in private in Auckland) were provided from the public sector, facility type was not included as a variable for analysis. However, we recognized the differences in socioeconomic, educational and behavioural characteristics of women receiving surgery in private sector and hence this was included as a variable in assessment of time delay and coverage of adjuvant radiation and chemotherapy.

Treatment of breast cancer:

Details of most of treatment variables include in analyses are shown in Table 3. For primary surgical therapy type and timeliness of therapy for breast and axilla were documented. A diagnosis to treatment gap of 31 days was considered as threshold delay to assess timeliness of surgery as described in Faster Cancer Treatment Indicators (Figure 14) published by the Ministry of Health (58). For adjuvant radiation and chemotherapy, coverage and timeliness were documented. Threshold limits of 60 days for chemotherapy (from date of definitive surgery) and 90 days for radiotherapy (from date of definitive surgery for women not undergoing chemotherapy) were used based on published literature.

Figure 14: Faster Cancer Treatment Indicators 2012-2013 (*Source - Ministry of Health*)



For adjuvant hormone therapy coverage and adherence with endocrine therapy was calculated based on data from the Pharmaceutical database. Coverage of adjuvant therapy was analysed based on accepted treatment guidelines over the period of the study to identify women who should have received respective types of adjuvant therapies (44, 272).

4.5. Outcome data

Primary outcome of interest in survival analysis was death (due to breast cancer or other causes) or survival. Details and dates of tumour recurrences were included for disease free survival analysis. Cause and date of death was identified from patient clinical records and from the Mortality Collection while tumour recurrence data were based on patient clinical records. End point for patient follow up was death or last follow up recorded up to 31/12/2013.

Table 6: ICD-9 and ICD-10 codes corresponding to breast cancer as underlying cause of death

Year of death	Coding system	Codes representing death due to breast cancer
1999	ICD-9-CM	1740, 1741, 1742, 1743, 1744, 1745, 1746, 1747, 1748, 1749 1750, 1751, 1752, 1753, 1754, 1755, 1756, 1757, 1758, 1759
2000-2013	ICD-10-CM	C500, C501, C502, C503, C504, C505, C506, C507, C508, C509

The Mortality collection assigns cause of death codes according to the World Health Organization rules and guidelines for mortality coding (Table 6). This is done based on information received from death certificates, post-mortem records, hospital discharge records and Coroners reports.

In general there was a good concordance (>90%) between cause of death derived from clinical notes review (where details of death or events preceding death were documented) and cause of death from the Mortality collection.

4.6. Sample size estimation

This study was estimated to include approximately 3,000 women (450 Māori and 2,550 NZ European) with breast cancer. It was estimated that 5-year breast cancer specific survival during the study period to be approximately 78% for Māori and Pacific women and 84% for NZ European women (9, 273). To show that a variable of interest results in a 5% worse 5-year survival amongst Māori (2-tailed p value, 95% confidence level and 80% statistical power) it was required to include 430 Māori and 2,170 NZ European women.

4.7. Data analyses

Different methods of analyses were applied for analyses given under different sub-chapters in the results section. Basic principles of analyses are described here and details of analyses including specific statistical tests applied for each study of interest are described in each results section.

Analyses under each section are broadly categorized into three areas. First, Māori and NZ European cohorts were compared in terms of demographics, disease and patient characteristics and healthcare access factors. Second, treatment characteristics were compared between Māori and NZ European women adjusting for age, tumour characteristics and health care access characteristics. Third, the impact of each characteristic/factor of interest on breast cancer mortality/survival was compared adjusting for covariates including ethnicity (Māori versus NZ European). In the final survival analysis breast cancer mortality hazard ratios were sequentially adjusted for demographics, health care access, tumour biological characteristics, comorbidity and treatment factors, to identify the overall quantitative impact of each of these factors on observed mortality inequity.

All analyses were performed in SPSS version 22 (261).

Chapter 5. Results

This chapter presents results from data analysis. It is set out in different sections. First section analyses the validity of data followed by eight sections that examine different areas and causes of breast cancer inequities between Māori and NZ European women. The final section is a combined analysis of results from previous eight sections which aims to create a model to describe quantitative impacts of patient, cancer and healthcare service factors on the survival disparity between Māori and NZ European women.

Each of the ten sections included are either published papers or papers that have been submitted for publication. These papers have been modified and abbreviated from their original versions to ensure segue between sections and to minimize repetitions. General changes to each section include shortening of introduction limiting them to study question/s, methods section limiting only to methods specific to each study and modifications to the discussion sections to make them more succinct and to minimize repetition.

Some of the studies included contain different sample sizes. This is either due to respective study been done prior to completion of full data collection or due to limitations of data availability from other sources which were used for data linkage with the WBCR (e.g. National Pharmaceutical Database).

Each section starts with an abstract and a short introduction to the topic with the study question followed by methods specific to the study and results. Discussion in each section is limited to discussing specific issues raised during each study. Next chapter (Chapter 6) provides a summary discussion which is aimed at summarizing all study findings and to bring together these findings for final interpretations.

5.1. How valid are the data used in this study?

Preface:

This chapter contains an abbreviated version of a manuscript published in *Cancer Epidemiology*.

- **Authors:** Seneviratne S, Campbell I, Scott N, Shirley R, Peni T, Lawrenson R.
- **Title:** Accuracy and completeness of the New Zealand Cancer Registry for staging of invasive breast cancer
- **Journal:** *Cancer Epidemiology*
- **Year of publication:** 2014
- **DOI:** 10.1016/j.canep.2014.06.008
- **Impact factor:** 2.56
- **Journal's aims and scope:** This journal is dedicated to increasing understanding about cancer causes, prevention and control. The scope of the journal embraces all aspects of cancer epidemiology including: descriptive epidemiology and statistics, studies of risk factors for disease initiation, development and prognosis, screening, early detection and accurate diagnosis, prevention and evaluation of interventions and methodological issues and theory.

Abstract:

Background:

Population based cancer registries are an invaluable resource for monitoring incidence and mortality for many types of cancer. Research and healthcare decisions based on cancer registry data rely on the case completeness and accuracy of recorded data. This study was aimed at assessing completeness and accuracy of breast cancer staging data in the New Zealand Cancer Registry (NZCR) against the Waikato Breast Cancer Register (WBCR).

Methods:

Data from 2562 women diagnosed with invasive primary breast cancer between 1999 and 2011 included in the WBCR were used to audit data held on the same individuals by the NZCR. WBCR data were treated as the benchmark.

Results:

Of 2562 cancers, 315 (12.3%) were unstaged in the NZCR. For cancers with a known stage in the NZCR, staging accuracy was 94.4%. Lower staging accuracies of 74% and 84% were noted for metastatic and locally invasive (involving skin or chest wall) cancers respectively, compared with localized (97%) and lymph node positive (94%) cancers. Older age (>80 years), not undergoing therapeutic surgery and higher comorbidity score were significantly ($p<0.01$) associated with unstaged cancer. The high proportion of unstaged cancer in the NZCR was noted to have led to an underestimation of the true incidence of metastatic breast cancer by 21%. Underestimation of metastatic cancer was greater for Māori (29.5%) than for NZ European (20.6%) women. Overall 5-year survival rate for unstaged cancer (NZCR) was 56.3% which was worse than the 5-year survival rate for regional (78.8%), but better than metastatic (18.2%) disease.

Conclusions:

Unstaged cancer and accuracy of cancer staging in the NZCR are major sources of bias for the NZCR based research. Improving completeness and accuracy of staging data and increasing the rate of TNM cancer stage recording are identified as priorities for strengthening the usefulness of the NZCR.

Background:

Population based cancer registries are a valuable resource for monitoring incidence and mortality from cancer and play a vital role in cancer control programmes (274). Many national cancer control strategies including the New Zealand Cancer Control Strategy have recognized the importance of a high quality national cancer registry as a core component of cancer control (275).

According to the World Health Organization, a modern cancer registry is expected to provide data on a number of key areas (274). These include enabling the assessment of the current magnitude of the cancer burden and future projections, providing a basis for research on cancer causes and prevention, providing information on prevalence of risk factors, and monitoring the effects of prevention, screening, treatment and palliative care. Quality of a cancer registry forms a cornerstone from which to achieve these tasks. The International Agency for Research on Cancer describes five main components of quality for cancer registries (276). These include completeness in cover, completeness in detail, accuracy in detail, accuracy of reporting and accuracy of interpretation.

Several studies have raised the issue that substantial proportions of cancers are unstaged or staged inaccurately in the NZCR (16, 94, 277). For example an audit on colon cancer by Cunningham and colleagues reported a staging accuracy of 80% in the NZCR compared with stage determined from a clinical notes review (16). Another audit comparing lung cancer staging in the NZCR against a regional database reported a staging accuracy of only 43.8% (94). The same audit reported that 12% of cases out of 565 included were not known to the NZCR. Missing or inaccurate cancer stage data may lead to biased research results. A good understanding of completeness, accuracy and characteristics associated with unstaged cancer in the NZCR is required to understand the magnitude of bias and will enable rational conclusions to be drawn from cancer research.

The Surveillance Epidemiology and End Results (SEER) program cancer staging definitions are preferred by many cancer registries for cancer stage recording (266), including the NZCR due to its simplicity. However, clinicians and pathologists widely use the Tumour Node Metastases (TNM) staging system which is more detailed and more relevant for clinical decision making (267). Since its introduction to the NZCR in 2001, TNM stage recording has slowly been increasing and was approximately 50% complete for breast cancer in 2010 (personal communication with the NZCR) which is well below the SEER stage completion

rate in the NZCR over this period (278). Comparatively, cancer registries from countries such as Denmark and the Netherlands have achieved TNM completion rates of more than 90% for many cancers including breast cancer (279, 280).

This study was conducted to evaluate the completeness and accuracy of breast cancer data from the NZCR against the WBCR. Further analyses were done to identify patient characteristics associated with unstaged cancer and to compare outcome for unstaged against staged cancers. Details of cancers from 2012 were not available at the time of this study, and hence only women diagnosed between 1999 and 2011 were included in this study.

Methods:

Data:

All newly diagnosed primary invasive breast cancer records over a 13-year period from 01/01/1999 to 31/12/2011 were identified from the WBCR and compared with the same records for the Waikato District Health Board (DHB) area from the NZCR. Each record was matched by date of diagnosis and National Health Index (NHI) number. From a total of 2623 invasive breast cancers identified for the period under review from the WBCR and the NZCR, women with a post mortem diagnosis of breast cancer (n=4) and women recorded under a different area (n=9) were excluded. Four cases from the WBCR not known to the NZCR and 43 cases from the NZCR not included in the WBCR (ineligible due to residence outside Waikato DHB area or due to records not available to the WBCR) were excluded from comparisons.

Variables:

Extent of disease (i.e. degree of spread of the tumour within the body / tumour stage) from the NZCR for selected breast cancers were compared with same data from the WBCR. WBCR data were treated as the benchmark and completeness and accuracy of the NZCR staging records were analysed against the WBCR.

All stage comparisons were performed according to SEER extent of disease classification which classifies tumours into 4 categories; localized, locally invasive (into skin or chest wall), involving regional lymph nodes (LN) and metastatic (i.e. tumour spread beyond breast and regional lymph node) disease (266).

As a pathology report from primary tumour excision would only be available for women undergoing primary surgical interventions, primary therapeutic surgical intervention was included as a predictor for staged cancer in the NZCR. Women undergoing only diagnostic or palliative surgical interventions or undergoing no surgical treatment were classified as no therapeutic surgical intervention.

Statistical analysis:

WBCR data for all women with an unknown stage in the NZCR were explored in a univariate analysis using Chi squared (χ^2) tests for trend. For staged cancers in the NZCR, sensitivity and specificity for each stage were calculated against the WBCR stage. Factors associated with unstaged cancer were explored in a multivariable logistic regression model. Survival for each cancer stage in the NZCR and the WBCR were compared using Kaplan-Meier survival curves. A Cox proportional hazard model was used to estimate the risk of mortality for unstaged compared with staged cancers adjusting for age, comorbidity, ethnicity and cancer stage.

Results:

From a total of 2623 newly diagnosed primary invasive breast cancers identified from the WBCR and NZCR, 2563 cancers were found to be eligible for this study. Of these, 1 cancer for which the stage was not recorded in the WBCR was excluded leaving 2562 cancers for stage comparison.

Table 7 shows the distribution of discrepancies between the WBCR and the NZCR in relation to extent of disease. Overall, 315 (12.3%) of cancers in the NZCR were recorded as unknown stage. Of the cancers with a known stage in the NZCR, 2121 (94.4%) were found to be accurately staged compared with the WBCR. Higher proportions of unstaged and inaccurately staged cancers were seen for metastatic and locally invasive cancers compared to localized and lymph node positive cancers. Sensitivity of each extent of disease category in the NZCR was 97.7%, 84%, 93.7% and 73.9% for localized, locally invasive, LN involved and metastatic cancer respectively. Specificities for respective extents of disease were 95.3%, 99.5%, 96.5 and 99.4% (Figure 15).

Table 7: Extent of cancer (stage) at diagnosis in the New Zealand Cancer Registry compared with extent of cancer at diagnosis in the Waikato Breast Cancer Register 1999-2011.

NZCR extent of cancer	WBCR extent of cancer									
	Localized		Locally invasive		LN involved		Metastatic		Total	
	n	%	n	%	n	%	n	%	n	%
Localized	1186	84.2	4	10.3	44	4.6	1	0.7	1235	48.2
Locally invasive	4	0.3	21	53.8	4	0.4	2	1.3	31	1.2
LN involved	20	1.4	0	0.0	837	86.8	27	17.9	884	34.5
Metastatic	4	0.3	0	0.0	8	0.8	85	56.3	97	3.8
Unknown	194	13.8	14	35.9	71	7.4	36	23.8	315	12.3
Total	1408	100	39	100	964	100	151	100	2562	100

Stage distribution for staged cancers in the NZCR was highly and significantly ($p<0.001$) correlated with the overall stage distribution in the WBCR over the study period (Figure 16). The highest correlation was observed for locally invasive cancers (correlation coefficient=0.81), while the correlations of 0.75 and 0.69 were observed for regional and metastatic cancer, respectively.

Figure 15: Distribution of accurately staged, inaccurately staged and unstaged breast cancer in the New Zealand Cancer Registry compared with the Waikato Breast Cancer Register 1999-2011.

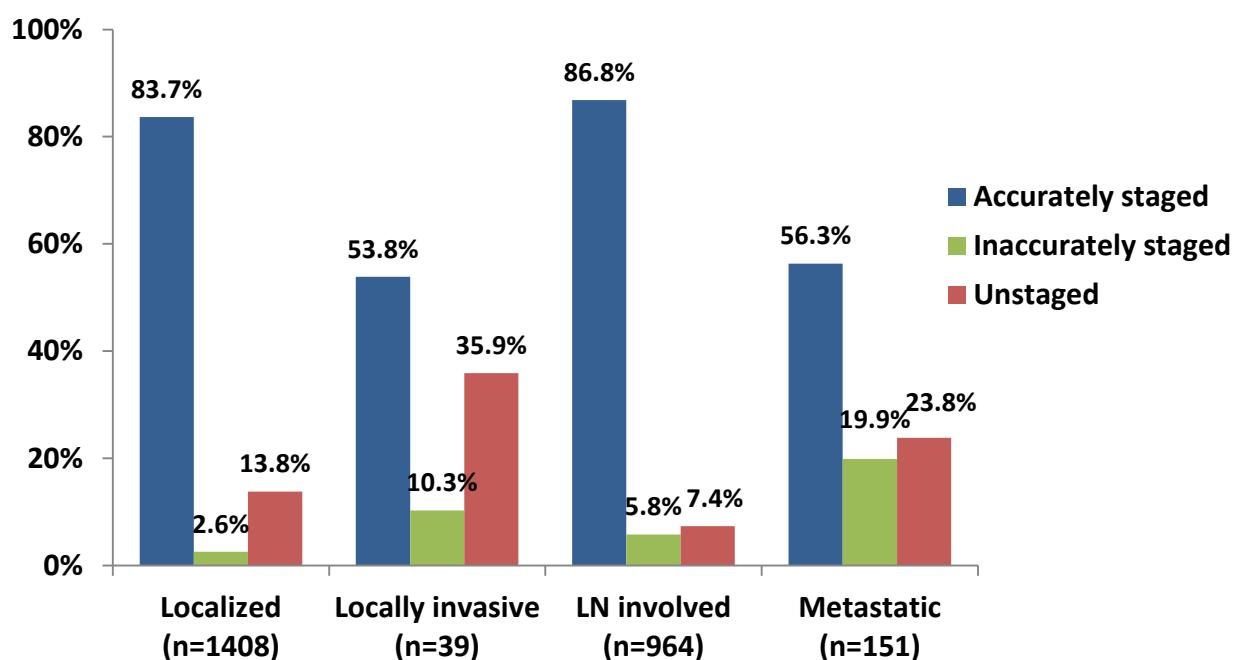


Figure 16: Trends in proportional distribution of cancer stage in the Waikato Breast Cancer Register (WBCR) compared with staged cancers in the New Zealand Cancer Registry (NZCR) 1999-2011.

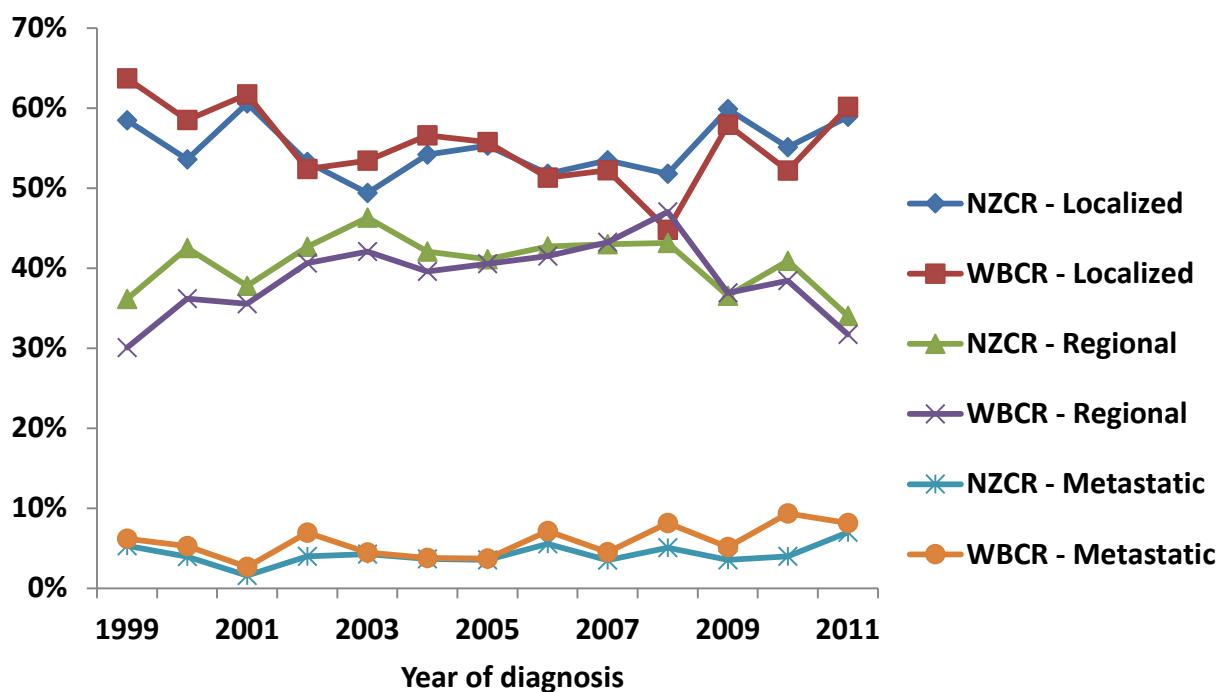


Table 8 shows a comparison of factors associated with stage known and unknown cancers in the NZCR. Advanced stage, higher comorbidity score, not undergoing therapeutic surgery and overall mortality were significantly higher for unstaged cancers ($p<0.001$). No significant difference in the rate of unstaged cancer between Māori and NZ European (the two main ethnic groups included) were observed. However, because a higher proportion of Māori women were noted to have metastatic breast cancer compared to NZ European women (11.6% vs. 4.7%), a separate analysis was performed for unstaged metastatic cancer by ethnicity. Of the Māori women with unstaged cancer, 27.7% (13 out of 48) had metastatic cancer compared to 7.8% (20 out of 257) for NZ European women, a difference which was statistically significant ($P<0.001$). Overall underestimation of the incidence of metastatic breast cancer in the NZCR was 21% (5.9% in the WBCR vs. 3.8% in the NZCR); 29.5% for Māori and 20.6% for NZ European women, respectively.

A multivariate logistic regression was performed with unstaged cancer as the outcome variable and age category, ethnicity, deprivation, comorbidity index and therapeutic surgery as covariates. This identified advancing age ($OR=1.63$, 1.37-1.93), higher comorbidity score ($OR=1.51$, 1.20-1.71) and not undergoing therapeutic surgery ($OR=7.43$, 5.37-10.3) as factors significantly associated with unknown cancer stage in the NZCR (Appendix 1).

Table 8: Distribution of characteristics associated with stage known and unknown breast cancers in the New Zealand Cancer Registry for the Waikato region 1999-2011.

Characteristic	Total (N=2563)		Stage known		Stage unknown		p
	n	%	n	%	n	%	
Age group							
<40	134	5.2%	124	92.5%	10	7.5%	<0.001
40-59	1150	44.9%	1055	91.7%	95	8.3%	
60-79	977	38.1%	877	89.8%	100	10.2%	
80+	302	11.8%	191	63.2%	111	36.8%	
Ethnicity							
NZ European	2077	81.0%	1820	87.6%	257	12.4%	
Māori	380	14.8%	332	87.4%	48	12.6%	0.887
Pacific	50	2.0%	40	80.0%	10	20.0%	0.164
Other	56	2.2%	55	98.2%	1	1.8%	0.028
Deprivation							
1-2	255	9.9%	229	89.8%	26	10.2%	0.586
3-4	257	10.0%	225	87.5%	32	12.5%	
5-6	573	22.4%	504	88.0%	69	12.0%	
7-8	813	31.7%	700	86.1%	113	13.9%	
9-10	665	25.9%	589	88.6%	76	11.4%	
Charlson Score							
0	2066	80.6%	1875	90.8%	191	9.2%	<0.001
1-2	418	16.3%	318	76.1%	100	23.9%	
3+	79	3.1%	54	68.4%	25	31.6%	
Therapeutic Surgery							
Yes	2348	91.6%	2143	91.3%	205	8.7%	<0.001
No	215	8.4%	104	48.4%	111	51.6%	
Outcome							
Non death	1875	73.2%	1729	91.0%	170	9.0%	<0.001
Death	686	26.8%	516	77.9%	146	22.1%	
Deaths (n=686)							
Breast cancer	409	59.6%	334	81.7%	75	18.3%	<0.001
Other cause	272	39.7%	177	65.1%	95	34.9%	
Unknown	5	0.7%	5	100.0%	0	0.0%	

A gradual and a significant reduction ($p<0.001$) in unstaged cancers and a complementary increase in accurately staged cancers in the NZCR were observed (Figure 17). Reduction in unstaged cancer was more pronounced from 1999 to 2004 and since had only a minimal change. Even in 2011, approximately 12% of breast cancers included in the NZCR were either unstaged or staged inaccurately (i.e. unstaged 6.9% and inaccurately staged 5.7%) compared with the WBCR.

A survival analysis was performed to compare overall crude survival rate by extent of cancer in the NZCR and the WBCR (Figure 18). Unstaged cancer in the NZCR showed a 5-year survival of 55.9% which was between the survival rates for regional (locally invasive and/or regional lymph node positive) at 77.3% and metastatic disease at 12.9% respectively. For women with regional disease, both the NZCR and the WBCR exhibited almost similar survival rates (5-year survival 77.3% vs. 76.4%). For localized disease WBCR women had a worse survival (5-year survival 86.6% vs. 90.1%) while for metastatic cancer, the WBCR survival was better (5-year survival 17.3% vs. 12.9%) compared with the NZCR.

Figure 17: Trends in unstaged, accurately staged and inaccurately staged breast cancer in the New Zealand Cancer Registry compared with the Waikato Breast Cancer Register 1999-2011.

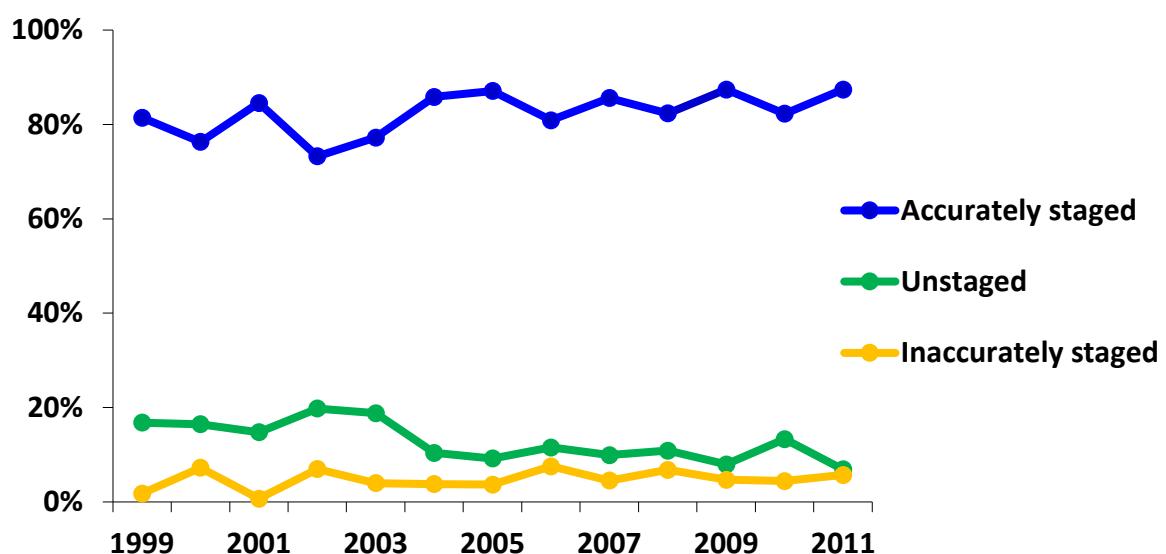
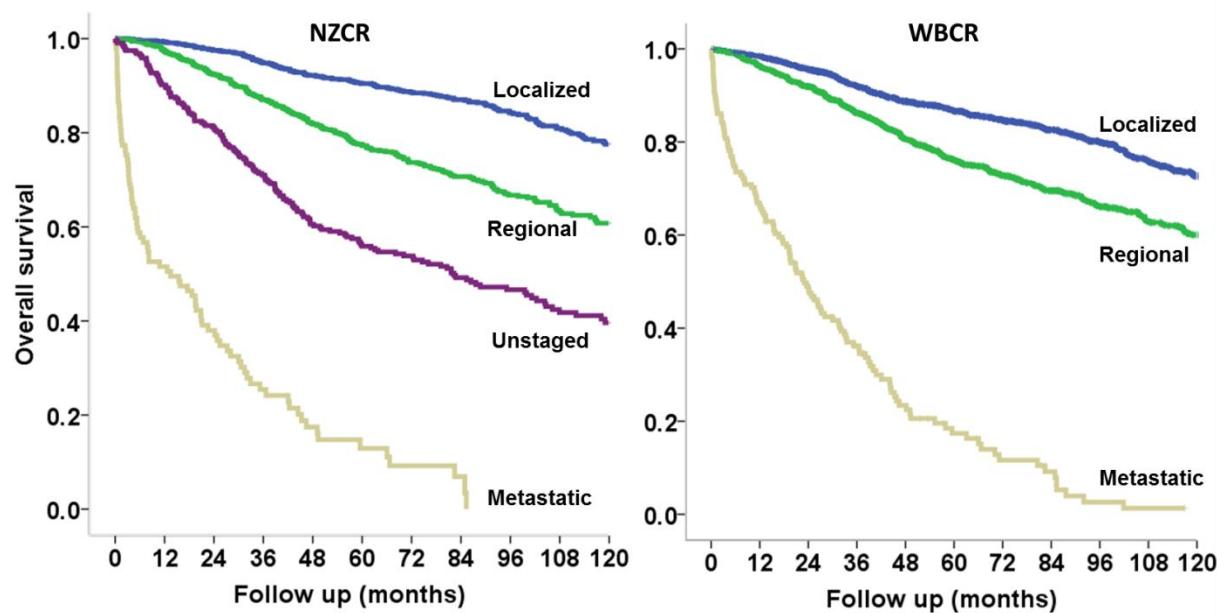


Figure 18: Kaplan-Meier survival curves by cancer stage for invasive breast cancers included in the New Zealand Cancer Registry (NZCR) and the Waikato Breast Cancer Register (WBCR) for the Waikato region 1999-2011.



Cox proportional hazard model (Table 9) identified that unstaged cancers were associated with a significantly higher risk of overall mortality ($HR=1.59$, $p<0.001$) compared with staged cancers in the NZCR after adjusting for age, comorbidity index and cancer stage.

Discussion:

A high rate of overall case completeness and a high accuracy of staging for staged breast cancer in the NZCR were observed in this study. Further, between the two registries, a high correlation in stage distribution over the study period and roughly comparable overall survival rates by stage was observed, despite the substantial proportion of unstaged invasive breast cancers included in the NZCR. Although the proportion of unstaged cancer has improved, in 2011 the proportion of unknown and inaccurate staging was still 12%. Women with advanced stage cancers, higher comorbidity score and women who were not receiving therapeutic surgical interventions were significantly over-represented among unstaged cancers. Māori women were significantly over-represented in unstaged metastatic breast cancer. Comparable rates of case completeness, staging accuracy and unstaged tumours have previously been reported for breast cancer from population based cancer registries in the United States, the United Kingdom, the Netherlands, Denmark and Germany (72, 280-284). To our knowledge this is the first independent audit of the breast cancer records of the NZCR performed since mandatory reporting was introduced in New Zealand in 1994.

Table 9: Multivariable Cox proportional hazard model for overall mortality risk for unstaged vs. staged cancer in the New Zealand Cancer Register

Characteristic		HR	95% CI	p
Staging status (NZCR)	Staged	Ref		<0.001
	Unstaged	1.59	1.32-1.92	
Charlson score ^a	0	Ref		<0.001
	1-2	2.16	1.81-2.57	
	3+	3.60	2.69-4.80	
Stage (WBCR) ^b	Localized	Ref		<0.001
	Locally invasive	2.39	1.58-3.61	
	Regional LN involved	1.87	1.58-2.23	
	Metastatic	12.2	9.77-15.3	
Age category (years)	<40	Ref		<0.001
	40-59	0.65	0.45-0.95	
	60-79	0.92	0.63-1.33	
	80+	2.19	1.48-3.24	

(HR – Hazard ratio, CI – Confidence interval, ^a Charlson Comorbidity Score, ^b Waikato Breast Cancer Register).

Reasons for unstaged cancer can be grouped into two categories; lack of staging and lack of reporting. Lack of staging occurs, for example when life expectancy is limited due to severe comorbidities or old age, due to patient refusal and in situations where necessary staging investigations were not available locally or where a patient could not afford investigations (285-287). Second, where the cancer stage was known to the treating physician or recorded in clinical documents but was not reported to the cancer registry (287). Since the breast and axilla are relatively easily accessible areas both clinically and with simple imaging, clinical stage at least is expected to be available for most, if not all women with breast cancer. This is confirmed by the fact that the WBCR has been able to record cancer stage for all but one woman, based on one or more of clinical, imaging and histopathology records.

Staging of cancers by the NZCR depends on diagnostic and therapeutic information obtained from pathology reports and other hospital records provided by reporting laboratories and hospitals. However, it appears that there has been a relative lack of non-pathologic (i.e. clinical and imaging) information being provided to the NZCR, which is evident by a high rate of unstaged cancer seen among women not undergoing therapeutic surgery. This is further

supported by a high proportion of metastatic breast cancer (43.7%), which in most situations is diagnosed through imaging, being under-staged or unstaged in the NZCR. This error has led to a significant underestimation of the true incidence of metastatic breast cancer by almost 30% for Māori and by 20% for NZ European women. This underestimation explains the reason for unstaged cancers exhibiting a rate of survival worse than regional disease. Similar patterns of survival for several types of unstaged cancers in the NZCR including breast, colon and lung have been reported by Gurney and colleagues (278).

As we have observed, unstaged cancer was more likely to be associated with metastatic disease compared to localized or lymph node involved disease. As such, statistical analyses which exclude these unstaged cancers, or analyses that consider these data as missing at random and apply statistical techniques such as simple multiple imputation or inverse probability weighting will likely lead to biased estimates of the true stage distribution (71). Although more complex methods including multiple imputation combined with either chained equations or stage modelling have been shown to provide more accurate estimates of stage distribution (72), these are not used widely due to their complex nature.

This study assumes that the WBCR breast cancer data were captured perfectly without errors from all available records. The WBCR involves collecting breast cancer data from clinical records and pathology reports and entering data into a database by trained data entry personnel. Close supervision by two breast surgeons and a stringent quality control and audit process is in place to maximize the completeness, quality and accuracy of the WBCR records. All these measures we believe have helped to minimize errors in the WBCR database and underlie the main strength of this study.

In 2010, an independent review of the NZCR recommended an increase in breadth of data collected, particularly through collection of clinical and imaging staging information at the time of diagnosis (clinical TNM/cTNM) to enhance accuracy of staging and to minimize number of unstaged cancers (288). As we have reported, more than 50% of unstaged breast cancers were from women not undergoing therapeutic surgical interventions and using cTNM was expected to capture clinical staging data for a majority of otherwise unstaged cancers. Based on these recommendations, a focussed pilot project is currently being trialled by the NZCR to identify the feasibility of collecting and relaying cTNM data through Multi-Disciplinary Meetings (MDM) to the NZCR (288). In New Zealand, the vast majority of cancers will be managed through MDM's once the National Tumour Standards of Service Provision are implemented. If this system is successful, it is expected to capture accurate

cTNM staging data for a majority of cancers. As more structured and reliable information is expected to be provided through synoptic reporting, the NZCR is considering a system for automated electronic transfer of pathology information for more efficient transfer of pathology data to the NZCR.

Population based national cancer registries including the NZCR has the objective of providing key cancer variables such as incidence, mortality, inequities, stage and basic cancer characteristics with a complete nationwide coverage. The NZCR has performed a commendable job over time to provide these key cancer variables with a very high coverage, which is on par with the top national cancer registries in the world. Despite some deficiency in stage coverage as observed in this study, the NZCR has captured proportional as well as trends in stage distribution over the study period with a fairly high accuracy. From an epidemiological point of view, this evidence confirms the NZCR stage as a valid marker for most population statistical purposes, despite some limitations in areas including metastatic breast cancer.

The NZCR does not possess details of other important cancer related data such as diagnostic process, treatment details and timeliness of treatment and outcomes including local and metastatic recurrence as these aspects are beyond the scope of a national cancer registry (288). Tumour specific regional or national registries like the regional breast cancer registries are equipped to capture comprehensive and accurate tumour specific information. Detailed information helps to identify quality of care issues around and to recognize where quality improvement could be undertaken to achieve better patient outcomes. Further, there is potential for these regional registries to be linked electronically to the NZCR in the future to enhance accuracy and completion of NZCR data. Currently, the four regional breast cancer registries, prospectively collect comprehensive breast cancer data from diagnosis through treatment, follow up and outcomes. Unfortunately, lack of recognition of the importance of these breast cancer registries and hence lack of funding is threatening the continuation of the registries and has prevented further expansion to incorporate other regions of the country.

In conclusion, while acknowledging the commendable performance of the NZCR, we emphasize that to increase the usefulness of the NZCR, improvements need to be made in completeness and accuracy of staging data and rate of TNM recording. To this end, it is crucial that all avenues for relaying cancer information to the NZCR are explored and that appropriate methods are implemented. Improvements to the completeness and quality of data on the NZCR will allow a more reliable estimation of important cancer issues, especially for

metastatic breast cancer incidence. We found an almost 30% underestimation of metastatic breast cancer incidence for Māori compared with an almost 20% underestimation for NZ European women. These findings provide reference for analysis of the NZCR data, in particular for consideration of analysis of unstaged cancers by ethnicity. Alongside these improvements in the NZCR, national and regional cancer registries need to be supported to continue and improve to provide detailed cancer data to inform cancer control for the New Zealand population.

5.2. What risk factors contribute to ethnic inequities in breast cancer? A preliminary analysis

Preface:

This chapter contains an abbreviated version of a manuscript published in *Public Health*

- **Authors:** Seneviratne SA, Campbell ID, Scott N, Lawrenson R, Shirley R, Elwood M.
- **Title:** Risk factors associated with mortality from breast cancer in Waikato, New Zealand: A case control study
- **Journal:** *Public Health*
- **Year of publication:** 2015
- **DOI:** 10.1016/j.puhe.2015.02.008
- **Impact factor:** 1.46
- **Journal's aims and scope:** *Public Health* is an international, multidisciplinary peer-reviewed journal. It publishes original papers, reviews and short reports on all aspects of the science, philosophy, and practice of public health. It is aimed at all public health practitioners and researchers and those who manage and deliver public health services and systems. It will also be of interest to anyone involved in provision of public health programmes, the care of populations or communities and those who contribute to public health systems in any way.

Abstract:

Background:

Indigenous Māori women have a 60% higher mortality rate compared with NZ European women. Many factors, much of which is unknown at present, are believed to be contributing to this disparity.

Methods:

We performed a case control study to identify key characteristics associated with mortality from breast cancer among women with newly diagnosed breast cancer between 01/01/2002 and 31/12/2010 in Waikato, New Zealand. A total of 258 breast cancer deaths were identified from 1767 invasive cancers diagnosed over this period.

Results:

Breast cancer deaths (n=246) were compared with an age and year of diagnosis matched control group (n=652) who were alive at the time of the death of the corresponding case and subsequently did not die from breast cancer. Diagnosis through symptomatic presentation, advanced stage, higher grade, absent hormone receptors (i.e. oestrogen and progesterone) and HER-2 amplification were associated with significantly higher risks of breast cancer mortality in bivariate analysis. Tumour stage, grade and hormone receptor status remained significant in the multivariable model, while mode of detection and HER-2 status were non-significant. In the bivariate analysis, Māori women had a higher risk of breast cancer mortality compared to NZ European women ($OR=1.34$) which was statistically non-significant. However in the adjusted model, risk of mortality was lower for Māori compared to NZ European women, although this was statistically not significant ($OR=0.85$).

Conclusions:

Mortality pattern from breast cancer in this study were associated with established risk factors. Ethnic inequity in breast cancer mortality in New Zealand appears to be largely attributable to delay in diagnosis and tumour related factors. Further research in a larger cohort is needed to identify the full impact of these factors on ethnic inequity in breast cancer mortality.

Background

This was a preliminary study that was conducted during the early phase of the research project with the aim of ascertaining key risk factors associated with breast cancer mortality. It was expected that these findings would provide an insight into the factors that are to be studied and to recognize areas needing more focus. Other objectives of this study included use of a different study design from the cohort design which is used throughout this project. As this study was conducted during the early phase of this research project, only women diagnosed during 2002-2010 were included.

Methods

Study design:

A nested case-control study was performed to identify key factors associated with death from breast cancer among women diagnosed with invasive primary breast cancer in the Waikato.

Study participants:

All women with an invasive primary breast cancer diagnosis over a 9-year period from 01/01/2002 to 31/12/2010 were identified from the WBCR (n=1919). To identify cases of BCSM, cause of death for all deceased women from this group were identified (censored at 31/12/2012) from the Mortality Collection of the Ministry of Health and compared with same data from the WBCR and patient clinical records.

The controls were age (+/- one year) matched women who had the same year of diagnosis and who were alive at the time of death of the corresponding case and subsequently did not die of breast cancer. These controls were followed up to the last recorded follow up which censored at 31/12/2012. Controls were randomly selected and individually matched for corresponding cases. We aimed to identify three controls per case. Same aged controls were given priority in the selection of controls, followed by age +/- one-year controls. Age +/- one year controls were selected randomly alternating between + and – ages based on availability. If no matched controls were available according to above criteria, such cases were excluded from analysis.

Data analysis:

Bivariate analyses were performed using Chi squared test or Wilcoxon rank for categorical variables and independent samples t-test for continuous variables. Odds ratios (OR) with 95%

confidence intervals (CI) were calculated individually and then in a multivariate model using conditional logistic regression to identify independent risk factors associated with BCSM. All variables with an unadjusted p value <0.20 in bivariate analyses were included in the multivariate models. Manual stepwise backward selection procedures were used to select variables for inclusion in multivariate models. Variables returning a p value of >0.05 were excluded one by one, starting with the variable with the highest p value. All excluded variables (i.e. with p>0.05) were reintroduced separately into final models and p>0.05 was reconfirmed. Survival times were calculated from date of diagnosis to date of death in years and separate multiple logistic regression models were developed by duration of survival of cases (≤ 3 or >3 years of survival).

Results

This nested case control study included 246 cases who died due to breast cancer, and 652 control women who survived (n=591) or died due to causes other than breast cancer (n=61); a total of 898 women with invasive breast cancer. No matched controls were available for 12 cases that were mostly from extremes of age (i.e. age <30 years or >90 years) and these cases were excluded from analyses.

Patient characteristics with bivariate analyses are summarized in Table 10. Symptomatic presentation compared with screen detection, advanced tumour stage and grade, negative ER and PR status and positive HER-2 status were associated with significantly ($P<0.001$) elevated risks of death from breast cancer.

A multivariable analysis was performed with conditional logistic regression (Table 11). Duration of symptoms was not included despite being $p<0.001$, since it was available only for women with symptomatically detected breast cancer. The risk of death from breast cancer was significantly ($P<0.001$) increased with more advanced tumour stage and grade and with negative hormone receptor status; it was also increased, although not significantly, with positive HER-2 status ($p=0.385$). A separate model with ethnicity adjusting only for cancer stage yielded an OR of 0.92 (95% CI 0.59-1.58, $p=0.89$) for BCSM for Māori compared to NZ European women.

Table 10: Bivariate analysis of risk factors and mortality

Variable	Cases (N=246)		Controls (N=652)		OR	95% CI	p
	n (%)	n (%)					
Mean age ± SD	61.1 ± 14.6		60.6 ± 13.9				0.591
Detection method							<0.001
Screen detected	35 (14.2)		250 (38.3)		Ref		
Non-screen	211 (85.8)		402 (61.7)		3.75	2.54 - 5.54	
Mean symptom duration ± SD ^a	14.9 ± 21.8		10.1 ± 14.6				0.193
Ethnicity							
NZ European	192 (78.0)		540 (82.2)		Ref		
Māori	43 (17.5)		90 (13.8)		1.34	0.90 - 2.00	0.154
Pacific	7 (2.8)		11 (1.69)		1.79	0.68 - 4.68	0.243
Other	4 (1.6)		11 (1.7)		1.03	0.32 - 3.25	0.971
Tumour stage							<0.001
I	16 (6.5)		271 (41.6)		Ref		
II	79 (32.1)		287 (44.0)		4.66	2.66 - 8.18	
III	84 (34.1)		88 (13.5)		16.2	9.00 - 29.1	
IV	67 (27.2)		6 (0.9)		189.1	71.3 - 501.7	
Tumour grade							<0.001
I	8 (4.2)		174 (29.0)		Ref		
II	83 (43.5)		322 (53.6)		5.61	2.65 - 11.8	
III	100 (52.4)		105 (17.5)		20.7	9.69 - 44.3	
Unknown	(55)		(51)				
ER/PR							<0.001
Positive	172 (72.6)		550 (89.6)		Ref		
Negative	65 (27.4)		64 (10.4)		3.25	2.21 - 4.78	
Unknown	(9)		(38)				
HER-2							<0.001
Negative	120 (60.9)		348 (72.8)		Ref		
Equivocal	15 (7.6)		59 (12.3)		0.74	0.40 - 1.35	
Positive	62 (31.5)		71 (14.9)		2.53	1.77 - 3.77	
Unknown	(49)		(174)				

Histology

Ductal	193 (85.4)	525 (81.3)	Ref			
Lobular	23 (10.2)	73 (11.3)	0.86	0.52 - 1.41	0.583	
Other	10 (4.4)	48 (7.4)	0.56	0.26 - 1.40	0.132	
Unknown	(20)	(6)				
Charlson Index						0.951
0	220 (89.4)	581 (89.1)	Ref			
1-2	8 (3.3)	24 (3.7)	0.88	0.39 - 1.98		
3+	18 (7.3)	47 (7.2)	1.01	0.57 - 1.78		

(OR – odds ratio, CI – confidence interval, ^a - symptomatic cancers only)

To identify factors associated with duration of survival among women with BCSM, cases were categorized into two groups [survival length \leq 3 years (n=199) and $>$ 3 years (n=74)]. Using individually matched corresponding controls, separate logistic regression analyses with conditional regression were performed for these two groups (Table 12). Tumour grade showed a stronger associations with mortality \leq 3 years compared to $>$ 3 years and, ER/PR negativity was associated with increased deaths only before 3 years, although the differences between the two time groups were not significant. HER-2 status was associated with increased deaths only after 3 years (OR 2.49, 95% CI 1.01-6.21) compared to HER-2 negative women (Table 12).

HER-2 receptor status was available for 73.2% (536 out of 732) NZ European and 86.5% (115 out of 133) Māori women. Of this, HER-2 amplification was seen among 92 (17.2%) NZ European and 33 (28.7%) Māori women. Only 3.2% (2 out of 62) of HER-2 amplified cases received treatment with trastuzumab (Herceptin®) compared with 25.4% (18 out of 71) of HER-2 amplified controls. To identify the impact of trastuzumab on survival among HER-2 positive women, a separate regression analysis was performed inclusive of trastuzumab treatment. This demonstrated trastuzumab treatment to be associated with a significantly lower risk of BCSM among women with HER-2 amplified tumours ($p=0.003$, OR 0.07, 95% CI 0.01–0.42). Of the HER-2 amplified tumours, 14 (15.2%) NZ European and 4 (12.1%) Māori women received treatment with trastuzumab.

Table 11: Multivariate model for factors associated with mortality

Variable	OR	95% CI	p
Detection method			0.085
Screen detected	Ref		
Symptomatic	1.52	0.94 – 2.45	
Ethnicity			0.567
NZ European	Ref		
Māori	0.85	0.49 – 1.48	
Tumour stage			<0.001
I	Ref		
II	2.68	1.47 – 4.90	
III	9.08	4.78 – 17.3	
IV	111.1	35.8 – 344.8	
Tumour grade			<0.001
I	Ref		
II	2.98	1.31 – 6.81	
III	6.88	2.92 – 16.2	
ER/PR			0.001
Positive	Ref		
Negative	2.43	1.49 – 3.97	
HER-2			0.385
Negative	Ref		
Equivocal	1.32	0.63-2.79	
Positive	1.54	0.92-2.60	

(OR – odds ratio, CI - confidence interval)

Table 12: Multivariate model (conditional logistic regression) for factors associated with mortality for women with a survival of ≤ 3 years and > 3 years against matched controls

Variable	Case survival ≤ 3 years (n=199)			Case survival > 3 years (n=74)		
	OR	95% CI	p	OR	95% CI	p
Detection method				0.013		
Screen detected	Ref			Ref		
Symptomatic	2.41	1.21-4.81		0.98	0.48-2.00	
Ethnicity				0.835		
NZ European	Ref			Ref		
Māori	1.08	0.54-2.16		0.64	0.22-1.82	
Tumour stage				<0.001		
I	Ref			Ref		
II	2.67	1.15-6.19		2.80	1.14-6.87	
III	10.2	4.29-24.3		7.05	2.59-19.2	
IV	122.6	30.3-496.1		107.6	10.5-980.1	
Tumour grade				<0.001		
I	Ref			Ref		
II	8.61	1.63-45.4		1.91	0.71-5.15	
III	23.9	4.45-125.4		3.58	1.15-11.2	
ER/PR				0.001		
Positive	Ref			Ref		
Negative	3.17	1.76-5.72		1.37	0.49-3.82	
HER-2				0.978		
Negative	Ref			Ref		
Equivocal	1.04	0.39-2.80		1.43	0.44-4.67	
Positive	1.16	0.60-2.24		2.49	1.01-6.21	

(OR – odds ratio, CI - confidence interval)

Discussion

In this case-control study we observed a pattern in concordance with known risk factors for breast cancer specific mortality (BCSM); i.e., tumour stage, grade and hormone receptor (ER/PR) status were independently associated with BCSM.

In the univariate analysis, Māori women had an estimated 34% higher risk of breast cancer death; while not significant, this is compatible with previous analyses which have assessed breast cancer mortality in Māori women (4, 31). For example, a study based on the NZCR data from 2002 to 2006 has shown a 73% higher age standardized breast cancer mortality rate for Māori compared to non-Māori women (4). However, no increased risk of death in Māori women was seen after taking into account the major predictors of stage, grade, and hormone receptor status, the adjusted odds ratio being 0.85. Even adjusting only for stage completely negated the increased risk of breast cancer death that was observed among Māori in the univariate analysis. This indicates that the increased death risk for Māori women with breast cancer may be largely due to presentation at a more advanced stage, similar to findings of Jefferys et al (9), suggesting that further efforts to improve early diagnosis are needed.

Reporting of HER-2 receptor status has only been routine in New Zealand since 2007. One recently published study based on the NZCR data has reported a significantly higher rate of HER-2 amplified tumours in Māori compared to non-Māori non-Pacific women (18.4% vs. 25.7%) (13). Trastuzumab (Herceptin) which has shown to improve survival among women with HER-2 amplified breast cancer (289) became available for the treatment of HER-2 amplified early breast cancer through the publicly funded system in New Zealand from 2007 (61). Prior to 2007, trastuzumab was available only for women who could privately fund this expensive therapy. A substantially higher proportion of HER-2 amplified breast cancer and a marginally lower rate of trastuzumab therapy for HER-2 amplified tumours were seen in Māori compared to NZ European women in our study. However, the significance of this treatment difference is uncertain due to small number of women receiving trastuzumab treatment included in this study. Ethnic inequities are known to exist even for publicly funded medications in New Zealand. For example in 2000, Māori and Pacific patients were 60% less likely to receive statin therapy despite having higher incidences of cardiovascular disease compared to Europeans (290). This raises an issue of ensuring prompt access to new therapies for Māori women particularly when they are more likely to have a greater benefit from such treatment.

This study has some limitations. The follow up duration was relatively short, with a median follow up of 6 years. As mortality from breast cancer is known to occur even after 20 years, this study is more likely to highlight the factors associated with short and medium term BCSM. The limited sample of Māori cases included in this study prevented a separate logistic regression analysis being performed for Māori women, which could have provided us with more information on the differences in distribution of risk factors and their impact on observed mortality disparity between Māori and European ethnic groups. We plan to examine these factors further in a larger cohort.

In conclusion, this is the first study of its kind in New Zealand investigating the association between death from breast cancer and, patient and tumour biological features from a comprehensive data set. These findings have important implications for targeting early diagnosis and providing access to targeted therapies especially for Māori women which could potentially reduce ethnic inequities in breast cancer mortality in New Zealand. Further research with a larger cohort of women is needed and is currently underway to further assess the impact of patient, tumour and treatment characteristics on ethnic inequity in breast cancer mortality in New Zealand.

5.3. Is breast cancer screening contributing to ethnic inequity in outcomes?

Preface:

This chapter contains an abbreviated version of a manuscript published in *BMC Public Health*

- **Authors:** Seneviratne S, Campbell I, Scott N, Shirley R, Lawrenson R.
- **Title:** Impact of mammographic screening on ethnic and socioeconomic inequities in breast cancer stage at diagnosis and survival in New Zealand: A cohort study
- **Journal:** *BMC Public Health*
- **Year of publication:** 2015
- **DOI:** 10.1186/s12889-015-1383-4
- **Impact factor:** 2.32
- **Journal's aims and scope:** *BMC Public Health* is an open access, peer-reviewed journal that considers articles on the epidemiology of disease and the understanding of all aspects of public health. The journal has a special focus on the social determinants of health, the environmental, behavioural, and occupational correlates of health and disease, and the impact of health policies, practices and interventions on the community.

Abstract:

Background:

Breast cancer screening coverage for Indigenous Māori women is significantly lower compared with NZ European women, and is believed to be contributing to more advanced cancer at diagnosis and worse survival in Māori women. This study was done to explore the impact of differences in rates of screen detected breast cancer on inequities in cancer stage at diagnosis and survival between Māori and NZ European women in the Waikato.

Methods:

All primary breast cancers diagnosed in screening age women (as defined by the BSA Programme) during 1999-2012 in the Waikato area ($n=1846$) were identified from the WBCR and the National Screening Database. Stage at diagnosis and survival were compared for screen detected ($n=1064$) and non-screen detected ($n=782$) breast cancer by ethnicity and socioeconomic status.

Results:

Indigenous Māori women were significantly more likely to be diagnosed with more advanced cancer compared with NZ European women ($OR=1.51$), and approximately a half of this difference was explained by lower rate of screen detected cancer for Māori women. For non-screen detected cancer, Māori had significantly lower 10-year breast cancer survival compared with NZ European (46.5% vs. 73.2%) as did most deprived compared with most affluent socioeconomic quintiles (64.8% vs. 81.1%). No significant survival differences were observed for screen detected cancer by ethnicity or socioeconomic deprivation.

Conclusions:

The lower rate of screen detected breast cancer appears to be a key contributor towards the higher rate of advanced cancer at diagnosis and lower breast cancer survival for Māori compared with NZ European women. Among women with screen-detected breast cancer, Māori women do just as well as NZ European women, demonstrating the success of breast screening for Māori women who are able to access screening. Increasing breast cancer screening rates has the potential to improve survival for Māori women and reduce breast cancer survival inequity between Māori and NZ European women.

Background:

In parallel with many other developed countries, New Zealand has experienced a substantial reduction in breast cancer mortality over the last two decades (1). While some of the observed reduction in breast cancer mortality in these countries has been attributed to advances in treatment, mammographic breast cancer screening has also played a major role (130). Since it was established in 1999, the BSA has provided free biennial mammographic screening for all women aged between 50 to 64 years and this age range was extended to include women aged 45 to 49 and 65 to 69 years in July 2004.

Mammographic screening coverage in New Zealand has gradually picked up over the last decade and has achieved the target biennial coverage of 70% for NZ European women since 2010 (39). However, poor screening coverage has remained a significant issue for Māori women for whom the coverage was only 62.7% in 2012 (39), well below the 70% target coverage. Further, there was a large variability in screening coverage rate for Māori by region, which ranged from 54% to 79% across the country in 2012 (40). There is, however, close monitoring of Māori coverage, and targets are set yearly with screening providers to improve this. It is this effort that has picked Māori coverage up from below 40% at the commencement of BSA programme in 1999 to the current level of over 60% (40). In spite of this, lower screening coverage remains a likely major contributor to inequities in breast cancer burden between Māori and NZ European women, as Māori have a higher breast cancer incidence and are more likely to present with advanced cancer compared with NZ European women (1).

This study was conducted to explore differences in rates of screen detected cancer by ethnicity and socioeconomic deprivation in a cohort of screening age women, and to determine the contribution of these differences to ethnic and socioeconomic inequities in breast cancer survival in New Zealand.

Methods:

Study population:

All screening age women with newly diagnosed breast cancer between 01/01/1999 and 31/12/2012 identified from the WBCR were eligible for this study (n=1846). Screening age was defined according to the BSA. This included women between 50 and 64 years up to June 2004 and women between 45 and 69 years from July 2005 onwards. Screening status was

classified into screen-detected (n=1064, 57.6%), interval (if diagnosis within 24 months from last screening mammogram, n=241, 13.1%) and non-interval symptomatic (n=541, 29.3%). Cancers diagnosed through BSA (n=954, 89.7%) and through opportunistic screening mammograms arranged by physicians outside BSA (n=110, 10.3%) were included under screen detected cancers. Screening status for each woman diagnosed through BSA was confirmed by comparing with screening data from the BSA database, which include data (i.e., screen detected and interval) for all women with breast cancer diagnosed through the BSA programme. Details of opportunistic screening were based on the WBCR records, and were reconfirmed by accessing clinical and mammographic records of all these women. For women with more than one episode of breast cancer during the study period, only the first cancer was included for analysis.

Outcome variables:

Date and cause of death for all deceased women (censored at 31/12/2013) were identified from the WBCR and from the Mortality Collection of the Ministry of Health. Follow up duration was calculated from the date of diagnosis to the date of death, or to the date of the last follow up when the patient was known to be alive (censored at 31/12/2013).

Statistical analysis:

Chi squared (χ^2) test for trend was used to test for univariate differences between groups of interest. Multivariate logistic regression analyses were used to test for differences in early versus advanced stage at diagnosis between Māori and NZ European women sequentially adjusting for age, year of diagnosis, screening status, socioeconomic deprivation and residential status. Impact of differences in screen detected cancer towards mortality disparity between Māori and NZ European women was explored in Cox proportional hazard models sequentially adjusting for same covariates. Interaction terms were included into regression models to identify possible interactions between ethnicity, deprivation and screening status (i.e., ethnicity x deprivation, ethnicity x screening and deprivation x screening). We also investigated 5-year and 10-year breast cancer specific survival rates for invasive cancers by screening status, ethnicity and socioeconomic deprivation using Kaplan-Meier survival curves. Survival comparisons by ethnicity were performed for Māori and NZ European women. Pacific and Other ethnic group women were excluded from these analyses.

Results:

This study included a total of 1846 screening age women (1548 invasive and 298 in-situ) with newly diagnosed first primary breast cancer over the study period. Of these women 1064 (57.6%) were screen detected and 782 (42.4%) were symptomatic. Of symptomatic women, 241 (30.8%) had interval and 541 (69.2%) had non-interval symptomatic cancers. Mean follow-up was 65.5 months (median 58 months). Sixty-seven percent of women were followed up for a minimum of five years or until death and 32% were followed up for ten years or until death. Overall mean age of included women was 56.8 years (median 56). Mean ages for in-situ and invasive breast cancers were 56.5 (median 56.5) and 56.9 years (median 56) respectively.

Lower proportions of cancers were observed within 45-49 and 65-69 age categories as these two age categories were included in the BSA only from July 2004 onwards (Table 1). When women diagnosed since July 2004 were considered alone, almost similar proportions of women were observed to be included in each age category, which ranged from 19.0% (55-59 age category) to 21.1% (60-64 age category).

No difference in age distribution was seen for Māori and NZ European women where the median age at diagnosis was 56 years. Women of higher socioeconomic deprivation quintiles were significantly older at diagnosis compared with women of lower deprivation quintiles which ranged from a mean age of 55.2 years for deprivation quintile 1-2 to a mean age of 57.2 years for deprivation quintile 9-10 ($p<0.001$).

Overall, 62.7% of all breast cancers among NZ European women within screening age were screen detected compared with 49.2% among Māori women of this age range ($p<0.001$). Of the screen detected cancers, a higher proportion of cancers in NZ European women were detected through opportunistic screening (10.9%) compared with Māori (7.3%), but this difference was statistically not significant ($p=0.183$). The difference in proportion of screen detected cancer between NZ European and Māori women was significant for invasive cancers (58.3% vs. 45.1%, $p=<0.001$), but was not statistically significant for in-situ cancers (85.4% vs. 74.4%, $p=0.063$).

Table 13: Characteristics of women associated with early stage [compared with advanced stage] at diagnosis of breast cancer by ethnicity for screening age women with newly diagnosed breast cancer in the Waikato, New Zealand 1999-2012

Characteristic	NZ European		Māori		All cancers				
	(N=1459)	Early ^a	(N=311)	Early ^a	(N=1846)	Early ^a	OR	95% CI	p
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)				
Screening status									<0.001
Screen detected	915 (62.7)	654 (71.5)	153 (49.2)	107 (69.9)	1106 (59.9)	786 (71.1)	Ref		
Interval	192 (13.2)	63 (32.8)	20 (6.4)	3 (15.0)	218 (11.3)	69 (31.7)	5.30	4.15-6.74	
Non-screen	352 (24.1)	118 (33.5)	138 (44.4)	36 (26.1)	522 (28.3)	162 (31.0)	5.46	4.11-7.33	
Age group (years)									
45-49	208 (14.3)	110 (52.9)	51 (16.4)	23 (45.1)	275 (14.9) ^b	143 (52.0)	Ref		0.005
50-54	375 (25.7)	206 (54.9)	77 (24.8)	31 (40.3)	469 (25.4)	245 (52.2)	0.99	0.74-1.33	
55-59	323 (22.1)	180 (55.7)	74 (23.8)	32 (43.2)	416 (22.5)	218 (52.4)	0.98	0.73-1.33	
60-64	337 (23.1)	196 (58.2)	73 (23.5)	36 (49.3)	425 (23.0)	241 (56.7)	0.83	0.61-1.12	
65-69	216 (14.8)	143 (66.2)	36 (11.6)	24 (66.7)	261 (14.1) ^b	170 (65.1)	0.58	0.41-0.82	

Deprivation								
Dep 1-2	184 (12.6)	101 (54.9)	9 (2.9)	1 (11.1)	203 (11.0)	108 (53.2)	Ref	0.094
Dep 3-4	157 (10.8)	104 (66.2)	23 (7.4)	13 (56.5)	186 (10.1)	120 (64.5)	0.63	0.42–0.94
Dep 5-6	339 (23.2)	189 (55.8)	62 (19.9)	29 (46.8)	411 (22.3)	223 (54.3)	0.96	0.68–1.34
Dep 7-8	492 (33.7)	279 (56.7)	95 (30.5)	43 (45.3)	614 (33.3)	338 (55.0)	0.93	0.68–1.28
Dep 9-10	287 (19.7)	162 (56.4)	122 (39.2)	60 (49.2)	432 (23.4)	228 (52.8)	1.02	0.73–1.42
Residence								
Urban	783 (53.7)	435 (55.6)	150 (48.2)	75 (50.0)	990 (53.6)	539 (54.4)	Ref	0.794
Semi-urban	370 (25.4)	222 (60.0)	107 (34.4)	50 (46.7)	492 (26.7)	277 (56.3)	0.93	0.75–1.15
Rural	306 (21.0)	178 (58.2)	54 (17.4)	21 (38.9)	364 (19.7)	201 (55.2)	0.97	0.76–1.23
Year of diagnosis								
1999-2002	249 (17.1)	128 (51.4)	44 (14.1)	20 (45.5)	300 (16.3)	153 (51.0)	Ref	0.423
2003-2006	450 (30.8)	270 (60.0)	75 (24.1)	33 (44.0)	542 (29.4)	308 (56.8)	0.79	0.60-1.05
2007-2009	363 (24.9)	203 (55.9)	86 (27.7)	45 (52.3)	479 (25.9)	263 (54.9)	0.86	0.64-1.14
2010-2012	397 (27.2)	234 (58.9)	106 (34.1)	48 (45.3)	525 (28.4)	293 (55.8)	0.82	0.62-1.09

(^a early stage = in-situ & stage I, ^b only cancers diagnosed from July 2004 onwards are included)

Univariate analysis of factors associated with early stage disease (in-situ & stage I, n=1017) at diagnosis compared with more advanced stage (stages II, III & IV, n=829) is shown in Table 13. Non-screen compared with screen detection was significantly associated with more advanced stage at diagnosis ($OR=5.46$, $p<0.001$) as did Māori compared with NZ European ethnicity ($OR=1.51$, 95% CI 1.18-1.93, $p=0.001$). No significant differences were observed in early versus advanced stage at diagnosis by deprivation status ($p=0.094$). Table 14 shows odds ratios from multivariate logistic regression analyses for advanced versus early stage at diagnosis in Māori compared with NZ European women with sequential adjustment for covariates. Adjusting for screening status reduced the odds ratio for more advanced stage at diagnosis in Māori compared with NZ European from 1.49 (1.15-1.91) to 1.25 (0.96-1.64). A minimal further attenuation in odds ratio was observed with additional adjustments for socioeconomic deprivation and residential status ($OR=1.24$, 0.95-1.65). Similarly, odds of advanced stage at diagnosis remained largely unchanged after introducing interaction terms into the model ($OR=1.28$, 0.74-2.23). In a separate analysis (data not shown), socioeconomic deprivation was introduced into the model prior to screening status, but made no difference to the odds ratio ($OR=1.49$, 1.16-1.93).

Table 14: Odds ratios for stage at diagnosis (i.e., advanced ^b versus early ^a) in Māori compared with NZ European women with stepwise adjustment for age, year of diagnosis, screening status, socioeconomic deprivation and urban/rural residential status

Characteristic	OR	95% CI	p
Model A (Unadjusted))	1.51	1.18–1.93	0.001
Model B (Age adjusted)	1.49	1.16-1.91	0.002
Model C (Model B + Year of diagnosis ^c)	1.49	1.15-1.91	0.002
Model D (Model C + Screening status)	1.25	0.96-1.64	0.101
Model E (Model D + Deprivation)	1.24	0.94-1.64	0.133
Model F (Model E + Urban/Rural residence)	1.24	0.95-1.65	0.125
Model H (Model E + interaction terms ^d)	1.28	0.74-2.23	0.373

(^a early stage = in-situ & stage I, ^b advanced stage = stages I to III, ^c year categories as in Table 1, ^d – ethnicity*deprivation, ethnicity*screening and deprivation*screening)

Next we repeated a similar regression analyses only including invasive cancers to identify factors associated with more advanced invasive cancer (stages II, III & IV, n=829) versus early invasive (stage I, n=719) cancer at diagnosis (data not shown). This analysis yielded results similar to initial analysis with Māori having significantly more advanced disease at diagnosis (unadjusted) compared with NZ European women (OR=1.53, 1.17-2.01, p=0.002). Adjusting for screening status resulted in a reduction of age and year adjusted odds ratio for advanced cancer in Māori compared with NZ European from 1.52 (1.15-1.99) to 1.30 (0.97-1.75). Further adjustment for deprivation made no difference to this odds ratio (OR=1.30, 0.96-1.75).

Table 15: Adjusted (age and year of diagnosis) breast cancer specific mortality hazard ratios from Cox regression model

Characteristic	All cancers			Screen detected			Non-screen detected		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Ethnicity									
NZ European	Ref			Ref			Ref		
Māori	1.33	0.33-3.18	0.964	1.45	0.33-6.39	0.620	3.13	1.58-6.18	0.001
Mode of diagnosis									
Screen detected	Ref			-			-		
Non-Screen	2.81	1.57-5.04	0.001						
Deprivation quintile									
1-2	Ref	0.118		Ref	0.627	Ref			0.019
3-4	0.84	0.39-1.78		0.77	0.19-3.10		0.76	0.35-2.13	
5-6	0.86	0.45-1.66		0.91	0.28-2.79		0.68	0.39-1.84	
7-8	1.26	0.58-2.74		1.13	0.35-3.60		0.08	0.93-3.76	
9-10	0.73	0.32-1.69		0.56	0.15-2.06		0.71	0.52-2.56	
Residential status									
Urban	Ref	0.311		Ref	0.370	Ref			0.155
Semi-urban	0.77	0.53-1.12		1.51	0.73-3.14		0.65	0.42-1.01	
Rural	0.81	0.54-1.21		0.78	0.31-1.94		0.85	0.54-1.32	
Ethnicity x Deprivation	0.65	0.31-1.36	0.253	0.39	0.05-3.07	0.370	0.69	0.31-1.54	0.468
Ethnicity x Screening	3.29	1.10-9.85	0.033	-			-		
Deprivation x Screening	1.47	0.71-3.06	0.302	-			-		

Adjusted breast cancer specific mortality hazard ratios from Cox regression models by screening status for women with invasive breast cancers are shown in Table 15. Māori women were observed to have higher hazards of breast cancer mortality overall (HR=1.33, 0.33-3.18) and for screen detected (HR=1.45, 0.33-6.39) and non-screen detected cancers (HR=3.13, 1.58-6.18), although this was statistically significant only for non-screen detected cancer.

Breast cancer specific mortality hazard ratios for Māori compared with NZ European women with sequential adjustment for covariates is shown in Table 16. In the model for all cancers, adjusting for screening status reduced the mortality hazard for Māori from 2.33 to 2.01, while further adjusting for deprivation resulted in a marginal increase of hazard up to 2.09.

Adjusting for socioeconomic deprivation before adjusting for screening (data not shown) saw a similar increase in hazard for Māori from 2.33 to 2.37. For screen detected cancers, Māori women had non-significant lower hazards of mortality before (HR=0.77) and after adjusting for covariates (HR=0.85), but was non-significantly higher after introduction of interaction terms (HR=1.45). In contrast, for non-screen detected cancers Māori had a significantly higher risk of mortality which was more than double that for NZ European women before (HR=2.28) and after adjusting for covariates (HR=2.37) and introduction of interaction terms (HR=3.13).

Unadjusted five and 10-year breast cancer specific survival rates for invasive cancers by screening status, ethnicity and deprivation are shown in Table 17. Screen detected invasive cancers demonstrated the highest five and 10-year breast cancer specific survival rates and the lowest rates were seen for non-interval symptomatic breast cancers. Māori women had significantly lower crude five (90.2% vs. 77.6%) and 10-year (83.5% vs. 73.8%) breast cancer survival rates compared with NZ European women. Compared with women from more affluent (1-2, 3-4 to 5-6) quintiles, women from more deprived quintiles (7-8 and 9-10) had significantly worse 10-year breast cancer survival rates (84.3% vs. 77.2%, p=0.011).

Māori women with non-screen detected invasive cancer had significantly worse five and 10-year breast cancer survival rates compared with NZ European women (83.1% vs. 64.2% and 73.2% vs. 46.5% respectively, p<0.001). In contrast, for screen detected breast cancer, Māori women had, if anything, better five and 10-year breast cancer specific survival rates (96.9% and 94.1%) compared with NZ European women (95.8% and 90.3%), although this was statistically non-significant (p=0.651) (Figure 19).

Table 16: Hazard ratios for breast cancer-specific mortality risk in Māori compared with NZ European women with stepwise adjustment for age, year of diagnosis, screening status, socioeconomic deprivation and urban/rural residential status

Characteristic	All cancers		Screen detected		Non-screen detected	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Model A (Unadjusted)	2.25 (1.62-3.12)	<0.001	0.77 (0.27-2.15)	0.617	2.28 (1.59-3.26)	<0.001
Model B (Age adjusted)	2.29 (1.69-3.18)	<0.001	0.80 (0.29-2.25)	0.674	2.34 (1.63-3.35)	<0.001
Model C (Model B + Year of diagnosis ^a)	2.33 (1.64-3.25)	<0.001	0.84 (0.31-2.36)	0.738	2.27 (1.59-3.25)	<0.001
Model D (Model C + Screening status)	2.01 (1.44-2.80)	<0.001	-	-	-	-
Model E (Model D + Deprivation)	2.09 (1.49-2.94)	<0.001	0.85 (0.30-2.40)	0.762	2.39 (1.65-3.46)	<0.001
Model F (Model E + Urban/Rural residence)	2.11 (1.50-2.97)	<0.001	0.85 (0.30-2.41)	0.760	2.37 (1.64-3.47)	<0.001
Model G (Model F + Interaction terms ^b)	1.33 (0.33-3.18)	0.964	1.45 (0.33-6.39)	0.620	3.13 (1.58-6.18)	0.001

(^a year categories as in Table 1, ^b – ethnicity x deprivation, ethnicity x screening and deprivation x screening

Table 17: Five-year and 10-year breast cancer specific survival rates by screening status, ethnicity and socioeconomic deprivation for screening age women with invasive breast cancer in the Waikato, New Zealand 1999-2012

Characteristic	No. of women	Total breast cancer deaths	5-year survival	95% CI	10-year survival	95% CI
Screening status						
Screen detected	858	40	96.2%	94.6 - 97.8	91.8%	88.3 - 95.3
Interval	217	36	83.9%	79.3 - 88.5	73.5%	64.1 - 82.9
Non-screen non-interval	473	108	76.4%	70.9 - 81.9	66.3%	60.2 - 72.4
Ethnicity						
NZ European	1220	126	90.2%	88.2 - 92.2	83.5%	77.4 - 89.6
Māori	268	50	77.6%	71.5 - 83.7	67.8%	58.4 - 77.2
Deprivation						
Dep 1-2	165	14	89.5	83.8 - 95.2	87.1	80.2 - 94.0
Dep 3-4	155	15	89.7	84.2 - 95.2	85.8	79.7 - 93.9
Dep 5-6	347	33	90.8	87.1 - 94.5	85.0	76.6 - 89.6
Dep 7-8	513	81	84.1	80.4 - 87.8	75.4	69.9 - 80.9
Dep 9-10	368	41	88.2	84.7 - 91.7	79.7	72.6 - 86.8

Figure 19: Kaplan-Meier curves for breast cancer specific survival for screen detected (Panel A) and symptomatically detected (Panel B) breast cancers in screening age women by ethnicity

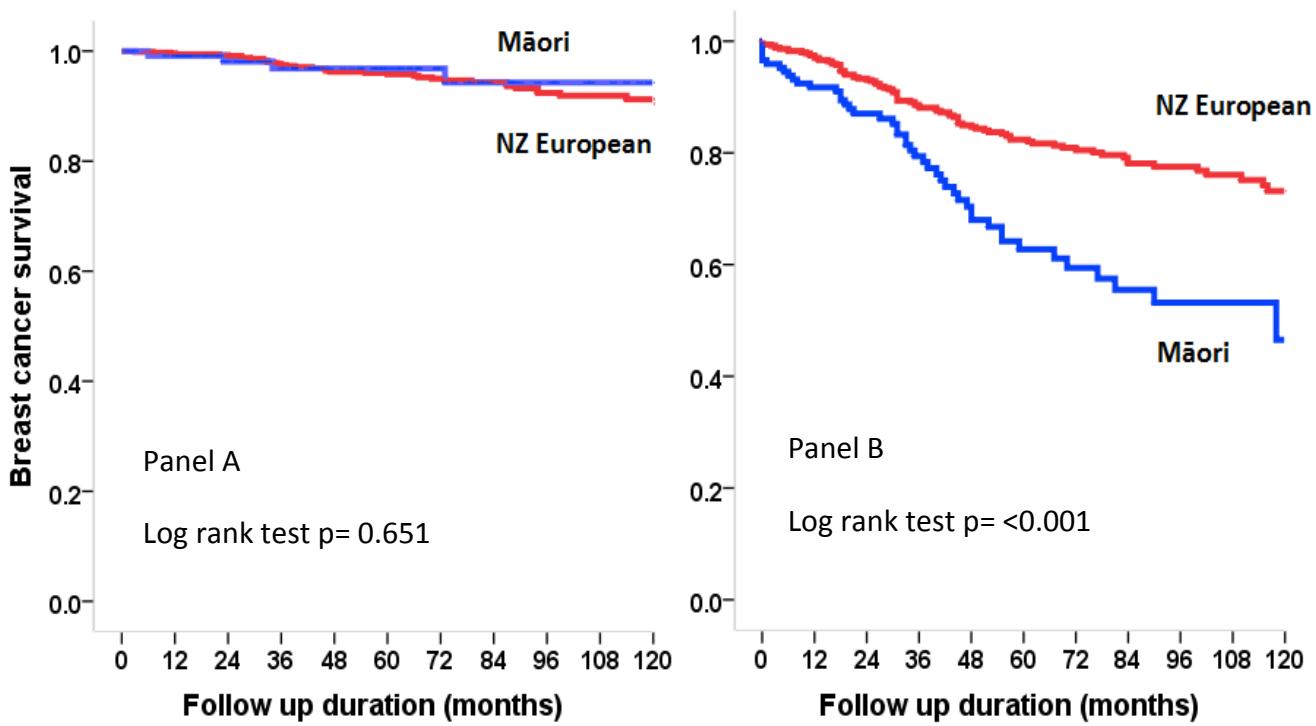


Figure 20 shows the association between screening status and socioeconomic deprivation on 10-year breast cancer specific survival rates based on Kaplan-Meier survival analysis. There was a tendency for higher survival in women from more affluent quintiles. The difference in breast cancer specific survival rates between more and less affluent women was substantially lower for women with screen detected breast cancer than for non-screen detected breast cancer. This has resulted in a greater survival difference between screen and non-screen detected cancer with increasing socioeconomic deprivation.

Figure 20: Ten-year breast cancer specific survival rates by socioeconomic deprivation (based on Kaplan-Meier survival curves by socioeconomic deprivation quintile) for screening age women

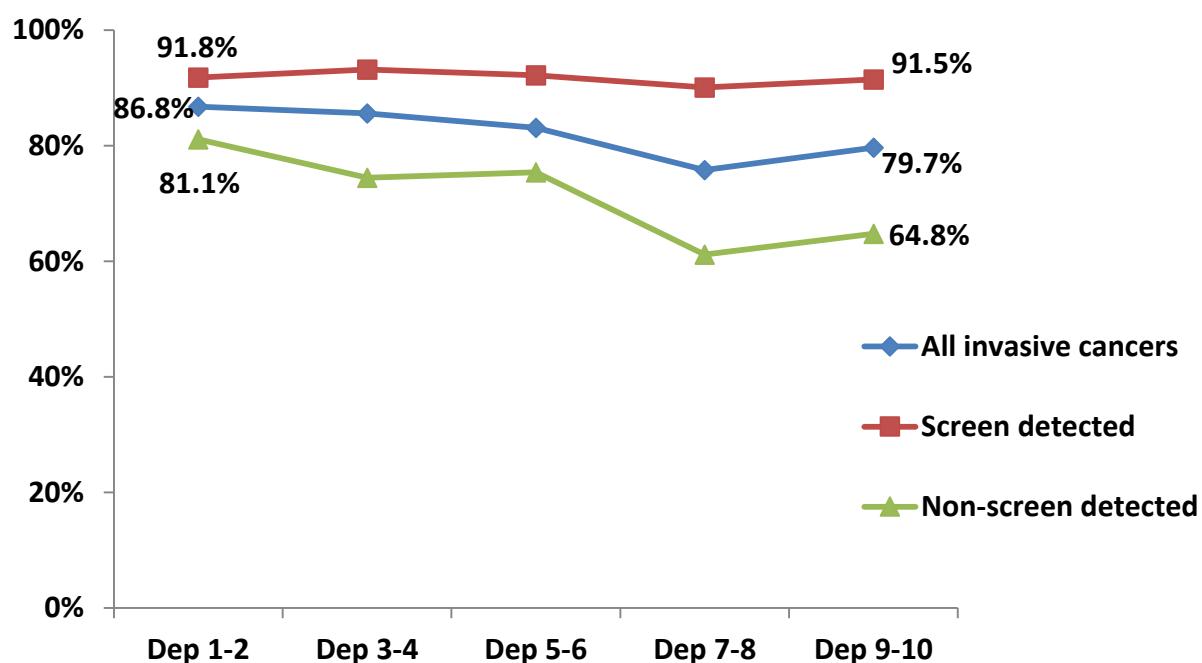
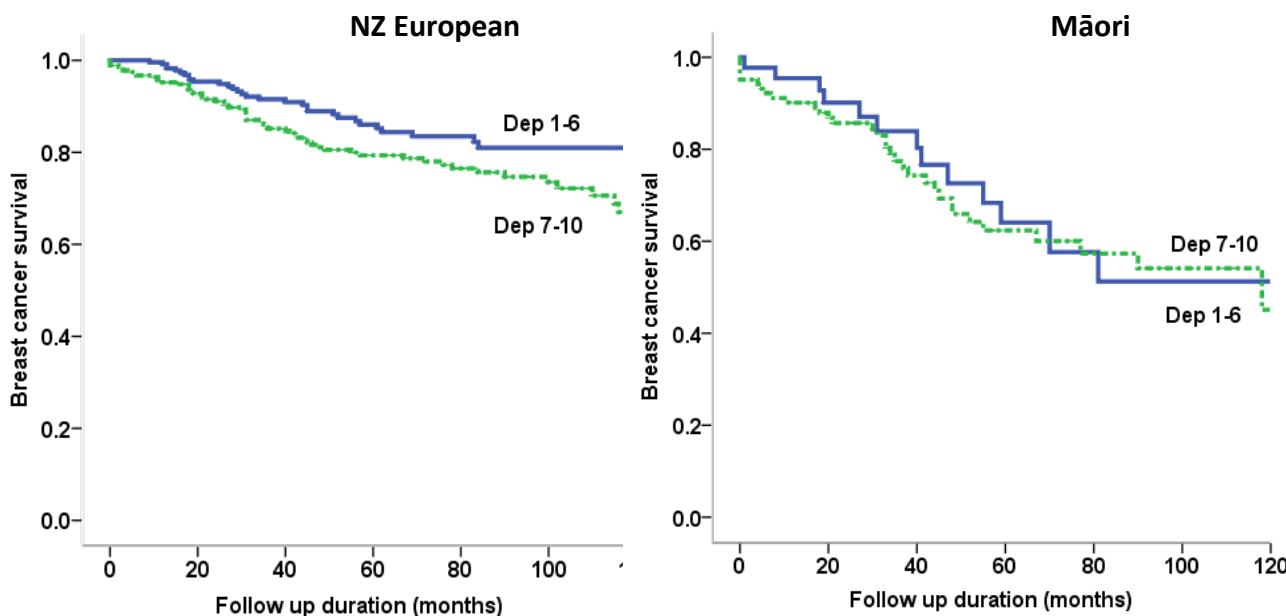


Figure 21 illustrates breast cancer specific survivals for women with non-screen detected cancer by socioeconomic deprivation (Dep 1-6 versus Dep 7-10) and ethnicity. Among NZ Europeans, women of higher socioeconomic groups (Dep 1-6) had significantly better survival rates compared with women of lower socioeconomic groups (Dep 7-10) (10-year survival 81% vs. 67.6%, $p=0.026$). In comparison, survival rates did not vary by deprivation status among Māori women with non-screen detected cancer (10-year survival 51.2% vs. 44.4%, $p=0.715$).

Figure 21: Kaplan-Meier survival curves for non-screen detected cancers in screening age NZ European and Māori women by socioeconomic deprivation status



Discussion:

From this study we found that breast cancer survival inequities between Māori and NZ European women in the screening age group were significant for women diagnosed through the non-screen pathway, but absent for women diagnosed through screening. Five and 10-year survival for women diagnosed through screening were 2.8% and 5.2% higher respectively, for Māori compared with NZ European women, while Māori women diagnosed through the non-screen pathway had a 9.9% lower 5-year and a 17.7% lower 10-year survival than NZ European women. We found that patterns of inequities by socioeconomic deprivation were similar to those found between Māori and NZ European women. For non-screen detected cancer, 10-year breast cancer specific survival was 16.3% lower for most deprived compared with women from most affluent socioeconomic quintile.

Benefits of population based mammographic breast cancer screening have been proven by several randomized trials (130, 291). It has been shown that provision of biennial screening with a 70% coverage confers an approximately a 30% reduction in breast cancer mortality for the screening population (292). The breast cancer incidence for NZ European women is similar to the rates seen in breast cancer screening trials (55, 292), but incidence in Māori is much higher (293). Hence, at a 70% biennial screening rate, more Māori women may benefit than non-Māori, and given that Māori women with symptomatic cancer tend to present at a later stage than non-Māori, Māori women may also have a greater reduction in breast cancer mortality with screening. Our data lend support to this hypothesis.

Compared with NZ Europeans, a higher proportion of breast cancer is observed among younger Māori women due to the younger age structure of Māori population (164). Further, the screen detection rate for Māori women between 45 to 49 years in initial mammographic screens is more than twice that for non-Māori, and is 50% greater even for subsequent screening mammograms (40). Breast cancer in younger women tends to be more aggressive and is more likely to be associated with poorer outcomes (294). Thus, it may be worthwhile exploring the usefulness of providing breast cancer screening for Māori women below the current screening age limit, for instance for women between 40 and 44 years. However, a thorough evaluation of potential benefits versus harms of mammographic screening should be an essential part of such an initiative.

Obese women are more likely to present with more advanced breast cancer compared with non-obese women and are more likely to be diagnosed through screening mammography than non-obese (295). Approximately 48% of adult Māori women are obese, which is almost twice the rate observed in NZ European women (33). Evidence from the USA suggests that up to 30% of later stage breast cancer diagnosed in African American women compared with White American women are attributable to higher rates of obesity in African American women (296). At present, no New Zealand data are available on the impact of obesity on ethnic differences in breast cancer stage at diagnosis or outcomes. Nonetheless, higher obesity prevalence is likely to be another factor that would confer a greater benefit from increased mammographic screening coverage for Māori compared with NZ European women.

Survival differences for screen detected breast cancer were not seen, either by ethnicity or socioeconomic deprivation, while differences in survival were marked and significant for non-screen detected cancer by both. Similar observations have been reported from the UK, the USA and the Netherlands (137, 293, 297). Inequities in breast cancer survival by ethnicity and socioeconomic status for women diagnosed through non-screen pathway are likely due to a range of factors. While later stage at diagnosis for Māori and women of socioeconomically deprived groups is the likely major factor for these differences, higher rates of obesity, comorbidities and differences in treatment compared with NZ European and more affluent women, respectively are also likely to be important. In addition, women who participate in mammographic screening may be more likely to have better access to health care, education, health literacy and health seeking behaviours compared with women from similar ethnic or socioeconomic backgrounds, who do not participate in screening (298).

Furthermore, there is a stringent quality framework and an audit process for the treatment of breast cancer detected through BSA, but not for cancers diagnosed outside BSA (39). Results for each regional screening provider are regularly audited and a feedback process ensures that adequate measures are undertaken by providers who fail to achieve these targets. Similar audit processes or quality frameworks are not in place for non-screen detected cancer treatment. Lack of a framework is a likely key reason for the disparities observed amongst women with non-screen detected cancers by ethnic and socioeconomic grouping. To overcome these disparities in cancer care, the Ministry of Health is in the process of introducing quality measures for the management of all common cancers through the National Cancer Control Strategy. These include the Faster Cancer Treatment Indicators (58) and the Standards of Service Provision for Breast Cancer Patients in New Zealand (59). These measures will provide benchmarks for quality cancer care and are expected to improve care for all women with breast cancer as well as reducing and hopefully eliminating inequities in access, timeliness and quality of care along the symptomatic breast cancer care pathway.

The main strengths of this study include the completeness and comprehensive nature of the study sample and data linkage with the national screening database which enabled us to define and validate screen detected, interval and symptomatic non-interval cancers. Limitations of this study include the absence of data on previous breast cancer screening behaviours of these women, which is a factor known to be associated with cancer stage at diagnosis and long term outcomes (137). Also, we were unable to ascertain the reasons for non-screening participation in women with symptomatic non-interval cancer, which however is beyond the scope of the present study.

In conclusion, we have observed a significantly higher rate of advanced stage breast cancers among screening age Māori compared with NZ European women, of which approximately a half was explained by lower rate of screen detected cancer among Māori women. Significant differences in breast cancer survival by ethnicity and socioeconomic deprivation were observed for non-screen detected, but not for screen detected breast cancer. Māori women who do have screen detected breast cancers appear to do just as well as NZ European women demonstrating the success of BSA for Māori women who are able to access this programme. Achieving at least the national 70% biennial breast cancer screening rate for eligible Māori women will likely make a significant contribution to reducing cancer deaths for Māori as well as reducing inequities in cancer deaths between Māori and NZ European women in New Zealand.

5.4. Are there ethnic differences in breast cancer biology?

Preface:

This chapter contains an abbreviated version of a manuscript published in *PLOS ONE*.

- **Authors:** Seneviratne S, Scott N, Shirley R, Kim B, Lawrenson R, Campbell I.
- **Title:** Breast cancer biology and ethnic disparities in breast cancer mortality in New Zealand: a cohort study
- **Journal:** *PLOS ONE*
- **Year of publication:** 2015
- **Impact factor:** 3.73
- **Journal's aims and scope:** *PLOS ONE* is an open access peer-reviewed scientific journal published by the Public Library of Science (PLOS) since 2006. It is the world's largest journal by number of papers published. It covers primary research from any discipline within science and medicine. All submissions go through an internal and external pre-publication peer review, but are not excluded on the basis of lack of perceived importance or adherence to a scientific field. The PLOS ONE online platform employs a "publish first, judge later" methodology, with post-publication user discussion and rating features.

Abstract:

Background:

Differences in cancer biological characteristics between Indigenous Māori and NZ European women have been proposed as a possible contributor for higher breast cancer mortality in Māori women. This study investigated differences in cancer biological characteristics and their impact on breast cancer mortality disparity between Māori and NZ European women.

Methods:

Data on 2849 women with primary invasive breast cancers diagnosed between 1999 and 2012 were extracted from the WBCR. Differences in distribution of cancer biological characteristics between Māori and NZ European women were explored adjusting for age and socioeconomic deprivation in logistic regression models. Impacts of deprivation, stage at diagnosis and biological characteristics on breast cancer mortality disparity between Māori and NZ European women were explored in a Cox regression model.

Results:

Compared with NZ European women (n=2304), Māori women (n=429) had significantly higher rates of advance staged and higher graded cancers. Māori women also had non-significantly higher rates of ER/PR negative and HER-2 positive breast cancers. Higher odds of advanced stage and higher grade remained significant for Māori after adjusting for age and socioeconomic deprivation. Māori women had almost a 100% higher age and socioeconomic deprivation adjusted breast cancer mortality risk compared with NZ European women (hazard ratio=1.98, 1.55-2.54). Advanced stage at diagnosis and differences in breast cancer biological characteristics explained a greater portion of the excess breast cancer mortality in Māori compared with NZ European women (final hazard ratio=1.35, 1.04-1.75).

Conclusions:

More advanced cancer stage at diagnosis has the greatest impact while differences in biological characteristics appear to be only a minor contributor for inequities in breast cancer mortality between Māori and NZ European women. Underlying causes for these differences in biological characteristics are unclear at present and is an area for future research.

Background:

Advanced cancer stage at diagnosis in Māori has been shown to be the major contributor for lower breast cancer survival in Māori compared with NZ European women (4). However, significant ethnic differences in breast cancer survival remain after adjustment for stage at diagnosis (4). Hence, factors other than stage including differences in timeliness and quality of treatment and/or differences in cancer biology are likely to be important contributors to the mortality disparity between Māori and NZ European women.

Data on biological differences in breast cancer between Māori and NZ European women have so far been limited (70, 74, 169). The largest study to date was published by McKenzie et al based on a cohort of women diagnosed during 1994-2004 from the New Zealand Cancer Registry (70). The authors of this paper have reported significant differences in biological characteristics, including higher rates of poorly differentiated and human epidermal growth factor receptor type 2 (HER-2) positive cancers, and lower rates oestrogen (ER) and progesterone receptor (PR) negative cancers in Māori compared with non-Māori/non-Pacific (i.e. NZ European) women, which appeared to be independent of socioeconomic deprivation. Two other groups from Auckland and Christchurch have also investigated biological differences using smaller regional cohorts, but have reported on ethnic differences that significantly differ from McKenzie et al report, including for tumour grade and hormone receptor status (74, 169). Although all three studies have contributed significantly to the knowledgebase on ethnic differences in biological characteristics, the exact nature of these differences and their impact on breast cancer survival inequity between Māori and NZ European women remain unclear at present.

We conducted this study to further investigate differences in breast cancer biological characteristics between Māori and NZ European women, and to compare with previously reported figures. We also attempted to identify the impact of biological differences on ethnic disparities in breast cancer mortality in New Zealand.

Methods:

Study population:

All women with newly diagnosed invasive primary breast cancers from 01/01/1999 to 31/12/2012 were identified from the WBCR.

Study covariates:

Cancer stage at diagnosis was defined according to the Tumour, Node, and Metastasis (TNM) staging system (267). Invasive tumour grade was defined according to the Elston and Ellis modified Scarff-Bloom-Richardson breast cancer grading system (269). Oestrogen (ER) and progesterone (PR) receptor status was determined based on results of immunohistochemistry tests and classified as positive or negative. HER-2 status was based on Fluorescent In-Situ Hybridization (FISH) test or when this was not available, on immunohistochemistry (270).

Statistical analysis:

Categorical measures were summarized as numbers with percentages and continuous variables were summarized as means with standard deviation. Chi squared (χ^2) test for trend was used to test for univariate differences in age adjusted rates of cancer biological characteristics between Māori and NZ European women. Logistic regression models were used to explore associations of tumour biology with socioeconomic deprivation and ethnicity, adjusting for age.

Multivariable Cox proportional hazard models were used to calculate hazard ratios with 95% confidence intervals to identify the association of ethnicity, cancer stage and different cancer biological factors with breast cancer specific mortality independently, and adjusting for age and socioeconomic deprivation. Due to small numbers Pacific and Other ethnic group women were excluded from analyses and ethnic comparisons were performed for Māori and NZ European women. Breast cancer-specific survival curves for Māori and NZ European women were estimated using the Kaplan-Meier method and compared by log-rank test. Deaths due to causes other than breast cancer were considered as censored events. As some of the variables included high numbers of missing data, survival analysis was repeated using women diagnosed from 2006 onwards, where rates of missing data were significantly lower. A further analysis was performed using only cases with complete data for all variables. Results of this analysis were almost similar to those obtained from the full Cox proportional hazards regression model, and these data are not presented in this report. Imputation of missing values was not undertaken due to the similarity of these results.

Results:

A total of 2856 women with new primary invasive breast cancer diagnosed in the Waikato area over the study period were identified. Of these, Pacific (n=53) and Other (n=63) ethnic women and seven women in whom a diagnosis of breast cancer was made post-mortem were excluded, leaving 2733 for analysis. There were a total of 688 (25.2%) deaths, out of which 407 (59.2%) were due to breast cancer; 317 (77.9%) in NZ European and 90 (22.1%) in Māori women. The study cohort was followed up for a median of 58 months (mean 66 months) and 67% women were followed up for a minimum of five years or until death.

Majority of the study women were of NZ European ethnicity (n=2304, 80.9%) and 15.1% (n=429) were Māori. Distribution of tumour biological characteristics by ethnicity is shown in Table 18. Māori women were significantly younger with a mean age difference of approximately six years (61.5 vs. 55.6 years, p<0.001) keeping in with relatively younger Māori population compared with NZ Europeans. A significantly higher age adjusted rate of invasive ductal cancer was observed in Māori compared with NZ European women (85.0% vs. 80.5%, p=0.032). A corresponding reduction in the rate of invasive lobular carcinoma was seen in Māori compared with NZ European (8.7% vs. 11.7%, p=0.072), although this difference was not statistically significant. Māori women had higher likelihoods of larger breast tumours (p<0.001), positive lymphadenopathy (p<0.001), metastatic cancer (p<0.001) and overall more advanced staged cancer (p<0.001) compared with NZ European women. Breast cancers among Māori were of higher grade (p=0.008) compared with NZ European women, with less grade I and more grade II cancers after adjusting for age. Age adjusted rates of ER+ and PR+ cancers tended to be lower (61.9% vs. 64.2%, p=0.373), and ER- and PR- cancers tended to be higher in Māori (17.9% vs. 14.4%, p=0.071) compared with NZ European women. When ER status is considered alone, age adjusted rate of ER positive cancers was significantly lower in Māori compared with NZ European women (80.6% vs. 84.5%, p=0.011) (Appendix 4). Māori women had a statistically non-significant, higher age adjusted rate of HER-2 amplified tumours (20.2% vs. 16.3%, p=0.068) compared to NZ European women (Table 18).

As the rate of missing HER-2 data was relatively high (26.2%), an analysis was performed only including breast cancers diagnosed from 2006, where the rate of missing HER-2 status was only 4.3%. This showed figures similar to complete NZ European and Māori cohorts, with a higher age adjusted rate of HER-2 positivity in Māori compared with NZ European women (19.7% vs. 14.3%, p=0.076) (Table 18).

Table 18: Age and breast cancer biological characteristics at diagnosis compared between NZ European and Māori women.

Characteristic	NZ European (N=2304)		Māori (N=429)		<i>p</i>
	n (crude %)	<i>Age adjusted %</i>	n (crude %)	<i>Age adjusted %</i>	
Age					
Mean ± SD	61.5 ± 13.9		55.6 ± 12.2		<0.001
T Stage					
1	1249 (54.4)	53.2	178 (41.7)	42.5	<0.001
2	821 (35.8)	36.6	172 (40.4)	40.8	
3	100 (4.4)	4.5	27 (6.3)	5.8	
4	121 (5.3)	5.8	49 (11.5)	11.0	
Unknown	13		3		
N stage					
0	1404 (61.4)	62.9	220 (51.9)	53.3	<0.001
1	582 (25.5)	24.7	130 (30.7)	29.7	
2	188 (8.2)	7.8	40 (9.4)	9.3	
3	112 (4.9)	4.6	34 (8.0)	7.7	
Unknown	18		5		
M Stage					
0	2197 (95.4)	94.9	379 (88.3)	88.6	<0.001
1	107 (4.6)	5.1	50 (11.7)	11.4	
Stage category					
I	972 (42.2)	41.6	142 (33.1)	34.2	<0.001
II	887 (38.5)	39.1	163 (38.0)	37.5	
III	338 (14.7)	14.2	74 (17.2)	16.9	
IV	107 (4.6)	5.1	50 (11.7)	11.4	
Histology					
Ductal	1831 (81.2)	80.5	352 (85.2)	85.0	0.032 ^a
Lobular	258 (11.4)	11.7	35 (8.5)	8.7	0.072 ^b
Mixed	42 (1.9)	1.8	9 (2.2)	2.3	
Other	125 (5.5)	5.9	17 (4.1)	4.0	
Unknown	48		16		

Grade					
Grade I	543 (25.3)	25.6	69 (17.6)	18.5	0.008
Grade II	1118 (52.1)	52.7	229 (58.4)	59.7	
Grade III	485 (22.6)	21.7	93 (23.7)	21.8	
Unknown	158		38		
ER/PR					
ER+/PR+	1414 (64.1)	64.2	252 (60.9)	61.9	0.204
ER+/PR-	430 (19.5)	20.2	75 (18.1)	18.6	0.071 ^c
ER-/PR+	28 (1.3)	1.1	8 (1.9)	1.6	
ER-/PR-	333 (15.1)	14.4	79 (19.1)	17.9	
ER or PR	99		15		
Unknown					
HER-2					
Negative	1239 (74.8)	75.2	257 (72.4)	73.8	0.091
Equivocal	135 (8.1)	8.5	21 (5.9)	6.0	0.069 ^d
Positive	283 (17.1)	16.3	77 (21.7)	20.2	
Unknown	647		74		
TNBC ^e					
No	1455 (91.5)	91.7	316 (92.9)	93.0	0.446
Yes	135 (8.5)	8.3	24 (7.1)	7.0	
Unknown	714		89		
Post 2005		NZ European (N=1247)		Māori (N=278)	
		n (crude %)	Age adjusted %	n (crude %)	Age adjusted %
HER-2					
Negative	946 (79.5)	79.9	202 (74.8)	75.9	0.072
Equivocal	65 (5.5)	5.8	11 (4.1)	4.4	0.012 ^d
Positive	179 (15.0)	14.3	57 (21.1)	19.7	
Unknown	57		8		
TNBC ^e					
No	1054 (92.6)	92.6	238 (93.3)	93.5	0.536
Yes	84 (7.4)	7.4	17 (6.7)	6.5	
Unknown	109		23		

^a ductal vs. other histology types, ^b lobular vs. other histology types, ^c ER and PR negative vs. other receptor expressions, ^d HER-2 positive vs. negative/equivocal, ^e triple negative breast cancer.

Triple receptor status (ER, PR and HER-2) was determined for a total 1930 (70.7%) women with invasive breast cancer. Of this group, 8.3% of cancers were negative for all three receptors; i.e. triple negative breast cancer (TNBC). NZ European women had a higher age adjusted rate of TNBC compared with Māori women, which was statistically not significant (7.0% vs. 8.3%, p=0.446). Of women diagnosed from 2006 onwards, TNBC status was available for 1393 (91.3%) women. Age-adjusted rate of TNBC was higher in NZ European than in Māori, but this was still statistically non-significant (7.4% vs. 6.5%, p=0.532).

Increasing social deprivation significantly increased the risk of (age adjusted) advance staged (p=0.001) and ER/PR negative (p=0.011) invasive cancers. No significant associations were observed between deprivation and age adjusted rates of high tumour grade (p=0.095), HER-2 positivity (p=0.939) or TNBC status (p=0.270) (Table 19). Higher socioeconomic deprivation status was significantly higher in Māori compared with NZ European women (Dep. 7-10 72.2% in Māori vs. 51.7% in NZ European, p<0.001, data not shown). Compared to NZ European women, age and socioeconomic deprivation adjusted risk of advanced stage, higher grade, ER and PR negativity and HER-2 positivity were higher while the rate of TNBC was lower(8.3% vs. 7.0) in Māori women. Differences in stage and grade were statistically significant, while differences in ER /PR, HER-2 and TNBC were not (Table 20).

Results from the survival analysis with Cox regression model are shown in Table 21. Māori women had a significantly higher age adjusted breast cancer mortality compared with NZ European women (HR 2.07, p<0.001) (data not shown). Adjusting for socioeconomic deprivation marginally reduced the age-adjusted hazard of mortality for Māori compared with NZ European from 2.07 (1.64-2.61) to 1.98 (1.55-2.54). As the proportion of screen detected cancer was significantly higher in NZ European compared with Māori (37.4% vs. 30.1% p=0.002, data not shown), detection method was included as a covariate in the survival model. Adjusting for screening status and tumour stage (TNM stage) reduced the HR for mortality to 1.41 (1.09-1.82) (Appendix 5). Adjusting for tumour biological factors (i.e., grade, hormone receptor status, HER-2 status and histology type) further attenuated this estimate (HR 1.42, 1.04-1.75). Further adjustments for treatment characteristics (i.e., chemotherapy and endocrine therapy) and comorbidity resulted in a final hazard ratio of 1.25 (0.97-1.61), which was no longer statistically significantly (p=0.088) (Table 21). Multivariate Cox regression model was repeated only including women diagnosed from 2006 onwards, where rates of missing data were significantly smaller (Table 21). Overall results of this model were much similar to the model that included all women (final HR 1.25 vs. 1.28).

Table 19: Age adjusted odds ratios (OR) for tumour biological characteristics by socio-economic deprivation category (NZDep 2006).

Deprivation quintile	Stage ^a n=2849			Grade ^b n=2647			ER ^c n=2784			PR ^d n=2733			HER-2 ^e n=2101		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
	Dep 1-2	Ref	0.001	Ref	0.183	Ref	0.007	Ref	0.579	Ref	0.961				
Dep 3-4	0.84 (0.56-1.28)			0.78 (0.54-1.15)			1.07 (0.66-1.75)		0.91 (0.64-1.29)		0.88 (0.54-1.44)				
Dep 5-6	0.84 (0.59-1.20)			1.05 (0.75-1.46)			1.43 (0.95-2.15)		0.97 (0.72-1.30)		0.94 (0.63-1.40)				
Dep 7-8	1.22 (0.87-1.78)			0.99 (0.72-1.38)			1.47 (0.99-2.20)		0.87 (0.65-1.16)		0.90 (0.61-1.34)				
Dep 9-10	1.35 (0.94-1.94)			1.17 (0.84-1.64)			1.90 (1.27-2.82)		1.04 (0.77-1.39)		0.99 (0.66-1.47)				

^a - Stage III & IV compared with stage I & II, ^b - Grade II & III compared with grade I, ^c - ER negative compared with positive, ^d - PR negative compared with positive, ^e - HER-2 positive compared with HER-2 equivocal and negative

Table 20: Age and deprivation (NZDep 2006) adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for breast cancer biological characteristics for Māori compared with NZ European women.

Ethnicity	Stage ^a n=2733			Grade ^b n=2537			ER ^c n=2669			PR ^d n=2621			HER-2 ^e n=2012		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
	NZ European	Ref	<0.001	Ref	0.004	Ref	0.482	Ref	0.400	Ref	0.154				
Māori	1.63 (1.28-2.08)			1.52 (1.14-2.02)			1.13 (0.86-1.48)		1.13 (0.90-1.42)		1.24 (0.92-1.67)				

^a - Stage III & IV compared with stage I & II, ^b - Grade II & III compared with grade I, ^c - ER negative compared with positive, ^d - PR negative compared with positive, ^e - HER-2 positive compared with HER-2 equivocal and negative.

Table 21: Cox regression model for factors associated with breast cancer specific mortality in Waikato, New Zealand 1999-2012.

Characteristic	Univariate			Multivariate			Multivariate (Post 2005 only)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Ethnicity^a									
NZ European	Ref		<0.001	Ref		0.008			0.246
Māori	1.98	1.55-2.54		1.42	1.04-1.75		1.26	0.86-1.85	
Year of diagnosis									
1999-2002	Ref		0.556	Ref		0.034	-		
2003-2006	1.13	1.19-1.43		1.12	0.86-1.47		Ref		0.872
2007-2009	0.95	0.70-1.27		0.78	0.55-1.11		0.97	0.63-1.47	
2010-2012	0.97	0.66-1.41		0.84	0.56-1.27		0.88	0.52-1.46	
Mode of detection									
Non-screen	Ref		<0.001	Ref		0.007	Ref		0.045
Screen	0.26	0.20-0.35		0.67	0.48-0.90		0.52	0.28-0.98	
T stage									
T1	Ref		<0.001	Ref		<0.001	Ref		<0.001
T2	3.33	2.56-4.33		1.91	1.45-2.51		3.33	1.80-6.18	
T3	8.68	6.01-12.5		3.38	2.24-5.10		5.16	2.38-11.1	
T4	18.6	13.8-25.1		3.35	2.33-4.82		4.95	2.41-10.1	
N stage									
N0	Ref		<0.001	Ref		<0.001	Ref		<0.001
N1	2.03	1.58-2.60		1.61	1.23-2.09		1.36	0.86-2.16	
N2+	4.04	3.01-5.42		2.75	1.99-3.78		2.90	1.71-4.94	
M Stage									
M0	Ref		<0.001	Ref		<0.001	Ref		<0.001
M1	15.4	12.2-19.4		4.16	3.08-5.62		5.61	3.64-8.63	
Grade									
I	Ref		<0.001	Ref		<0.001	Ref		<0.001
II	4.93	2.90-8.38		3.19	1.84-5.45		4.73	2.78-22.5	
III	13.4	7.85-22.7		6.15	3.52-10.8		7.90	3.77-36.1	

ER/PR								
ER/PR +	Ref	<0.001	Ref	<0.001	Ref		0.009	
ER & PR -	2.47	1.98-3.07		1.56	1.22-1.88		1.69	1.14-2.53
HER-2								
Negative	Ref	<0.001	Ref	0.197	Ref		0.192	
Equivocal	0.62	0.38-1.03		0.96	0.58-1.59		1.18	0.56-2.52
Positive	1.80	1.39-2.33		0.90	0.68-1.18		0.66	0.43-1.01
Histology								
Ductal	Ref	0.293	Ref	0.436	Ref		0.484	
Lobular	0.87	0.62-1.22		0.91	0.63-1.29		0.31	0.18-0.52
Mixed	0.91	0.45-1.83		1.01	0.49-2.06		1.07	0.42-2.74
Other	0.58	0.32-1.05		0.69	0.37-1.29		0.49	0.22-1.07

HR - hazard ratios, 95% CI - 95% confidence intervals, ^a – adjusted for age and socio-economic deprivation

Discussion:

From this study we have observed some differences in breast cancer biological characteristics between Māori and NZ European women. Although Māori women had higher likelihoods of exhibiting certain biological characteristics associated with worse breast cancer outcomes, this appears to be only a minor contributor while advanced stage at diagnosis in Māori had the greatest impact towards the breast cancer survival inequity between Māori and NZ European women. Overall, Māori women had higher rates of advance staged and higher grade, and possibly a higher rate of HER-2 positive cancers. No significant differences were observed in rates of ER/PR negative or triple negative breast cancers (TNBC).

We have observed several key differences in our findings compared with previous studies (70, 74, 169). For example, McKenzie study based on the New Zealand Cancer Registry, reported that Māori women have higher rates of ER/PR positive and poorly differentiated (i.e. grade III) cancers compared with NZ European women (70). A higher rate of grade III cancers in Māori was reported from a study based on the Auckland Breast Cancer Register (74), while a third study from Christchurch reported Māori women to have a significantly lower rate of grade III cancers compared with NZ European women (169). Differences in sample selection, rates of missing data, statistical methods used for analysis and possible regional variations in breast cancer could explain some of these differences. For instance, McKenzie study based on

the New Zealand Cancer Registry included very high rates of missing data; 65.1% for tumour grade and 59.8% for ER status. Further, as the authors of the Christchurch study have proposed (169), regional variations in breast cancer biological characteristics, may also have contributed, especially for differences observed between Auckland and Christchurch datasets. Such regional differences have been reported from the USA (86, 166), which could be related to differences in distribution of risk factors associated with tumour biological expressions.

African American women with breast cancer in both the USA and the UK are known to harbour more high grade, ER/PR negative and TNBC than their European American counterparts (11, 165-167). Further, these differences are known to be major contributors for excess breast cancer mortality in African American women (11, 166). Although, compared to NZ European women, Māori women had a higher rates of ER/PR negative cancers (crude rate 15.1% vs. 19.1%) and grade III cancers (crude rate 22.6% vs. 23.7%), these rates were much lower than rates of respective characteristics observed in African American women, in whom the rates of ER/PR negative or grade III cancers were approximately 30-35% (86). Further, in contrast to African American women, the rate of TNBC tended to be lower in Māori compared with NZ European women, although this difference was not significant in either unadjusted or adjusted analyses. It appears that differences tumour biology in Māori women may be a contributor to higher mortality; though it certainly is not as significant a contributor as it is for African American women.

Studies from the USA and the UK have demonstrated that women of lower socioeconomic groups to have significantly higher rates of advance staged, ER/PR negative, high grade and invasive ductal cancers compared with women living in affluent socioeconomic circumstances (299, 300). Although many New Zealand studies have reported on the influence of socioeconomic status on cancer stage at diagnosis for many cancers including breast (9, 122), only the McKenzie study to date has reported on biological differences in breast cancer by socioeconomic status (70). This study did not observe significant differences in tumour grade, ER/PR and HER-2 status among different socioeconomic groups. In contrast, we observed a higher age-adjusted rate of ER/PR negative cancers in women of low socioeconomic groups, which was marked for women from the most deprived socioeconomic quintile. Further, in our study, adjusting for age and socioeconomic status resulted only in a marginal attenuation of higher grade cancers observed in Māori compared with NZ Europeans. Despite the differences in the nature of biological differences between the two studies, both indicate that Māori

women may have differences in breast cancer biology compared with NZ European women, which are likely to be independent of age at diagnosis and socioeconomic deprivation.

Reasons for ethnic differences in breast cancer biology are largely unknown (301). It is unlikely that there are innate genetic differences between ethnic groups resulting in more aggressive breast cancers for some groups. Ethnic groups are not always from discrete ancestry groups. For example, NZ European and Māori women descend from a wide range of ancestry groups and each group shares common ancestry groups as Māori women will have European ancestry and some NZ European women will have Māori ancestry. It is likely that socio-environmental factors put minority, Indigenous and other socially disadvantaged women at risk of having more aggressive breast cancers than privileged ethnic groups (302). Race theory suggests that there is not enough genetic heterogeneity within the human species to subdivide humans into groups with distinct genetic groups (303). However, socio-environmental factors can influence epigenetics (304).

There were a few limitations in our analysis. First, some biological characteristics had significant proportions of missing data. For example HER-2 data were missing for approximately 25% of women, most of who were diagnosed prior to 2006 when HER-2 testing was not routine in New Zealand. Further, even among women diagnosed post-2006, in addition to missing HER-2 rate of 4.3%, a further 5% had an equivocal result, which may have been a source of misclassification bias. Second, we acknowledge the possible differences in analysis and reporting of biological characteristics by different laboratories (305). More than 95% of the pathology tests for cancers included in our study were performed by two laboratories; one public and one private. These two laboratories have used similar equipment, tests and reporting protocols over the time period and are expected to have had minimal analysis and reporting variations.

In conclusion, we have observed Māori ethnicity and lower socioeconomic status to be significantly associated with some breast cancer biological characteristics associated with worse cancer outcomes. However, differences in tumour biological factors appear to be contributing minimally, while delay in diagnosis in Māori appears to have a major impact on the breast cancer mortality inequity between Māori and NZ European women. Strategies aimed at reducing breast cancer mortality in Māori should focus on earlier diagnosis through increasing screening coverage and other methods, which will likely have a greater impact on minimizing the breast cancer mortality inequity between Māori and NZ European women.

5.5. Are there ethnic differences in delay in surgical treatment?

Preface:

This chapter contains an abbreviated version of a manuscript published in *Ethnicity & Health*

- **Authors:** Seneviratne S, Campbell I, Scott N, Coles C, Lawrenson R.
- **Title:** Treatment delay for Māori women with breast cancer in New Zealand
- **Journal:** *Ethnicity & Health*
- **Year of publication:** 2015
- **DOI:**10.1080/13557858.2014.895976
- **Impact factor:** 1.20
- **Journal's aims and scope:** This is an international academic journal designed to meet the world-wide interest in the health of ethnic groups. It embraces original papers from the full range of disciplines concerned with investigating the relationship between 'ethnicity' and 'health' (including medicine and nursing, public health, epidemiology, social sciences, population sciences, and statistics). The journal also covers issues of culture, religion, gender, class, migration, lifestyle and racism, in so far as they relate to health and its anthropological and social aspects.

Abstract

Background:

Differences in delay in treatment have been shown to be a factor contributing to ethnic inequities in breast cancer mortality. This study investigated differences in delay for surgical treatment of breast cancer by ethnicity, and evaluated roles of health system, socio-demographic and tumour factors towards these differences.

Methods:

A retrospective analysis of prospectively collected data included in the WBCR for cancers diagnosed from 01/01/2005 to 31/12/2010 was done. Differences in proportions of women with delays longer than 31 and 90 days were analysed by ethnicity, adjusting for covariates.

Results:

Approximately 95% (1449 out of 1514) of women with breast cancer diagnosed in the Waikato over the study period were included. Of women undergoing primary surgery (n=1264), 59.6% and 98.2% underwent surgery within 31 and 90 days of diagnosis respectively. Compared with NZ European women (mean 30.4 days), significantly longer delays for surgical treatment were observed among Māori (mean=37.1 days, p=0.005) and Pacific women (mean=42.8 days, p=0.005). Māori women were more likely to experience delays longer than 31 (p=0.048) and 90 days (p=0.286) compared with NZ European women. Factors predicting delays longer than 31 and 90 days in the multivariable model included public sector treatment (OR 5.93, 8.14), DCIS (OR 1.53, 3.17), mastectomy (OR 1.75, 6.60), higher co-morbidity score (OR 2.02, 1.02) and earlier year of diagnosis (OR 1.21, 1.03). Inequities in delay between Māori and NZ European women were greatest for women under 50 years and those older than 70 years.

Discussion:

This study shows that significant inequities in timely access to surgical treatment for breast cancer exist in New Zealand, with Māori and Pacific women having to wait longer to access treatment than NZ European women. Overall, a high proportion of women did not receive surgical treatment for breast cancer within the guideline limit of 31 days. Urgent steps are needed to reduce ethnic inequities in timely access to breast cancer treatment, and to shorten treatment delays in the public sector for all women.

Background:

Delays in diagnosis and treatment for many cancers, including breast cancer, are associated with lower survival rates. A meta-analysis published by Richards and colleagues (198) demonstrated a definite and strong relationship between delay in treatment and lower survival from breast cancer. A delay of more than three months from onset of symptoms to initiation of treatment was associated with a 12% lower five-year survival compared with a delay of less than three months. A recently published study from the USA report that a delay of ≥ 60 days compared with <60 days from diagnosis to initiation of treatment was associated with 66% and 85% increased overall and breast cancer-related death rates respectively, among patients with advanced breast cancer (206). Advances in breast cancer treatment have contributed towards significant improvements in breast cancer survival over past few decades. Thus, delays in receipt of treatment could be an important contributor to ethnic disparities in survival among NZ women. Longer delays from diagnosis to treatment have been shown for Māori compared to non-Māori for colon and lung cancers in NZ (181, 182).

BSA quality standards state that at least 90% of women should receive their first surgical treatment within 20 working days of receiving their final diagnostic result. However, figures from BSA in 2008 show that this target was achieved for only 57.7% of Māori women compared with 71.2% of non-Māori women (132). Given the lack of standards and audit for management of women with symptomatic non-screen detected cancers, the disparities in treatment timeliness are likely to be even greater.

The aim of this paper is to identify differences in delay for surgical treatment of breast cancer between ethnic groups in the Waikato and to evaluate the role of health system, socio-demographic and tumour factors in ethnic inequities in breast cancer treatment.

Methods

All first primary incidental breast cancers, i.e. invasive and ductal in-situ cancers (DCIS), diagnosed during the period of the study from 01 January 2005 through 31 December 2010, were identified from the WBCR.

To assess time from diagnosis to surgery, we identified all women whose first treatment was surgery, with a pre-operatively confirmed breast cancer diagnosis. Women were excluded from analysis if they did not receive a pre-operative pathological diagnosis of breast cancer

(by a needle biopsy or punch biopsy), if their primary treatment was not surgery or if they received neo-adjuvant therapy. Delay was calculated in days; from the day, a decision to treat the breast cancer surgically was discussed with the patient, to the date of primary surgery. A threshold of 31 days was used as the limit for the longest acceptable delay in access to surgical treatment in keeping with the Faster Cancer Treatment Indicators (58) set by the New Zealand Ministry of Health. Additional calculations were performed using a three month (90 days) delay threshold, which has been shown to be associated with a significant survival disadvantage (198). Several authors have used the 30 and 90-day benchmarks for treatment delay (204, 306), so providing an opportunity for comparison.

Student's T tests and Chi squared tests were used to test differences in delay among groups by age, ethnicity, stage, mode of diagnosis and year of diagnosis. Mann–Whitney U test was used to compare delay with non-parametric variables such as deprivation and distance from residence. Multivariable logistic regression analyses were performed to determine variables associated with delays of more than 31 and 90 days. All variables with p values of <0.50 in univariate analyses were included in the multivariable model. A manual stepwise backward selection procedure was used to select variables to be included in multivariable model. All p values were two-sided and p values <0.05 were considered significant. Variables were retained as predictors in multivariable models if p<0.05 or if they were considered to be of significant clinical or population health importance. Odds ratios and 95% confidence intervals were calculated to quantify the risk of a delay of more than 31 and 90 days associated with each identified factor.

Results

During the period of the study a total of 1514 first primary incidental breast cancers (invasive and DCIS) were reported from the Waikato. Sixty-five women (4.3%) did not consent to participate in the WBCR and were excluded from this study. Data from 1449 women (95.7%) were available for analysis.

Socio-demographic and tumour factors:

Table 22 shows the distribution of age and tumour stage by ethnicity. Māori and Pacific women with breast cancer were significantly younger ($p<0.001$ and $p=0.003$ respectively) than NZ European women in keeping with younger age structure of Māori and Pacific populations

in NZ. Māori and Pacific women had more advanced staged cancers at diagnosis compared with NZ European women. The proportion of DCIS and stage I cancers (cancers <20mm) were significantly higher ($p=0.041$) among NZ European ($n=569$, 49.1%) compared with Māori women ($n=94$, 41.6%).

The majority of women (58.3%) in this study belonged to higher deprivation groups (quintiles 4 and 5). Significantly higher proportions of Māori ($n=173$, 76.5%, $p<0.001$) and Pacific women ($n=24$, 80.6%, $p<0.001$) were from deprivation quintiles 4 and 5 compared with NZ European women ($n=630$, 54.4%). Overall, more than two-thirds ($n=899$, 71.2%) of women were residing within 50km of their treatment facility and only 5.1% ($n=64$) were from highly rural (>100 km) areas (Table 24). A significantly higher proportion of Māori were from highly rural areas compared with NZ European women (9.3% vs. 4.1%, $p<0.001$).

Table 22: Distribution of age and tumour stage by ethnicity

Ethnicity	Total	NZ European	Māori	Pacific	Other	p
	<i>n</i> =1449	<i>n</i> =1159	<i>n</i> =226	<i>n</i> =30	<i>n</i> =34	
	(100%)	(80.0%)	(15.6%)	(2.1%)	(2.3%)	
	n %	n (%)	n %	n %	n %	
Age	Mean	59.9	61.2	55.4	54.2	53.2 <0.001
	<40	78 (5.4)	53 (4.6)	16 (7.1)	5 (16.7)	4 (11.8)
	40-49	272 (18.8)	198 (17.1)	59 (26.1)	6 (20.0)	9 (26.5)
	50-59	385 (26.6)	294 (25.4)	70 (31.0)	8 (26.7)	13 (38.2)
	60-69	378 (26.1)	313 (27.0)	51 (22.6)	8 (26.7)	6 (17.6)
	70+	336 (23.2)	301 (26.0)	30 (13.3)	3 (10.0)	2 (5.9)
Stage	I	491 (33.9)	404 (34.9)	69 (30.5)	5 (16.7)	13 (38.2) <0.001
	II	457 (31.5)	359 (31.0)	79 (35.0)	10 (33.3)	9 (26.5)
	III + IV	304 (21.0)	231 (19.9)	53 (23.5)	14 (46.7)	6 (17.6)
	DCIS	197 (13.6)	165 (14.2)	25 (11.1)	1 (3.3)	6 (17.6)

Breast cancer screening:

Compared to NZ European women (n=753, 65.0%), higher proportions of Māori (n=157, 69.5%) and Pacific women (n=20, 66.3%) belonged to the ‘screening age’ (45 – 69 years) as defined by the National Breast Cancer Screening Programme (BreastScreen Aotearoa / BSA). The majority of NZ European women (n=480, 63.7%) within the screening age group were diagnosed through breast cancer screening. In comparison, less than half of the Māori women (49.7%, n=78), within this age group were diagnosed through screening, a difference which was statistically significant ($p<0.001$).

Delay in surgical treatment:

Overall, 59.6% (n=731) and 98.2% (n=1241) women underwent surgery within 31 and 90 days of diagnosis respectively (Table 23). Delays in surgical treatment for Māori ($p=0.005$) and Pacific women ($p=0.005$) were significantly longer than for NZ European women. Māori were 74% more likely to have a delay of over 3 months and 37% more likely to have a delay of over 31 days compared with NZ European women. This difference was statistically significant ($p=0.048$) for a delay longer than 31 days but was not significant for a delay longer than 90 days ($p=0.286$) (Table 24).

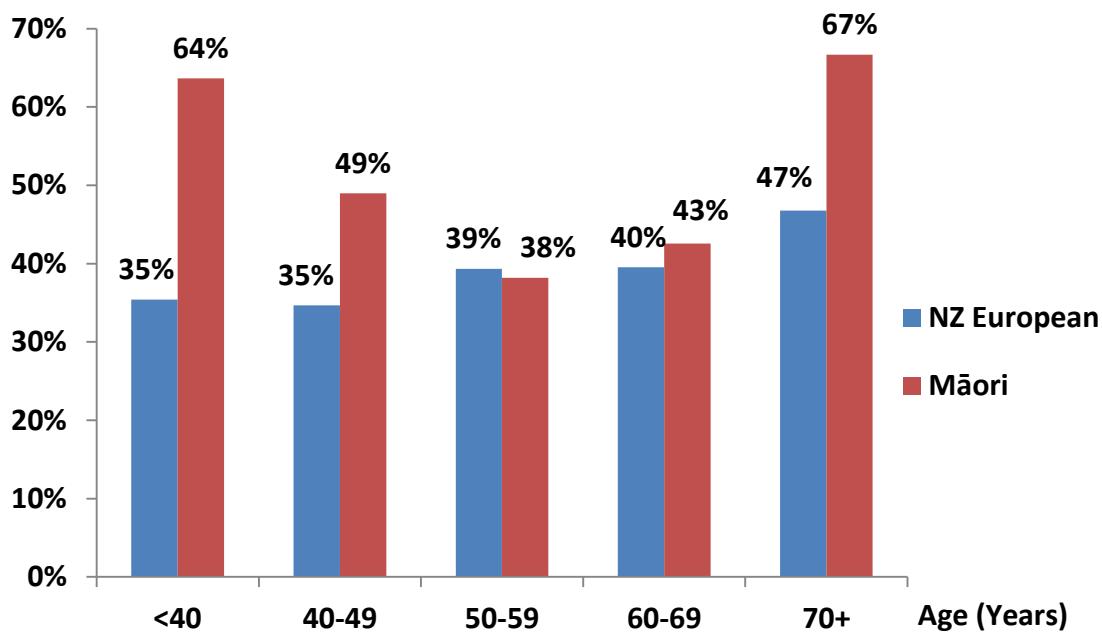
Table 23: Delay from diagnosis to primary surgery (in days) by ethnicity

	Overall (n=1264)	NZ European (n=1023)	Māori (n=186)	p	OR (95% CI)
Mean delay (days)	31.60	30.41	37.10	0.005	-
Delay >31 days	523 (41.4)	410 (40.2%)	89 (47.8%)	0.048	1.37 (1.00 – 1.88)
Delay >90 days	23 (1.8)	16 (1.6%)	5 (2.7%)	0.286	1.74 (0.63 – 4.80)

(OR – Odds Ratio, CI – Confidence Interval)

A significant positive correlation ($p=0.003$) was observed between a woman’s age at diagnosis and a delay longer than 31 days with older women experiencing longer delays. This correlation was significant for NZ European women ($p=0.001$) but was not for Māori women ($p=0.76$). Among Māori women, higher proportions women younger than 50 years and older than 70 years experienced a delay longer than 31 days compared to NZ European women (Figure 22).

Figure 22: Distribution of percentage of women with a delay longer than 31 days by ethnicity (Māori vs. NZ European) and age category



Compared to women with invasive cancer, higher proportions of patients with DCIS experienced a delay longer than 31 days (50.6% vs. 38.5%, $p=0.009$) and 90 days (3.5% vs. 1.6%, $p=0.078$). No significant differences in delay were observed among different stages of invasive disease ($p=0.78$). Overall only 2.4% ($n=31$) women had a CCI of ≥ 1 and rates of CCI ≥ 1 were 2.2% ($n=4$) for Māori and 2.6% ($n=26$) for NZ European women. Increasing comorbidity score showed a significant association with a delay longer than 31 days ($p=0.016$).

A comparison of mean delay and proportion with a delay of longer than 31 days was performed between women diagnosed through the BSA programme ($n=516$, 40.8%) and outside of it ($n=748$, 59.2%). No significant differences in mean delay (mean 31.4 vs. 31.7 days, $p=0.13$) or proportion with a delay of >31 days were observed between these two groups (41.9% vs. 41.0%, $p=0.77$). Women diagnosed through BSA had a higher likelihood of having DCIS compared to women diagnosed outside of BSA (22.9% vs. 7.9%). Therefore, we recalculated delay between BSA and non-BSA for women with invasive disease only. There remained no significant difference in mean delay ($p=0.12$) or proportion with a delay of >31 days ($p=0.84$) between the two groups. A similar analysis was performed for women treated within the public health system only ($n=904$). This demonstrated that a significantly higher proportion of non-BSA compared with BSA diagnosed women had a delay longer than 31 days (55.7% vs. 47.3%, $p=0.013$). This difference in delay among public sector treated BSA

compared to non-BSA was greater and more significant for Māori women (37.3% vs. 59.6%, p=0.004) while the difference was smaller and non-significant between non-BSA and BSA treated NZ European women (49.3% vs. 54.5%, p=0.164).

Table 24: Univariate analysis of factors associated with a delay of >31 days and >90 days

Characteristic	n (%)	Delay >31 days			Delay >90 days		
		OR	95% CI	p	OR	95% CI	p
Ethnicity							
NZ European	1023 (80.9)	1.00			1.00		
Māori	186 (14.7)	1.37	1.01 – 1.88	0.048*	1.74	0.63 - 4.80	0.286 ^a
Pacific	23 (1.8)	1.63	0.71 - 3.73	0.247*	2.86	0.36 - 22.5	0.318 ^a
Other	32 (2.5)	1.02	0.50 - 2.09	0.950*	2.03	0.26 - 15.8	0.499 ^a
Age category (yrs)							
<40	68 (5.4)	1.15	0.66 - 1.99		1.41	0.27 - 7.44	
40-49	238 (18.8)	1.00			1.00		
50-59	345 (27.3)	1.10	0.78 - 1.54		0.69	0.20 - 2.39	
60-69	355 (28.1)	1.08	0.77 - 1.52		0.40	0.09 - 1.68	
70+	258 (20.4)	1.57	1.10 - 2.25		1.49	0.48 - 4.62	
BSA vs. non-BSA^b							
BSA	516 (40.8)	1.00			1.00		
non-BSA	748 (59.2)	0.97	0.77 - 1.21		1.98	0.77 - 5.05	
Stage							
Stage 0 (DCIS)	172 (13.6)	1.51	1.07 - 2.14		2.46	0.81 - 7.42	
Stage I	483 (38.2)	1.00			1.00		
Stage II	438 (34.7)	0.96	0.74 - 1.26		1.27	0.45 - 3.52	
Stage III + IV	171 (13.5)	0.98	0.68 - 1.39		0.80	0.17 - 3.91	
Type of operation							
BCS	788 (62.3)	1.00		<0.001	1.00		<0.001
Mastectomy	476 (37.7)	1.67	1.33 - 2.10		6.15	2.27 - 16.7	

Facility type				<0.001		0.032
Public	904 (71.5)	1.00			1.00	
Private	360 (28.5)	0.17	0.13 - 0.24		0.11	0.01 - 0.83
Deprivation quintile				0.009		0.881
Dep 1-2	134 (10.6)	1.00			1.00	
Dep 3-4	122 (9.7)	1.37	0.82 – 2.29		3.35	0.34 – 32.6
Dep 5-6	275 (21.8)	1.31	0.84 – 2.02		2.46	0.28 – 21.2
Dep 7-8	393 (31.1)	1.72	1.13 – 2.60		2.41	0.29 – 19.7
Dep 9-10	340 (26.9)	1.69	1.11 – 2.58		2.80	0.34 – 22.9
Distance from hospital				0.152		0.513
<10 km	356 (28.2)	1.00			1.00	
10 – 50 km	543 (43.0)	0.91	0.69 – 1.19		0.58	0.22 – 1.51
50 – 100 km	301 (23.8)	0.97	0.71 – 1.32		0.52	0.16 – 1.70
>100 km	64 (5.1)	1.67	0.98 – 2.86		1.24	0.26 – 5.89
Charlson score				0.016		0.396
0	1233 (97.5)	1.00			1.00	
1	14 (1.1)	2.61	0.87 – 7.84		4.23	0.53 – 33.8
≥2	17 (1.3)	3.48	1.22 – 9.95		-	
Year of diagnosis				<0.001		0.102
2005	216 (17.1)	1.00			1.00	
2006	224 (17.7)	0.60	0.41 - 0.88		3.45	0.71 - 16.8
2007	214 (16.9)	0.91	0.62 - 1.33		0.50	0.05 - 5.58
2008	205 (16.2)	0.46	0.31 - 0.68		4.35	0.91 - 20.7
2009	222 (17.6)	0.41	0.28 - 0.61		1.47	0.24 - 8.86
2010	183 (14.5)	0.44	0.29 - 0.66		1.18	0.16 - 8.48

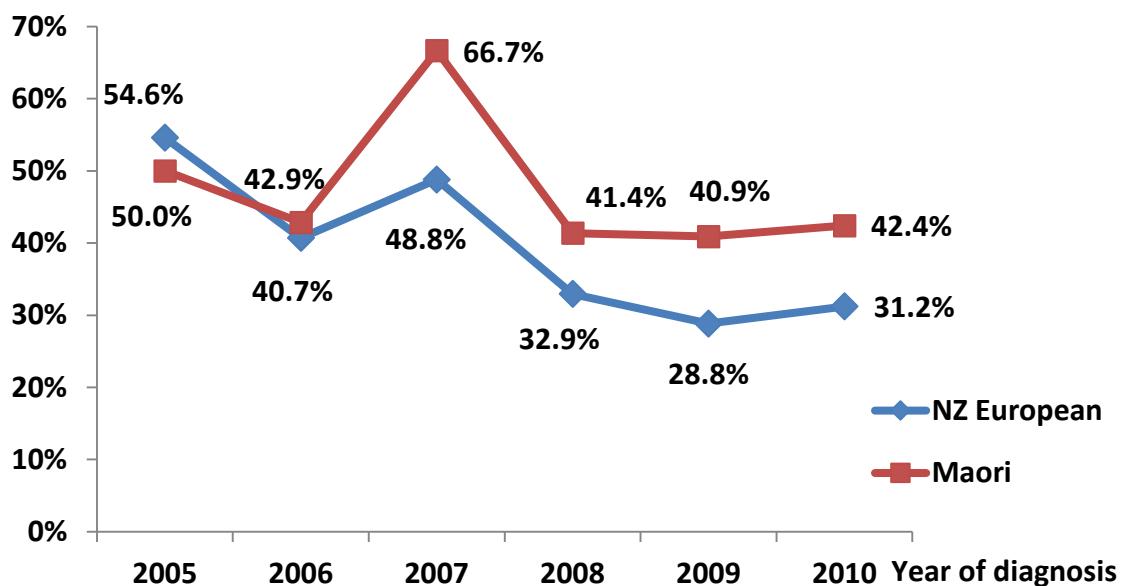
(OR – unadjusted Odds ratio, 95% CI – 95% Confidence interval, ^a - pairwise p value compared with NZ European women, ^b BreastScreen Aotearoa)

Women undergoing breast conserving surgery (BCS) as the primary surgical intervention had a significantly shorter mean delay compared with women undergoing mastectomy (28.7 vs. 36.4 days, $p<0.001$). The mastectomy group had significantly higher proportions of women with delays longer than 31 and 90 days compared with the BCS group (Table 24). A significantly higher proportion ($p=0.003$) of Māori (46.8%, $n=87$) underwent mastectomy as primary surgical treatment compared with NZ European women (35.4%, $n=362$).

We also examined delay among women who received primary surgical treatment from the private system ($n=360$) compared with the public system ($n=904$). Mean delay for surgery in the private sector was much shorter compared with the public sector (20.1 vs. 36.2 days, $p<0.001$). Similarly, a significantly lower proportion of women treated in the private sector experienced delays of >31 and >90 days compared with public sector (Table 24). A significantly higher proportion of NZ European women compared to Māori women (32.5% vs. 8.1%, $p<0.001$) received surgical treatment in the private sector. No significant differences in mean delay were observed between NZ European and Māori within public (35.5 vs. 38.9 days, $p=0.18$) or private sector (19.7 vs. 14.6 days, $p=0.06$). Within the public sector almost equal proportions of NZ European and Māori women experienced delays longer than 31 days (52% vs. 50.9%, $p=0.96$) and 90 days (2.3% vs. 2.9%, $p=0.65$).

A significant positive correlation was observed between increasing socio-economic deprivation and delay ($p=0.007$) as well as a delay longer than 31 days ($p=0.008$). However, this was not significant for a delay longer 90 days ($p=0.620$). A delay beyond 31 days was more pronounced among women from deprivation quintiles 4 and 5 (Table 24). Increasing deprivation showed a significant negative correlation ($p<0.001$) with proportion of women accessing treatment from the private sector. Only 21.7% ($n=70$) women from the highest deprived group (deprivation quintile 5) accessed private sector treatment compared with 44.1% ($n=56$) women from the least deprived group (deprivation quintile 1). When public sector women are considered alone, no significant associations were observed between deprivation and mean delay ($p=0.223$) or proportion of women with delays longer than 31 ($p=0.226$) or 90 days ($p=0.972$). Over the study period (2005 – 2010) a gradual, but significant ($p<0.001$) overall decline was observed in the proportion of patients with delays of >31 days (Table 24). However, despite these overall improvements, a higher proportion of Māori compared with NZ European women continue to experience delays longer than 31 days (Figure 23). For example in 2010, 42.4% Māori women experienced delays longer than 31 days compared to only 31.2% for NZ European women.

Figure 23: Yearly trend in proportional delay longer than 31 days by ethnicity (Māori vs. NZ European)



Multivariable logistic regression analysis identified treatment in the public sector, stage of disease, earlier year of diagnosis, higher Charlson Comorbidity Score (only for 31 day benchmark) and mastectomy as surgical treatment as factors significantly associated with longer treatment delays at 31 and 90 day benchmarks, after controlling for age, socioeconomic state, mode of diagnosis and distance from hospital (Table 25). A similar regression model was performed using only women with a CCI score of zero which yielded results much similar to Table 25.

Discussion

From this population-based study from the Waikato, we report that non-Indigenous New Zealand women are more likely to receive surgical treatment for breast cancer before Indigenous women. The main driver for this inequity in timeliness of access to breast cancer treatment between Māori and non-Māori women is greater access to private treatment for non-Māori women. It is known that women who access breast cancer treatment early have a greater chance of surviving their cancer. This significant difference in timely access to treatment is likely to contribute towards a higher breast cancer survival for non-Māori compared with Māori women.

Table 25: Multivariable logistic regression analysis of factors associated with a delay of >31 days and >90 days adjusted for age, stage, deprivation score, mode of diagnosis and distance from hospital (Only NZ European and Māori women (n=1219) included in the analysis)

Characteristic	Delay >31 days			Delay >90 days		
	OR	95% CI	p	OR	95% CI	p
Ethnicity	0.988			0.521		
NZ European	1.00			1.00		
Māori	1.00	0.70 – 1.43		1.42	0.48 – 4.17	
Stage	0.002			0.041		
Stage 0 (DCIS)	1.60	1.08 – 2.36		3.17	0.94 – 10.55	
Stage I	1.00			1.00		
Stage II	0.82	0.60 – 1.12		0.64	0.22 – 1.89	
Stage III + IV	0.62	0.40 – 0.95		0.34	0.07 – 1.76	
Type of operation	<0.001			<0.001		
BCS	1.00			1.00		
Mastectomy	1.73	1.30 – 2.29		6.60	2.31 – 18.88	
Facility type	<0.001			0.029		
Public	1.00			1.00		
Private	0.16	0.11 - 0.20		0.10	0.01 – 0.79	
Charlson score	0.009			0.976		
0	1.00			1.00		
≥1	2.02	1.18 – 3.44		1.02	0.22 – 4.78	
Year of diagnosis	<0.001			0.073		
2005	1.00			1.00		
2006	0.59	0.39 - 0.89		4.22	0.84 – 21.17	
2007	0.95	0.62 - 1.45		0.54	0.05 – 6.06	
2008	0.40	0.26 - 0.61		4.84	0.98 – 23.81	
2009	0.32	0.21 - 0.49		1.38	0.22 – 8.58	
2010	0.43	0.28 - 0.68		1.42	0.19 – 10.48	

(OR – Odds ratio, 95% CI – 95% Confidence interval)

We also found that less than two percent of women experienced a delay of more than three months for primary surgical treatment of breast cancer. A delay beyond three-months from diagnosis to treatment is known to result in lower survival for women with breast cancer (198). However, approximately 40% of women experienced delays between 31 days to three months and the clinical significance of this delay is unclear. McLaughlin and colleagues (206) recently reported a higher overall and breast cancer related mortality for women with advanced breast cancer (stage III and IV) who experienced a treatment delay of more than 60 days compared with a delay less than 60 days. As Māori women (as well as Pacific women) are more likely to be diagnosed with advanced disease, even moderate delays in treatment are likely to have a bigger impact on outcomes than they would for NZ European women (206).

Ability to access private sector care is dependent upon either financial affordability or availability of health insurance, both of which are related to socioeconomic status of patients. Socioeconomic status has also been shown to be associated with delay within the public sector because of cost of travel, time off work and availability of social support. In this study, Māori and Pacific women were highly over-represented in higher deprivation categories compared with NZ European women, which is similar to the distribution of deprivation for Māori and Pacific populations in New Zealand. Socioeconomic status is known to be a major contributory factor toward inequities in breast cancer treatment (4, 307-309) and outcome in many countries (13). High likelihood of ethnic minority and Indigenous women belonging to lower socioeconomic status groups is a phenomenon observed worldwide and, inequities by ethnicity persist after controlling for socioeconomic status. We observed a positive correlation between deprivation and longer delay for treatment, which was most pronounced among women from the two highest deprivation groups (deprivation quintiles 4 & 5). Low proportions of women from high deprivation groups accessing treatment from the private sector was the major contributor for this difference. Furthermore, almost 60% of women included in this study were from the two highest deprivation quintiles compared with 46% for the whole Waikato population (41). This discrepancy was larger compared to differences between the total population deprivation profile and the profile for people with cancer reported by the Ministry of Health (310).

In this study, we did not observe a significant difference in delay between Māori and European women within the public sector. These findings are in contrast to several previous studies, which have shown that non-Indigenous patients are advantaged within the New Zealand public health system with superior quality of care and shorter delays for diagnosis and treatment (35,

181). Although a lack of inequities in timeliness to treatment observed in the public sector could be attributed to a selection bias of a group of women with pre-operatively confirmed diagnosis of breast cancer, which itself is an indicator of better quality care, it is unlikely to fully explain this lack of difference. Delay in treatment represents only one facet of the multifaceted care for women and disparities in all facets of care need to be assessed and addressed to achieve equity in cancer treatment for all New Zealand women.

There is a stringent quality framework for the treatment of breast cancer detected through BSA providers and performance is regularly audited (132). Despite the lack of an overall difference in delay between BSA and non-BSA diagnosed women, a significant difference in delay was observed between BSA and non-BSA women treated within the public sector. This highlights the importance of audit and regular monitoring of performance within public sector hospitals to minimize treatment delays. Faster Cancer Treatment Indicators (58) were introduced by the Ministry of Health to supplement existing National Cancer Streams and Cancer Care Guidelines. Cancer Care Coordinators were recently introduced into the public health system to help cancer patients navigate through complex cancer care pathways that involve several disciplines of care (311). These measures are expected to standardize care within the public health system and thereby minimize delays and inequities associated with cancer treatment.

Additional procedures carried out to diagnose multi-centrality or multi-focality, which preclude BCS or delays associated with planning and performance of immediate surgical breast reconstruction could explain some of the delays observed among women undergoing mastectomy (309). Non-tumour related factors such as age, ethnicity, area of residence and socioeconomic status have been shown to be associated with a woman's decision-making process regarding mastectomy (312). Fear of complications of radiotherapy and difficulties in attending radiotherapy that invariably follows BCS are some of the major concerns, which may tilt the decision towards mastectomy instead of BCS among some women. Ethnic minority women are more likely to reside in rural areas and are more likely to belong to low socioeconomic groups and, these factors could influence the higher mastectomy rates observed among such women. Higher rates of mastectomy in turn lead to longer delays further confounding the understanding of association between ethnicity and delay.

Significant reductions in mean delay and the proportion of patients with a delay longer than 31 days have been achieved in the Waikato over the period from 2005 to 2010. It is likely that increases in the surgical team providing breast cancer services and streamlining of the cancer treatment pathway have helped to achieve these improvements. However, no significant

reductions in the gap between Māori and NZ European women in relation to treatment delay have been achieved. This is a major cause for concern in the context of increasing incidence and mortality from breast cancer among Māori compared to non-Māori women in New Zealand.

Limitations of our study include limited sample size and non-inclusion of details on clinical decision-making process which may have influenced observed differences. We did not assess the extent that body mass index (BMI) may have had on delay in this study. However, previous studies on treatment delay for breast cancer have not shown a strong association between BMI and delay (313). Surgical treatment of breast cancer is generally associated with lower risks of major or life threatening peri-operative complications for obese women (BMI >30) compared with surgical treatment of other cancers such as colon or lung (314, 315). This provides a likely explanation for absence of a significant association and, we believe that exclusion of BMI data is unlikely to influence the overall results of this study.

Inequities in delay in surgical treatment represents only one-step in the multi-step cancer care pathway through which women with breast cancer have to navigate. There is every reason to believe that Māori women are likely to encounter delays along each step of the cancer care pathway from the first presentation to a primary care clinician or a screening programme to completion of treatment. We highlight the need for improving the services in the public sector where >70% of all women and >90% of Māori women received breast cancer care, in order to reduce overall delays as well as to reduce ethnic inequities in delay.

Recent initiatives introduced by the Ministry of Health including Faster Cancer Treatment Indicators and Cancer Care Coordinators are expected to enhance efficiency of delivery of cancer care. Although these strategies may help to reduce delays within secondary and tertiary health care institutions, they are unlikely to eliminate barriers faced by ethnic minority women in access to primary care, transportation, health literacy and social support. Faster Cancer Treatment Indicators are also unlikely to address other barriers to quality care, which have not been clearly identified yet. While commending the initiatives implemented by the Ministry of Health we highlight the importance of further research and initiatives targeting inequities in cancer care between Māori and non-Māori women.

5.6. Are there ethnic differences in delay in initiating chemotherapy and radiation therapy?

Preface:

This chapter contains an abbreviated version of a manuscript published in *BMC Cancer*.

- **Authors:** Seneviratne S, Campbell I, Scott N, Kuper-Hommel M, Round G, Lawrenson R.
- **Title:** Ethnic differences in timely adjuvant chemotherapy and radiation therapy for breast cancer in New Zealand: A cohort study
- **Journal:** *BMC Cancer*
- **Year of publication:** 2014
- **DOI:** 10.1186/1471-2407-14-839
- **Impact factor:** 3.32
- **Journal's aims and scope:** *BMC Cancer* is an open access, peer-reviewed journal that publishes articles on all aspects of cancer research, including the pathophysiology, prevention, diagnosis and treatment of cancers. The journal also publishes articles on molecular and cellular biology, genetics, epidemiology, and clinical trials.

Abstract:

Background:

Indigenous and/or minority ethnic women are known to experience longer delays for treatment of breast cancer, which has been shown to contribute to ethnic inequities in breast cancer mortality. This study examined factors associated with delay in adjuvant chemotherapy and radiotherapy for breast cancer, and their impact on the mortality inequity between Indigenous Māori and European women in New Zealand.

Methods:

All women with newly diagnosed invasive non-metastatic breast cancer during 1999-2012, who underwent adjuvant chemotherapy ($n=922$) or radiation therapy ($n=996$) as first adjuvant therapy after surgery were identified from the WBCR. Factors associated with delay in adjuvant chemotherapy (60-day threshold) and radiation therapy (90-day threshold) were analysed in univariate and multivariate models. Association between delay in adjuvant therapy and breast cancer mortality were explored in Cox regression models.

Results:

Overall, 32.4% and 32.3% women experienced delays longer than thresholds for chemotherapy and radiotherapy, respectively. Higher proportions of Māori compared with NZ European women experienced delays longer than thresholds for adjuvant radiation therapy (39.8% vs. 30.6%, $p=0.045$) and chemotherapy (37.3% vs. 30.5%, $p=0.103$). Rural compared with urban residency, requiring a surgical re-excision and treatment in public compared with private hospitals were associated with significantly longer delays ($p<0.05$) for adjuvant therapy in the multivariate model. Breast cancer mortality was significantly higher for women with a delay in initiating first adjuvant therapy ($HR=1.45$, 95% CI 1.05-2.01). Mortality risks were higher, albeit non-significantly for women with delays in chemotherapy ($HR=1.34$, 95% CI 0.89-2.01) or radiation therapy ($HR=1.28$, 95% CI 0.68-2.40).

Conclusions:

Indigenous Māori women appeared to experience longer delays for adjuvant breast cancer treatment, which may be contributing towards higher breast cancer mortality in Māori compared with NZ European women. Measures to reduce delay in adjuvant therapy may reduce ethnic inequities and improve breast cancer outcomes for all women with breast cancer.

Background:

Ethnic disparities in receipt of breast cancer care are well documented, and have been shown to contribute towards worse breast cancer outcomes among Indigenous and/or minority ethnic women (316, 317). Indigenous and/or minority ethnic women are more likely to experience longer delays in initiation of treatment for breast cancer (313, 318, 319), which are known to increase risks of breast cancer recurrence and mortality (198, 209, 210, 320).

A substantial reduction in breast cancer mortality has been observed in developed countries over the last two decades, which has been attributed to earlier diagnosis with widespread use of screening mammography and advances in breast cancer treatment (321). Timeliness of instituting treatment is crucial in order to obtain the maximum potential benefit from these new and advanced treatments. Two recent meta-analyses have shown a 6% and 15% increase in relative mortality rate with each 4-week delay in initiating adjuvant chemotherapy (207, 208). Although timeline thresholds given in treatment guidelines are sometimes arbitrary and controversial, longer delays for surgery, chemotherapy and radiation therapy have all been proven to be associated with poorer breast cancer outcomes including higher risks of recurrence and mortality (198, 207-210).

In New Zealand, longer delays experienced by Māori in the receipt of cancer care have been reported for surgical treatment of lung cancer (182) and for receipt of adjuvant chemotherapy for bowel cancer (181). To date, no data are available on delays in adjuvant therapy experienced by New Zealand women with breast cancer or ethnic differences in the receipt of such treatment.

We conducted this study to identify ethnic differences in delay in initiating adjuvant chemotherapy or radiation therapy following surgical treatment for invasive breast cancer. We also explored time trends in delays and impact of delay on breast cancer outcomes in this cohort of women with breast cancer.

Methods

Study population:

All newly diagnosed invasive female breast cancers during the period from 01/01/1999 to 31/12/2012, were identified from the WBCR (n=2848) for this study. Of this, women with

metastatic cancer at diagnosis (stage IV) (n=166), women who did not undergo primary surgery (n=114) and women who received neo-adjuvant therapy (n=87), were excluded.

Delay in adjuvant therapy:

To assess time gap from surgery to initiation of first adjuvant therapy (i.e. chemotherapy or radiation therapy), all women with non-metastatic invasive breast cancer undergoing surgery as primary breast cancer treatment modality were identified (n=2481). Chemotherapy was considered as the first adjuvant therapy for all eligible women undergoing adjuvant chemotherapy (n=922, 37.2%) and radiation therapy was considered as the first adjuvant therapy for women undergoing radiation therapy without prior adjuvant chemotherapy (n=996, 40.1%). The time gap to adjuvant chemotherapy and radiation therapy was defined as number of days from the most definitive operation for the breast cancer to the first administration of chemotherapy or radiation therapy (319). The definitive surgical procedure at the primary site captured the most invasive surgical procedure at the primary site and included excisional biopsy, wide local excision and mastectomy. Women who had delays of more than 365 days for either chemotherapy or radiation therapy were excluded.

A threshold of 60 days was used as the acceptable threshold delay for initiating chemotherapy, based on evidence from three recently published papers. These include two meta-analyses which have demonstrated 6% and 15% worse overall and disease free relative mortality rates for each 4-week delay in initiating chemotherapy (207, 208). A third study from the USA, which included more than 6000 women found significantly worse disease free survival for women with stage II-III or triple negative or HER-2 positive cancers, who experienced delays longer than 60 days (210). As some previous studies have used a 90-day threshold delay for chemotherapy (320, 322-324), we performed additional analyses with a 90-day threshold for chemotherapy. For radiation therapy, a 90-day threshold was used, which has conventionally been used in the assessment of radiation therapy delay (209).

Data analysis:

Continuous variables were summarized as mean/median with standard deviation (SD). Independent samples median test was used to test differences in continuous variables. Chi squared tests (χ^2) for trend was used to test differences in delay among groups including age, ethnicity, stage, mode of diagnosis (screen detected or symptomatic) and year of diagnosis. Multivariable logistic regression analyses were performed to estimate independent association between above factors and delays in initiating adjuvant therapy. Separate Cox regression

models were used to identify the association between breast cancer specific mortality and delay (overall, chemotherapy and radiation therapy) adjusting for covariates.

Results:

This study included a total of 1918 women of whom 922 (711 NZ European and 153 Māori) received chemotherapy and 996 (853 NZ European and 113 Māori) received radiation therapy as first adjuvant therapy. The median time gap for initiating adjuvant chemotherapy was 49 days (mean 52.6, SD 21.3) and for adjuvant radiation therapy was 76 days (mean 81.4, SD 32.5). Māori women experienced significantly longer median delays compared with NZ European women for both adjuvant chemotherapy (median delay 54 vs. 49 days, $p=0.017$) and radiation therapy (median delay 83 vs. 75 days, $p=0.046$). Overall, 318 (31.9%) women experienced a delay longer than 90 days to receive radiation therapy and the number of women who did not receive chemotherapy within 60-day threshold was 301 (32.4%). A total of 619 (32.3%) women experienced a delay in receiving first adjuvant therapy. Five per cent ($n=46$) women experienced a delay longer than 90 days for chemotherapy. A significantly higher proportion of Māori women experienced a delay longer than 90 days compared with NZ European women (8.7% vs. 4.2%, $p=0.025$)

Univariate analysis of factors associated with delay in receiving first adjuvant therapy, chemotherapy and radiation therapy are shown in Table 26 and the multivariable logistic regression in Table 27. Māori or Pacific ethnicity compared with NZ European ethnicity, earlier year of diagnosis, requiring a re-excision following primary surgery, longer distance from the tertiary care hospital and receiving surgical treatment from a public versus private hospital were associated with significantly longer delays ($p<0.05$) for first adjuvant therapy in both unadjusted and adjusted models. For chemotherapy, a significant inverse association ($p=0.048$) was observed between stage and proportion with delays longer than 60 days with the smallest proportion observed for stage III disease. Delays longer than threshold limits for chemotherapy and radiation therapy were significantly associated with re-excisions after primary surgery and treatment in public hospital in both univariate and multivariate models. Distance from treatment facility was significantly associated with delay in radiation therapy ($p=0.021$), but not for delay in chemotherapy ($p=0.540$). Delay for radiation therapy has significantly reduced over time ($p<0.001$), while delays for chemotherapy have increased during 1999-2009, although a decline is observed over 2010-2012.

Table 26: Univariate analysis of factors associated with delay in first adjuvant therapy ^a, delay in radiation and delay in chemotherapy for women with newly diagnosed invasive breast cancer

Characteristic	Total (N=1918)	Delay in first adjuvant therapy ^a	Delay in radiation therapy >90 days	Delay in chemotherapy >60 days	p		
	n (%)	n (%)	n (%)	n (%)			
Ethnicity							
NZ European	1564 (81.5)	478 (30.6)	261 (30.6)	217 (30.5)			
Māori	266 (13.9)	101 (38.0)	0.022	45 (39.8)	0.045	57 (37.3)	0.103
Pacific	38 (2.0)	19 (50.0)	0.013	6 (54.5)	0.101	13 (48.1)	0.057
Other	50 (2.6)	21 (42.0)	0.112	7 (35.0)	0.676	14 (46.7)	0.065
Age (years)							
<40	117 (6.1)	38 (32.5)	0.846	9 (40.9)	0.704	29 (30.5)	
40-49	433 (22.6)	130 (30.0)		43 (32.8)		87 (28.8)	
50-59	583 (30.4)	193 (33.1)		89 (34.2)		104 (32.2)	
60-69	494 (25.8)	165 (33.4)		94 (29.2)		71 (41.3)	
70-79	212 (11.1)	70 (33.0)		60 (33.0)		10 (33.3)	
80+	79 (4.1)	23 (29.1)		23 (29.1)		0	
Stage at diagnosis							
I	800 (41.7)	228 (28.5)	<0.001	176 (27.0)		52 (35.4)	
II	772 (40.3)	291 (37.7)		112 (43.1)		179 (35.0)	
III	346 (18.0)	100 (28.9)		30 (36.1)		70 (26.6)	
Year of diagnosis							
1999-2002	393 (20.5)	166 (42.2)	<0.001	105 (62.5)		61 (27.1)	
2003-2006	579 (30.2)	181 (31.3)		107 (35.9)		74 (26.3)	
2007-2009	452 (23.6)	146 (32.3)		50 (20.0)		96 (47.5)	
2010-2012	494 (25.8)	126 (25.5)		56 (20.0)		70 (32.7)	
Screening status							
Non-screen	1110 (57.9)	372 (33.5)	0.162	171 (36.3)	0.005	201 (31.5)	
Screen detected	808 (42.1)	247 (30.6)		147(28.0)		100 (35.3)	
Deprivation							
Dep 1-2	213 (11.1)	55 (25.8)	0.257	29 (28.7)		26 (23.2)	
Dep 3-4	206 (10.7)	66 (32.0)		36 (34.3)		30 (29.7)	
Dep 5-6	487 (25.4)	161 (33.1)		75 (29.8)		86 (36.6)	
Dep 7-8	532 (27.7)	174 (32.7)		98 (32.7)		76 (32.8)	

Dep 9-10	480 (25.0)	163 (34.0)	80 (33.6)	83 (34.3)	
Primary surgery			0.913	0.014	0.058
BCS	1318 (68.7)	425 (32.2)	260 (30.4)	165 (35.6)	
Mastectomy	600 (31.3)	194 (32.3)	58 (40.8)	136 (29.7)	
Re-excision			<0.001	<0.001	0.002
No	1659 (86.5)	491 (29.6)	250 (28.6)	241 (30.7)	
Yes	259 (13.5)	128 (49.4)	68 (55.3)	60(44.1)	
Distance from hospital			0.019	0.021	0.540
<10km	630 (32.8)	192 (30.5)	94 (28.1)	98 (33.1)	
10-50km	740 (38.6)	221 (29.9)	107 (29.2)	114 (30.5)	
50-100km	462 (24.1)	169 (36.6)	100 (38.9)	69 (33.7)	
>100km	86 (4.5)	37 (43.0)	17 (43.6)	20 (42.6)	
Surgical facility type			<0.001	0.009	0.001
Private	632 (33.0)	163 (25.8)	73 (25.8)	90 (25.8)	
Public	1286 (67.0)	456 (35.5)	245 (34.4)	211 (36.8)	
Charlson score			0.175	0.434	0.520
0	1677 (87.4)	534 (31.8)	265 (31.7)	269 (32.0)	
1+	241 (12.6)	85 (35.3)	53 (33.3)	32 (39.0)	

^a delay in radiation therapy longer than 90 days or delay in chemotherapy longer than 60 days

Adjusted multivariable logistic regression model identified year of diagnosis, re-excision and surgical treatment facility type to be independently associated with delay in first adjuvant therapy as well as for delay in chemotherapy and radiation therapy (Table 27). Overall, Māori, Pacific and Other ethnicity were associated with higher likelihoods of delay for chemotherapy, radiation therapy and for first adjuvant therapy, although this was statistically significant only for delay in radiotherapy for Māori and delay in first adjuvant therapy for Pacific women in the multivariable model. Sensitivity analysis with 90-day chemotherapy delay threshold yielded similar results in the multivariable regression model (Appendix 6) with year of diagnosis ($OR=1.37$, $p<0.001$), re-excision ($OR=3.96$, $p=0.001$) and public hospital care ($OR=4.89$, $p=0.001$) showing significant associations. Māori women had a non-significantly higher risk for a chemotherapy delay longer than 90 days ($OR=1.41$, $p=0.291$) compared with NZ European women in this model.

Table 27: Multivariable model for factors associated with delay in first adjuvant therapy, delay in radiation therapy longer than 90 days and delay in chemotherapy longer than 60 days^a

	Delay in first adjuvant therapy ^b			Delay in radiation therapy >90 days			Delay in chemotherapy >60 days		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Ethnicity									
NZ European	Ref.			Ref			Ref		
Māori	1.32	0.98-1.77	0.069	1.87	1.17-3.02	0.010	1.17	0.78-1.74	0.452
Pacific	2.05	1.03-4.08	0.041	2.47	0.54-11.2	0.242	1.87	0.82-4.26	0.136
Other	1.71	0.94-3.11	0.082	1.32	0.46-4.05	0.564	2.03	0.93-4.44	0.076
Year of diagnosis ^c	0.79	0.72-0.87	<0.001	0.49	0.42-0.56	<0.001	1.17	1.03-1.34	0.017
Re-excision	2.47	1.85-3.28	<0.001	3.55	2.32-5.44	<0.001	1.81	1.19-2.73	0.005
Surgical facility type	1.53	1.22-1.93	<0.001	1.59	1.12-2.26	0.010	1.58	1.15-2.16	0.005
Distance from hospital	1.10	1.02-1.18	0.024	1.23	1.09-1.39	0.001	1.03	0.92-1.15	0.654

^a Adjusted for age, tumour stage, socioeconomic deprivation and comorbidity score, ^b Delay in radiation therapy longer than 90 days or delay in chemotherapy longer than 60 days, ^c Year categories as in Table 26.

Time trends in 60-day chemotherapy and 90-day radiation therapy delay by ethnicity is shown in Figure 24. Higher proportions of Māori women have consistently experienced longer delays for radiation therapy compared with NZ European women over the study period which were significant during 2003-2006 and 2007-2009 periods ($p=0.010$ and $p=0.012$, respectively). The reduction in radiation therapy delay has been greater for NZ European than for Māori over 1999-2009, which has resulted in a widening of disparity in delay between Māori and NZ European, although this gap seems to have narrowed over last three year period of the study. Higher proportions of Māori have experienced delays longer than 60 days for chemotherapy over 1999-2009 period, but since has declined below the rate for NZ European women over 2010-2012. For delays in chemotherapy longer than 90 days (Figure 25), the highest proportion was seen during 2007-2009 period (overall 10.9%, NZ European 9.7%, Māori 15.8%) and since has declined to 5.2% (NZ European 4.6%, Māori 6.8%) during 2010-2012.

Figure 24: Time trends in delay in adjuvant radiation therapy longer than 90 days (Panel A) and adjuvant chemotherapy longer than 60 days (Panel B) for invasive breast cancer in Waikato, New Zealand 1999-2012

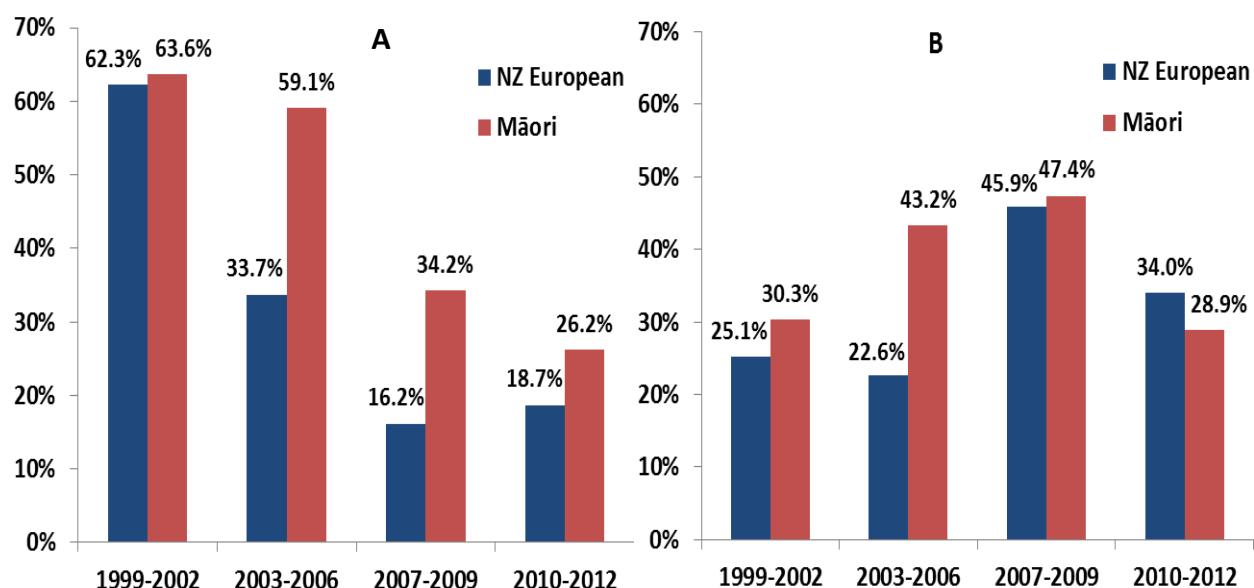
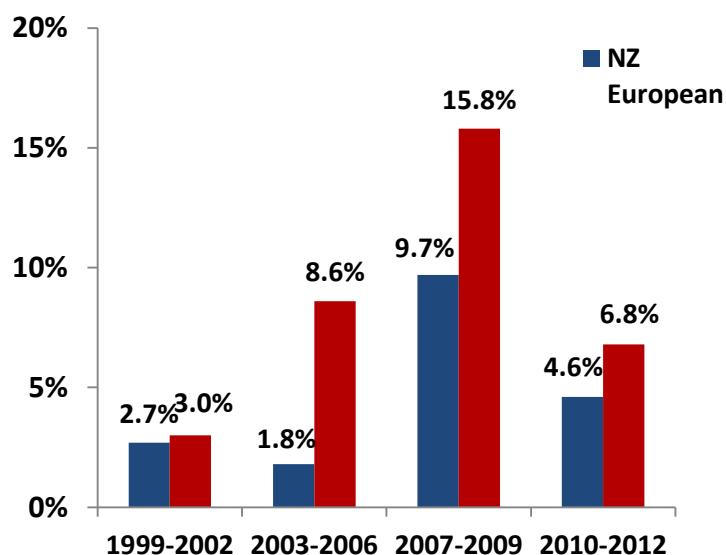


Figure 25: Time trends in delay in adjuvant chemotherapy longer than 90 days for invasive breast cancer in Waikato, New Zealand 1999-2012



A survival analysis using a multivariable Cox regression analysis adjusting for covariates showed a significantly higher breast cancer specific mortality risk ($HR=1.45$, $p=0.024$) among women who experienced delays in first adjuvant therapy (Table 28). A sensitivity analysis with a 90-day delay threshold for chemotherapy yielded a similar increased trend for breast cancer mortality for women who experienced a delay for first adjuvant therapy ($HR=1.29$,

0.81-2.05, p=0.288), although this difference was no longer statistically significant. Delay in chemotherapy (HR=1.34, p=0.157) and radiation therapy (HR=1.28, p=0.449) were also tended to be associated with higher hazards of breast cancer mortality although these did not reach statistical significance.

Table 28: Cox proportional models for breast cancer specific mortality by delay in first adjuvant therapy, radiation therapy and chemotherapy

	HR^{a b}	95% CI	p
Delay in first adjuvant therapy	1.45	1.05-2.01	0.024
Delay in radiotherapy >90 days	1.28	0.68-2.40	0.449
Delay in chemotherapy >60 days	1.34	0.89-2.01	0.157

^a Performed in three separate Cox regression models, ^b For stage I-III invasive breast cancer adjusted for age, ethnicity, stage of disease (i.e. tumour size and number of positive lymph nodes), tumour grade, oestrogen receptor status, lympho-vascular invasion, year of diagnosis, comorbidity score and receipt of adjuvant therapy)

Discussion:

From this study we found that among women with non-metastatic invasive breast cancer in the Waikato, New Zealand, almost a third (32.3%) experienced a delay in initiating radiation therapy or chemotherapy as first adjuvant therapy following primary surgical treatment. Furthermore, Māori and Pacific compared with NZ European, rural compared with urban dwelling women and women who received surgical treatment in public compared with private hospitals had significantly higher likelihoods of experiencing delays longer than thresholds for adjuvant therapy. Increasing socioeconomic deprivation tended to be non-significantly associated with longer delays in adjuvant therapy while no association was observed between delay and patient age. Although delay in radiation therapy seems to have improved over time, substantial proportions of women continue to experience clinically significant delays for both chemotherapy and radiation therapy.

Delays in adjuvant therapy for breast cancer experienced by disadvantaged populations including minority and Indigenous ethnic groups are well documented (316, 317). From a study based on over 100,000 women from the US National Cancer Database, Fedewa and

colleagues reported that Black African women were 30% and 50% more likely to experience delays longer than 60 and 90 days respectively, for initiation of adjuvant chemotherapy compared with White European women (319). We observed a similar pattern where greater proportions of Māori women experienced longer delays for chemotherapy (23% higher for 60-day and 100% higher for 90-day delay) compared with NZ European women. However, from 2007-2009, there were no significant inequities between Māori and NZ European women and, in 2010-2012 Māori women were less likely to experience a delay in accessing chemotherapy. Timeliness in initiating treatment for breast cancer is of greater importance for women with more advanced or more aggressive cancers (i.e. stage II or III, hormone receptor negative, HER-2 positive) (206, 210). Māori women are more likely to be diagnosed with more advanced disease and are more likely to have hormone receptor negative and HER-2 positive breast cancers (4, 13), and hence longer delays in adjuvant therapy, as demonstrated in this study are likely to have a greater impact on breast cancer survival in Māori women. However, women with more advanced cancers seem to have had shorter delays, possibly due to prioritized care for these higher risk women and, hence likely to have had a minimal differential impact on higher mortality in Māori compared with NZ European women.

Delays in cancer adjuvant therapy are associated with factors including lack of access to healthcare, difficulties with navigating the health system, geographic distance to treatment facility, availability of transport and ability to take time-off work to attend adjuvant therapy (316, 325, 326). Further, women of some ethnic minority populations including Black Africans in the USA have been shown to be less willing to undergo adjuvant treatments because of greater fear of side-effects and lack of knowledge on potential benefits (255, 327). Longer delays for adjuvant therapy observed among Māori compared with NZ European women in this study were likely due to a combination of these factors as Māori are more likely to be socioeconomically deprived and live in rural areas with less access to transport compared with NZ Europeans (34). These differences were observed despite temporary accommodation and/or free transport been provided by the Waikato District Health Board for women requiring these facilities to attend adjuvant chemotherapy and radiation therapy. Furthermore, the higher risk of Māori compared with NZ European women for longer delays persisted even after adjusting for deprivation and residence which probably was due to the impact of unmeasured or under-measured confounders in the present study. For instance, Māori women are more likely to have lower levels of education, lower health literacy and are less likely to have a health insurance policy compared with NZ European women (34), factors which are known to

be associated with longer delays in cancer treatment (319). These factors were not included in our analyses due to unavailability of these data from the WBCR.

We also observed that significantly smaller proportions of women who received surgical treatment in the private sector had experienced delays beyond the threshold limits for both chemotherapy and radiation therapy compared with women treated in the public sector. Ability to afford treatment from private sector has a strong correlation with higher socioeconomic status and/or having a health insurance policy. Hence, this observation supports, though indirectly, affluent socioeconomic background and health insurance as factors influencing shorter delays in the receipt of adjuvant therapy. This disparity is observed, despite more than 95% women included in the present study receiving their adjuvant chemotherapy and radiation therapy free of charge from the public sector.

Rural residency is known to influence delay as well as a woman's decision to undergo adjuvant radiation therapy for breast cancer (328). Radiation therapy requires women to attend a radiation facility five days a week over a period ranging from three to six consecutive weeks and due to this many rural women prefer mastectomy over BCS (328). This is of greater importance for the study women as the Waikato District Health Board covers an area of over 20,000 square kilometres and yet has provided radiation therapy services through a single central facility. In comparison, chemotherapy in most instances requires only once in three weeks and/or once a week visits to a chemotherapy facility and is less likely to be influenced by rural residence. Consistent with this, no significant differences in delays for chemotherapy were observed between urban and rural women in the present study.

Several effective strategies for minimizing delays in adjuvant therapy and reducing inequities in delay between socioeconomic and ethnic groups are reported in literature. These include improving access through increasing supply or efficient usage of existing cancer resources through coordinated cancer care, decentralization of cancer services and through improving patient health literacy (329-332). As we have observed, almost a third of women have experienced delays in adjuvant therapy beyond the threshold limits and it appears that overloading of oncology services was a likely factor. The greatest proportion of women experiencing delays longer than three months for radiation therapy was seen during 1999-2002 which was a time when a severe nationwide shortage of radiation therapy services was experienced in New Zealand (237). Since then the supply of radiation facilities has increased resulting in a gradual reduction in proportion of women experiencing delays longer than three months. However, the increase in supply of radiation therapy facilities has been inadequate or

lagging behind to keep up with the increase in number of patients requiring radiation therapy. As a result, even in 2010-2012, about 20% women were observed to have experienced delays longer than three months for radiation therapy. Delays in chemotherapy appeared to have worsened during 1999-2009 followed by an improvement in the last time period. These different patterns of delay in chemotherapy and radiation therapy may reflect issues at national level as well as local issues of service capacity compared with demand.

Increasing the supply of oncology services alone are unlikely to eliminate inequities in delay, as disadvantaged women (i.e. ethnic minority, socioeconomically deprived, rural, etc.) will still be more likely to be subjected to longer delays. Improved patient navigation through cancer care coordinators (CCC) has been shown to help reduce delays, especially for women who are at-risk for longer delays which include women of minority ethnicity and low socioeconomic groups (224). The Waikato District Health Board has two full-time CCC's providing support for women with breast cancer since 2009. It is likely that CCCs have made a major contribution towards the observed reduction in delay and reduction in inequities between Māori and NZ European women observed during 2010-2012. The Ministry of Health has also identified CCC's as a key strategy to increase quality and reduce inequalities in cancer care and since 2012 has provided funding for all District Health Boards to employ CCC's for management of common cancers in New Zealand (229).

This study did not examine the type, duration, dose or rates of completion of adjuvant chemotherapy or radiation therapy which are also known to impact on the efficacy of these adjuvant therapies (333, 334). Further, although we have observed several associations with longer delays, we were unable to identify causes for these delays i.e. whether delays were due to longer wait time for appointments or due to patients not attending appointments, additional investigations required due to patient comorbidity, etc. Another limitation of this study was the inclusion of only small numbers of Pacific and Other women. Although we have observed longer delays among Pacific women small sample size prevented further analyses.

In conclusion, we have observed significantly longer delays experienced by Indigenous Māori women, rural women and women receiving surgical care in the public sector. Although delays in adjuvant therapy appear to have improved over the study period, it is concerning to note the substantial proportion of women continuing to experience clinically significant delays for adjuvant breast cancer therapy. Reducing delays through improvements in availability, efficiency and access to oncology services will not only minimize ethnic inequities in delay but may improve outcomes for all women with breast cancer in New Zealand.

5.7. Are there differences in the use of adjuvant therapy for breast cancer by ethnicity

Preface:

This chapter contains an abbreviated version of a manuscript submitted for publication in *Australian and New Zealand Journal of Public Health*

- **Authors:** Seneviratne S, Campbell I, Scott N, Lawrenson R.
- **Title:** Ethnic differences in use of adjuvant therapy for breast cancer in New Zealand
- **Journal:** *Australian and New Zealand Journal of Public Health*
- **Impact factor:** 1.89
- **Journal's aims and scope:** The *Australian and New Zealand Journal of Public Health* (ANZJPH) publishes peer-reviewed research into public health, relevant to researchers, practitioners and policy makers. The Journal has a major focus on Australia and New Zealand but articles from other countries are accepted provided that the implications for Australia and New Zealand are addressed. Authors from Australia and New Zealand are encouraged to locate their papers in the international literature. The Journal is multidisciplinary and aims to publish methodologically sound research from any of the academic disciplines that constitute public health.

Abstract:

Background:

Inequities in use of breast cancer adjuvant therapy by ethnicity and socioeconomic status are well documented, and are known to be contributing to lower breast cancer survival among women of minority ethnicity and lower socioeconomic status. We investigated ethnic and socioeconomic inequities in use of adjuvant radiotherapy and chemotherapy in a cohort of women with breast cancer in the Waikato, New Zealand.

Methods:

All women with newly diagnosed invasive breast cancer during 1999-2012 were identified from the WBCR. Oestrogen (ER) and progesterone receptor (PR) negative tumours $\geq 10\text{mm}$ in diameter and ER and/or PR positive tumours $\geq 20\text{mm}$ in diameter in women younger than 70 years were deemed eligible for the use of chemotherapy (N=1212). Use of radiotherapy was considered for all women who underwent breast conserving surgery (BCS), and in women who underwent mastectomy, if the tumour diameter was $\geq 50\text{mm}$ or ≥ 4 of the lymph nodes were involved (N=1708).

Results:

Of the women deemed to be eligible based on criteria used, 836 (69%) and 1491 (87.3%) women were observed to have received chemotherapy and radiotherapy, respectively. In the multivariate model, significantly lower use of radiotherapy was associated with Māori compared with NZ European ethnicity (OR=0.62, 95% CI, 0.39-0.98), comorbidity (OR=0.32, 95% CI, 0.23-0.43), distance from radiation facility (OR=0.87, 95% CI, 0.77-0.98), mastectomy compared with BCS (OR=0.32, 95% CI, 0.19-0.56) and non-screen compared with screen detection (OR=0.51, 95% CI, 0.34-0.77). No significant associations were observed between chemotherapy use and ethnic or socio-demographic factors.

Conclusions:

Significantly lower use of adjuvant radiotherapy observed in Indigenous Māori and rural women indicate the existing barriers to access radiotherapy for these women. Increasing availability and improving access for radiotherapy, especially for women who are at high risk due to ethnicity, geography or socioeconomic status need to be recognized as priorities.

Background:

Differences in quality and timeliness in treatment of breast cancer, including differences in the use of adjuvant therapy have also been reported to be important contributors for ethnic and socioeconomic disparities in breast cancer survival (80, 322, 335).

Indigenous Māori in New Zealand are known to have lower access, receive inferior quality cancer care and experience longer cancer treatment delays compared with NZ Europeans for a variety of cancers. For instance, Māori patients have been reported to experience longer delays for surgical treatment lung cancer (182), and a lower use of chemotherapy for bowel cancer (181) compared with NZ European patients. To date, data are sparse on possible ethnic differences in use, quality or timeliness of adjuvant therapy for breast cancer in New Zealand.

We hypothesized that Māori women were less likely to have received adjuvant chemotherapy and/or radiation therapy compared with NZ European women, based on standard treatment guidelines (44, 52), which might have contributed to higher breast cancer mortality in Māori women. To answer this question, we analysed cancer treatment data from a regional, population based sample of women with breast cancer diagnosed over a period of 14 years. Rates of adjuvant chemotherapy and radiation therapy use by socio-demographic and tumour characteristics were analysed individually, and adjusting for covariates, to identify associations between use of adjuvant therapy, and ethnicity and socioeconomic status.

Methods:

Study population:

All women with newly diagnosed primary invasive breast cancers during the period from 01/01/1999 through 31/12/2012, were identified from the WBCR (n=2848). Of this, women with metastatic cancer at diagnosis (n=166) and women who did not undergo primary surgery (n=114) were excluded.

Use of adjuvant therapy:

Chemotherapy: Chemotherapy eligibility was considered only for women younger than 70 years. For oestrogen (ER) and progesterone (PR) receptor negative cancers, a maximum tumour diameter of $\geq 10\text{mm}$ (n=276, 22.8%) was considered as the threshold for chemotherapy. For ER and/or PR positive tumours, defining a threshold for chemotherapy was

complicated as this decision in most situations was based on multiple factors including lymph node involvement, tumour grade, lympho-vascular invasion, HER-2 status, and more recently, with Ki-67 and tumour genotyping (336). For ER and/or PR positive or unknown tumours cancers, we considered $\geq 20\text{mm}$ maximum tumour diameter as the threshold for chemotherapy (n=936, 77.2%) (44, 52). Of the women considered to be eligible for chemotherapy (N=1212), women who received either adjuvant or neo-adjuvant chemotherapy were considered to have received chemotherapy. We also performed a separate analysis with a different threshold for ER and/or PR positive cancers. For this analysis, cancers were considered eligible only if one or more of lymph node positivity, tumour grade >1 or lympho-vascular invasion were present in addition to the tumour diameter of $\geq 20\text{mm}$.

Radiation therapy: Women who were deemed to be eligible for radiation therapy (n=1708) were identified based on following criteria. All women undergoing breast conserving surgery without a completion mastectomy (n=1354, 79.3%) were considered eligible, and for women undergoing a mastectomy, if the maximum tumour diameter was $\geq 50\text{mm}$ or if ≥ 4 lymph nodes were positive for tumour metastasis (n=354, 20.7%) were considered eligible (44, 52).

Data analysis:

Categorical measures were summarized as numbers observed with percentages and Chi squared tests (χ^2) for trend were used to test differences in use of chemotherapy and radiation therapy among groups categorized by age, ethnicity, stage, mode of diagnosis and year of diagnosis. Multivariable logistic regression analyses were performed to identify factors independently associated with use of adjuvant chemotherapy and radiation therapy.

Results:

Use of chemotherapy:

Of the women deemed eligible for chemotherapy, 836 (69%) women had received chemotherapy. No significant differences in the rates of chemotherapy use were observed between Māori and NZ European women (68.3% vs. 68.7%, p=0.916). Chemotherapy use was significantly higher in younger women (p<0.001), in women with a zero comorbidity score (p<0.001), for women surgically treated in private hospitals (p=0.002) and for women with non-screen detected cancer (p=0.033) (Table 29). Increasing socioeconomic deprivation tended to be associated with lower use of chemotherapy overall, and for Māori and NZ

European women, although this was not statistically significant ($p=0.402$). As expected, chemotherapy use was higher for cancers which were associated with adverse prognostic features including size larger than 5cm, positive lymph node status, higher grade, lympho-vascular invasion (LVI) and HER-2 positivity. Similar trends in the use of chemotherapy by tumour characteristics were observed for Māori and NZ European women.

Table 29: Socio-demographic and tumour characteristics associated with use of adjuvant chemotherapy for invasive breast cancer ^a in the Waikato, New Zealand 1999-2012

Characteristic	Chemotherapy use								p	
	Total population (N=1212)		Total (N=1212)		NZ European (N=924)		Māori (N=218)			
	n	%	n	%	n	%	n	%		
Age (yrs.)									<0.001	
<40	100	8.3%	90	90.0%	58	89.2%	18	90.0%		
40-49	338	27.9%	276	81.7%	200	81.3%	56	81.2%		
50-59	434	35.8%	309	71.2%	245	72.5%	53	68.8%		
60-69	340	28.1%	161	47.4%	132	48.0%	22	42.3%		
Deprivation									0.402	
Dep 1-2	139	11.5%	100	71.9%	88	71.5%	8	80.0%		
Dep 3-4	126	10.4%	89	70.6%	72	70.6%	12	75.0%		
Dep 5-6	313	25.8%	216	69.0%	174	67.7%	29	70.7%		
Dep 7-8	315	26.0%	213	67.6%	160	67.8%	39	61.9%		
Dep 9-10	319	26.3%	218	68.3%	141	68.4%	61	69.3%		
Surgical hospital type									0.002	
Private	406	33.5%	303	74.6%	271	74.0%	21	80.8%		
Public	806	66.5%	533	66.1%	364	65.2%	128	66.7%		
Diagnostic type									0.033	
Screen detected	407	33.6%	235	57.7%	195	57.9%	30	57.7%		
Non-screen detected	805	66.4%	601	74.7%	440	75.0%	119	71.7%		
Charlson score									<0.001	
0	1056	87.1%	754	71.4%	582	70.5%	124	71.7%		
1+	156	12.9%	82	52.6%	53	53.5%	25	55.6%		

Diagnosis year									0.003
1999-2002	269	22.2%	201	74.7%	160	73.7%	31	79.5%	
2003-2006	374	30.9%	267	71.4%	216	72.5%	38	66.7%	
2007-2009	292	24.1%	183	62.7%	128	60.7%	39	65.0%	
2010-2012	277	22.9%	185	66.8%	131	66.2%	41	66.1%	
Grade									<0.001
Grade I	168	13.9%	70	41.7%	62	43.4%	6	33.3%	
Grade II	617	50.9%	409	66.3%	305	66.0%	83	66.9%	
Grade III	395	32.6%	340	86.1%	254	85.8%	57	83.8%	
Unknown	32	2.6%	17	53.1%	14	60.9%	3	37.5%	
ER/PR status									<0.001
ER &/or PR +	926	76.4%	598	64.6%	457	64.3%	103	63.6%	
ER & PR -	276	22.8%	233	84.4%	173	84.4%	46	83.6%	
Unknown	10	0.8%	5	50.0%	5	62.5%	0		
T stage									<0.001
T1	368	30.4%	234	63.6%	196	62.6%	29	69.0%	
T2	692	57.1%	484	69.9%	364	71.4%	83	62.4%	
T3	83	6.8%	64	77.1%	40	74.1%	19	82.6%	
T4	62	5.1%	50	80.6%	31	77.5%	18	90.0%	
N stage									<0.001
0	406	33.5%	223	54.9%	165	54.6%	37	50.0%	
1	537	44.3%	381	70.9%	291	70.0%	72	74.2%	
2+	269	22.2%	232	86.2%	179	86.9%	40	85.1%	
LVI									<0.001
Negative	783	64.6%	484	61.8%	362	61.0%	88	62.0%	
Positive	429	35.4%	352	82.1%	273	82.5%	61	80.3%	
HER-2									<0.001
Negative	658	54.3%	414	62.9%	314	63.2%	79	60.8%	
Equivocal	48	4.0%	25	52.1%	17	48.6%	6	66.7%	
Positive	219	18.1%	188	85.8%	134	86.5%	37	80.4%	
Unknown	287	23.7%	209	72.8%	170	71.7%	27	81.8%	

^a ER and PR negative cancers ≥10mm and ER and/or PR positive cancers ≥20mm are included

Multivariate analysis of factors associated with chemotherapy use is shown in Table 30. Age, comorbidity score and adverse tumour characteristics remained significant while socio-demographic factors including ethnicity and surgical hospital type were not significant.

Table 30: Multivariable logistic regression analysis for factors associated with use of adjuvant chemotherapy for invasive breast cancer in the Waikato, New Zealand 1999-2012

Characteristic	OR	95% CI	p
Māori ethnicity	1.01	0.66-1.52	0.992
Age ^a	0.88	0.78-0.98	0.017
Year of diagnosis ^b	0.96	0.82-1.12	0.588
ER and/or PR positive	0.36	0.24-0.54	<0.001
Deprivation	0.97	0.86-1.08	0.558
Charlson score	0.31	0.21-0.46	<0.001
Hospital type	0.77	0.56-1.06	0.109
T stage	1.19	0.96-1.47	0.105
N stage	2.03	1.67-2.46	<0.001
Grade	2.01	1.61-2.49	<0.001
LVI	1.82	1.30-2.54	<0.001
HER-2	1.82	1.30-2.54	<0.001

^a age categories as in Table 29, ^b year categories as in Table 29

An additional analysis was performed with a different chemotherapy threshold for ER and/or PR positive cancers, considering these cancers as eligible for chemotherapy only if the cancer had one or more of lymph node positivity, lympho-vascular invasion or tumour grade >1 in addition to a maximum tumour diameter of $\geq 20\text{mm}$. This analysis yielded results much similar to the analysis in Table 29 (Appendix 7). According to new criteria, 1168 women were found to be eligible, and of this 824 (70.5%) have received chemotherapy; 623 (70.1%) of NZ European and 149 (70.3%) of Māori women. Multivariable logistic regression analysis showed trends similar to Table 30 and, for Māori, the adjusted odds of chemotherapy use was 1.25 (0.85-1.87, p=0.258).

Use of radiation therapy:

Characteristics associated with use of radiation therapy are shown in Table 31. Overall, radiation therapy was used for 1491 (87.3%) of the women deemed to be eligible for radiation based on selection criteria. Radiation therapy use was non-significantly lower among Māori compared with NZ European women (84% vs. 87.8%, p=0.138). Younger age at diagnosis, lower deprivation, later year of diagnosis, surgical care in a private hospital, shorter distance from the hospital, screen detection, undergoing BCS and adverse tumour characteristics including higher grade, stage and positive lymph node status were significantly associated with increased likelihoods of receiving radiation therapy. Although a similar increasing trend in the use of radiation therapy were seen for Māori and NZ European women over each year category, these respective rates were lower for Māori compared with NZ European women.

Table 31: Socio-demographic and tumour characteristics associated with use of adjuvant radiation therapy for invasive breast cancer in the Waikato, New Zealand 1999-2012

Characteristic	Radiation therapy use				p
	Total population (N=1708)		Total (N=1708)	NZ European (N=1418)	
	n (%)	n (%)	n (%)	n (%)	
Age (yrs.)					<0.001
<40	79 (4.6)	76 (96.2)	50 (96.2)	16 (94.1)	
40-49	328 (19.2)	302 (92.1)	231 (93.9)	52 (86.7)	
50-59	499 (29.2)	456 (91.4)	377 (92.0)	66 (90.4)	
60-69	471 (27.6)	417 (88.5)	361 (90.5)	45 (75.0)	
70-79	218 (12.8)	172 (78.9)	161 (78.9)	8 (72.7)	
80+	113 (6.6)	68 (60.2)	65 (60.7)	2 (50.0)	
Diagnosis year					0.003
1999-2002	357 (20.9)	296 (82.9)	255 (83.9)	30 (76.9)	
2003-2006	506 (29.6)	443 (87.5)	396 (88.0)	37 (86.0)	
2007-2009	406 (23.8)	354 (87.2)	284 (87.4)	50 (84.7)	
2010-2012	439 (25.7)	398 (90.7)	310 (91.4)	72 (85.7)	
Deprivation					0.006
Dep 1-2	178 (10.4)	167 (93.8)	156 (94.0)	5 (83.3)	
Dep 3-4	186 (10.9)	163 (87.6)	140 (87.5)	17 (94.4)	

Dep 5-6	414 (24.2)	364 (87.9)	318 (88.1)	37 (90.2)
Dep 7-8	491 (28.7)	423 (86.2)	356 (87.9)	54 (77.1)
Dep 9-10	439 (25.7)	374 (85.2)	275 (84.4)	76 (84.4)
Distance				0.005
<10km	546 (32.0)	489 (89.6)	409 (90.5)	54 (85.7)
10-50km	650 (38.6)	579 (89.1)	488 (88.1)	70 (85.6)
50-100km	428 (25.1)	364 (85.0)	310 (85.4)	49 (83.1)
>100km	74 (4.3)	59 (79.7)	38 (79.2)	16 (76.2)
Diagnostic type				<0.001
Screen detected	750 (43.9)	698 (93.1)	602 (93.3)	76 (90.5)
Non-screen	958 (56.1)	793 (82.8)	643 (83.2)	113 (80.1)
Hospital type				<0.001
Private	535 (31.3)	488 (91.2)	453 (91.5)	25 (86.2)
Public	1173 (68.7)	1003 (85.5)	792 (85.8)	164 (83.7)
Surgery type				<0.001
BCS	1354 (79.3)	1213 (89.6)	1031 (89.7)	143 (88.8)
Mastectomy	354 (20.7)	278 (78.5)	214 (79.9)	46 (71.9)
Grade				0.493
Grade I	441 (25.8)	381 (86.4)	341 (87.0)	27 (79.4)
Grade II	865 (50.6)	754 (87.2)	626 (88.0)	102 (82.9)
Grade III	371 (21.7)	331 (89.2)	257 (89.2)	56 (87.5)
Unknown	31 (1.8)	25 (80.6)	21 (77.8)	4 (100)
T stage				<0.001
T1	1020 (59.7)	915 (90.1)	790 (90.1)	98 (89.9)
T2	518 (30.3)	437 (84.4)	356 (85.8)	57 (76.0)
T3	100 (5.9)	79 (79.0)	54 (76.1)	20 (87.0)
T4	70 (4.1)	58 (82.9)	43 (84.3)	14 (77.8)
N stage				0.042
0	1029 (60.3)	900 (87.8)	762 (87.8)	106 (86.9)
1	363 (21.2)	321 (88.9)	266 (90.2)	45 (83.3)
2+	316 (18.5)	266 (84.2)	215 (93.1)	36 (76.6)
Charlson score				<0.001
0	1456 (85.2)	1312 (90.1)	1111 (90.7)	151 (85.8)
1+	252 (14.8)	179 (71.0)	134 (69.4)	38 (77.6)

Multivariable analysis of factors associated with radiation therapy is shown in Table 32. Māori compared with NZ European ethnicity (OR=0.62, 95% CI, 0.39-0.98), older age (OR=0.78, 95% CI 0.70-0.87), longer distance from the radiation facility (OR=0.87, 95% CI, 0.77-0.98, higher comorbidity score (OR=0.32, 95% CI, 0.23-0.43), mastectomy compared with BCS (OR=0.32, 95% CI, 0.19-0.56) and non-screen compared with screen detection (OR=0.51, 95% CI, 0.34-0.77) were significantly associated with lower likelihoods of receiving radiation therapy in this model.

Table 32: Multivariable logistic regression analysis for factors associated with use of adjuvant radiotherapy for invasive breast cancer in the Waikato, New Zealand 1999-2012

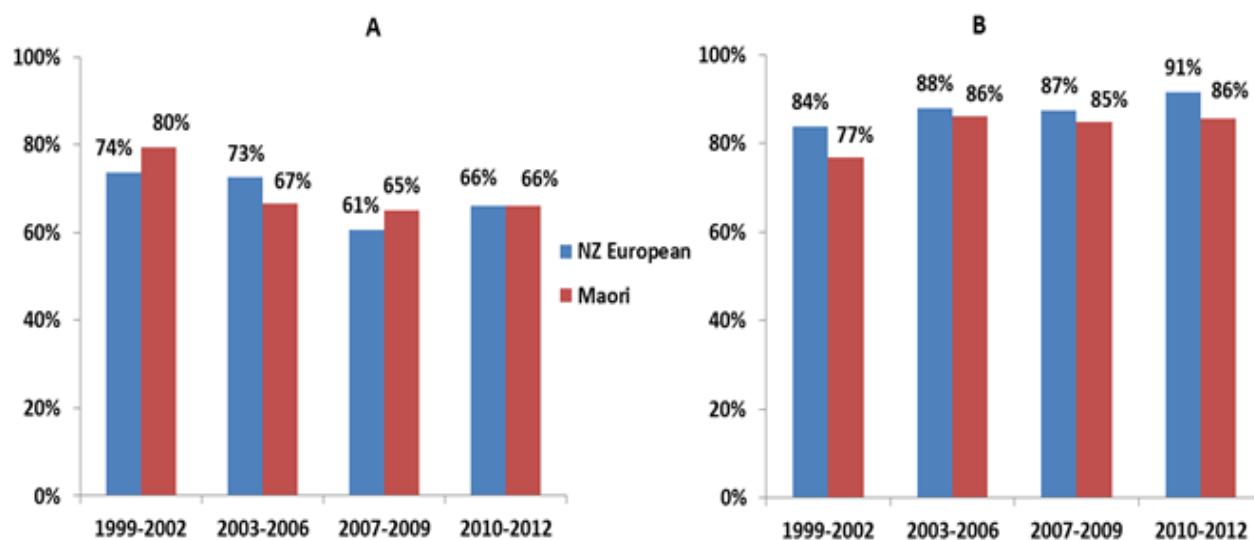
Characteristic	OR	95% CI	p
Māori ethnicity	0.62	0.39-0.98	0.041
Age ^a	0.78	0.70-0.87	<0.001
Year of diagnosis ^b	1.21	1.05-1.40	0.004
Deprivation	0.94	0.83-1.08	0.394
Distance	0.87	0.77-0.98	0.024
Charlson score	0.32	0.23-0.43	<0.001
Surgery in public vs. private	0.76	0.53-1.09	0.144
Non-screen vs. screen detection	0.51	0.34-0.77	0.001
Mastectomy vs. BCS	0.32	0.19-0.36	<0.001
T stage	0.95	0.75-1.19	0.645
N stage	1.21	0.97-1.50	0.085

^a age categories as in Table 29, ^b year categories as in Table 31

Further analyses were performed for women undergoing BCS and mastectomy separately. These analyses confirmed that Māori were less likely to receive radiation following mastectomy (OR=0.56, 0.25-1.25, p=0.157) and BCS (OR=0.72, 0.39-1.34, p=0.304), although these differences were not statistically significant. Significantly lower likelihoods of receiving radiation following both BCS and mastectomy were seen for women of older age (OR=0.68, 95% CI 0.60-0.78 & OR=0.81, 95% CI 0.68-0.95 respectively), non-screen compared with screen detected (OR=0.39, 95% CI, 0.27-0.54 and OR=0.70, 95% CI 0.29-1.65, respectively) and for women with higher comorbidity scores (OR=0.27, 95% CI 0.19-0.39 and OR=0.30, 95% CI 0.17-0.53, respectively).

Figure 26 shows time trends in the use of chemotherapy and radiation therapy by ethnicity. Chemotherapy use seems to have gradually declined for both Māori and NZ European women from 1999-2002 to 2007-2009. Rates of radiation therapy use seem to be increasing gradually in NZ European women while the rates have plateaued for Māori since 2003-2006.

Figure 26: Time trends in use of chemotherapy (Panel A) and radiotherapy (Panel B) by ethnicity



Discussion:

This study has shown that the use of adjuvant radiation therapy for breast cancer was significantly lower in Māori compared with NZ European women based on accepted practice guidelines (44, 52). No significant difference in the use of chemotherapy was observed between Māori and NZ European women. Significantly lower use of radiation therapy was also seen among rural compared with urban dwelling women and non-screen compared with screen detected women. Overall, the use of radiation was lower than expected based on guidelines (44, 52), and was substantially worse for post-mastectomy radiation (78.5%) than for radiation following BCS (89.6%). Although use of radiation therapy seems to have improved over time, even during 2010-2012 a substantial proportion of women (10%) were observed to have not received radiation therapy.

Lower use of adjuvant chemotherapy for minority ethnic cancer patients are well documented in the USA and include chemotherapy for breast, colon and lung among many other cancers (316, 337). Not only that these patients have experienced lower use of adjuvant chemotherapy,

but on many occasions were subjected to longer delays and use of chemotherapy regimens not in keeping with recommended guidelines (317, 338, 339). Similarly, lower use and longer delays for adjuvant chemotherapy for bowel cancer in Māori compared with non-Māori patients have supported the existence of similar ethnic disparities in New Zealand (181).

Despite that, we did not observe a significant difference between Māori and NZ European women in the use of adjuvant chemotherapy for breast cancer, either in univariate or multivariate models. Further, we have not analysed the use of recommended regimens of chemotherapy or rates of completion of chemotherapy in the present study. Hence, although we have not observed an ethnic disparity in overall adjuvant chemotherapy use, further research is needed to investigate possible disparities in other areas of chemotherapy use including rates of completion and use of recommended regimens.

Overall, use of radiation therapy fell short of recommended guidelines, and was significantly lower for Māori compared with NZ European women (44, 52). Similar inequities in the use of adjuvant radiation therapy for breast cancer have been reported from the USA, between minority African American and White American women (83, 316). It appears that socio-demographically disadvantaged women (i.e. Māori, rural residence and high socioeconomic deprivation) had higher likelihoods of not receiving adjuvant radiation, while no such differences were observed for chemotherapy. Differences in difficulty in access for radiation therapy in comparison to chemotherapy might have at least partially been responsible for this difference. Adjuvant radiation for the study population was provided through the central radiation facility at the tertiary hospital in Hamilton, and radiation therapy required these women to attend the radiation facility five days a week over a period, ranging from four to six weeks. For women residing in remote and rural areas this would have posed an obvious difficulty due to difficulties with and cost of travel. Many rural women with breast cancers suitable for BCS opting for mastectomy due to these reasons is well documented in the literature (340). Women of low socioeconomic groups also face similar difficulties due to difficulties with transport, taking time off work or due to lack of support to care for dependants, resulting in lower use of radiotherapy (341). Higher proportions of Māori live in rural areas and are more likely to be socioeconomically deprived contributing to lower radiation therapy use in Māori. However, lower use of radiation in Māori persisted even after adjusting for these factors, which suggested an independent association between Māori and the use of radiation therapy.

Women with screen detected cancer were significantly more likely to have received radiation therapy compared to women with non-screen detected women, a pattern seen following both mastectomy and BCS. Diagnostic and treatment indicators for women diagnosed through BSA programme are routinely measured and performance of each screening provider is regularly audited against pre-established criteria. However, similar quality measures or audit processes were non-existent for symptomatically detected cancer. This provides a likely explanation for higher radiation therapy rates seen for screen detected cancer, despite these cancers carrying a lower risk of local recurrence compared with non-screen detected cancer. This observation highlights a failure of the healthcare system, where women with lower risk cancers have likely been prioritized to receive treatment over women with higher risk cancers. Such inequities in care are likely to further exacerbate inequities in breast cancer outcomes seen between Māori and NZ European women, especially since Māori women have a significantly lower screening coverage (39), and as a result, a lower proportion of screen detected cancer.

There were several limitations included in this study. First, although we observed differences in adjuvant therapy among some groups of interest and several associations, we could not ascertain exact causes for non-use (i.e. not referred, not seen by an oncologist or patient declined) due to non-availability of these data. Selection of patients for chemotherapy is complicated and is based on multiple factors including age, tumour size, grade, ER/PR, lymph node status and lympho-vascular invasion. As a result, criteria used for selection of women eligible for chemotherapy were not absolute, especially for women with ER/PR positive cancers. We did not observe major differences in distribution of these tumour characteristics between Māori and NZ European women, and hence, these factors are unlikely to have influenced selection for chemotherapy in a differential manner.

In conclusion, we observed significantly lower use of radiation therapy for Māori and rural women, although similar disparities were not observed for chemotherapy. Difficulties in accessing radiation therapy appeared to be a major contributor towards differences observed by ethnicity, geographic location and socioeconomic status. Failures of the healthcare system to providing equitable care were also evident by the discrepancy in radiation therapy seen between screen and non-screen detected women. Increasing availability and improving access for breast cancer adjuvant therapy for women who are at high risk of not receiving adjuvant therapy due to ethnicity, geography or socioeconomic position need to be recognized as priorities, which may help minimize breast cancer outcome inequities.

5.8. Does patient adherence with treatment contribute to inequity?

Preface:

This chapter contains an abbreviated version of a manuscript published in *The Breast*

- **Authors:** Seneviratne S, Campbell I, Scott N, Kuper-Hommel M, Kim B, Pillai A, Lawrenson R.
- **Title:** Adherence to adjuvant endocrine therapy: Is it a factor for differences in breast cancer outcomes by ethnicity in New Zealand?
- **Journal:** *The Breast*
- **Year of publication:** 2014
- **DOI:** 10.1016/j.breast.2014.11.011
- **Impact factor:** 2.58
- **Journal's aims and scope:** *The Breast* is an international, multidisciplinary journal for clinicians, which focuses on translational and clinical research for the advancement of breast cancer prevention and therapy. The Editors welcome the submission of original research articles, systematic reviews, viewpoint and debate articles, and correspondence on all areas of pre-malignant and malignant breast disease, including: Surgery, Medical oncology and translational medicine, Radiation oncology, Breast endocrinology, Epidemiology and prevention, Gynaecology, Imaging, screening and early diagnosis, Pathology, Psycho-oncology and quality of life, Advocacy, Supportive and palliative care and Nursing.

Abstract:

Background:

Despite the benefits of adjuvant endocrine therapy for hormone receptor positive breast cancer, many women are non-adherent or discontinue endocrine treatment early. We studied differences in adherence to adjuvant endocrine therapy by ethnicity in a cohort of New Zealand women with breast cancer and its impact on breast cancer outcomes.

Methods:

We analysed data on all women (n=1149) with newly diagnosed hormone receptor positive, non-metastatic, invasive breast cancer who were treated with adjuvant endocrine therapy in the Waikato during 2005 to 2011. Linked data from the Waikato Breast Cancer Registry and National Pharmaceutical Database were examined to identify differences by ethnicity in adherence to prescribed adjuvant endocrine therapy and the effect of sub-optimal adherence on cancer recurrence and mortality.

Results:

Overall, a high level of adherence of $\geq 80\%$ was observed among 70.4% of women, which declined from 76.8% to 59.3% from the first to fifth year of treatment. Māori women were significantly more likely to be sub-optimally adherent ($< 80\%$) compared with European women (crude rate 37% vs. 28%, $p=0.005$). In the adjusted model Māori women were still significantly more likely to sub-optimally adhere to endocrine therapy than European women ($OR=1.51$, 95% CI 1.04-2.17). Sub-optimal adherence was associated with a significantly higher risk of breast cancer mortality ($HR=1.77$, 95% CI, 1.05-2.99) and recurrence ($HR=2.14$, 95% CI, 1.46-3.14).

Conclusions:

Sub-optimal adherence to adjuvant endocrine therapy appeared to be a likely contributor for breast cancer mortality inequity between Māori and European women. Urgent research is needed to identify effective ways to increase adherence to endocrine therapy, especially for Māori women.

Background:

Adjuvant endocrine therapy forms an integral part in breast cancer treatment and has shown to reduce mortality from hormone receptor positive breast cancer by about 30% (49, 342). Traditionally, endocrine therapy [tamoxifen or an aromatase inhibitor (AI) as single agent or in sequence] was prescribed for 5 years, although recent studies have shown additional improvement of breast cancer specific survival by continuing tamoxifen beyond 5 years (51). Despite proven benefits, many women either do not take their medication daily as prescribed (i.e. low adherence) or do not complete the full duration of treatment (i.e. discontinuation) for the minimum of 5 years (343, 344). Based on previous studies, up to 22% of women discontinue endocrine therapy before the end of first year of therapy and only about 50% complete the full 5-years, while maintaining an optimum level of adherence (217, 345, 346). These studies have also shown higher risks of breast cancer recurrence and mortality in women who are sub-optimally adherent or who discontinue their treatment (344, 347).

This study was conducted to estimate the degree of adherence to adjuvant endocrine therapy and to investigate ethnic, socio-demographic, tumour and treatment related factors associated with poor adherence among women with hormone receptor positive breast cancer in New Zealand. We also investigated the association between sub-optimal adherence and breast cancer outcomes to determine the impact of adherence on ethnic inequities in breast cancer outcomes.

Methods:***Study population:***

All women newly diagnosed with invasive breast cancer from 01/01/2005 to 31/12/2011 were identified from the WBCR (n=1558). Of this, 1207 women with hormone receptor positive, non-metastatic (stage I to III), first primary breast cancer, who received adjuvant endocrine therapy were identified from the national pharmaceutical database. All women with at least one prescription for endocrine therapy after the date of primary surgery were deemed to have started endocrine therapy. Of this group, a further 57 women who were started on endocrine therapy not as adjuvant treatment, but as treatment following development of local or metastatic recurrence, or first endocrine therapy prescription issued later than a year after the

date of diagnosis were excluded. The remaining 1149 women were analysed for treatment adherence and outcomes.

Study covariates:

Follow-up duration was calculated from the first dispensing date of adjuvant endocrine treatment to date of death or to date of last follow up when the patient was known to be alive (censored on 31/12/2013).

Treatment adherence:

Prescription records for tamoxifen and AIs (i.e. anastrozole, letrozole and exemestane) for each eligible woman for the period from 01/01/2005 to 31/12/2013 were obtained from the National Pharmaceutical database. Prescription records were linked through the National Health Index number, which is a unique identifier that is used to identify individuals within the New Zealand health system. Dispensing date, drug type and number of days covered by each prescription were recorded. An adherence index / medication possession ratio (MPR) for each woman was calculated by dividing the number of days covered by prescriptions, by the total number of days for the follow up period, until death, or up to 5 years. Any gaps in treatment for more than 180 days were considered as discontinuation of therapy (347) and were censored at the last date covered by final prescription prior to discontinuation. An adherence index (MPR) of $\geq 80\%$ was considered as a high/optimal level of adherence, which is a figure widely used in previous literature (217, 347). Adherence indices were calculated separately for each year of follow up and for the total follow up, to a maximum of 5 years.

Statistical analysis:

Chi squared (χ^2) tests for trend was used to test for univariate differences in distribution of treatment adherence and outcomes among groups of interest. Factors associated with adherence were explored in a multivariable logistic regression model. Multivariable Cox proportional hazard models were used to calculate hazard ratios with 95% confidence intervals to identify the association of adherence with breast cancer specific mortality, all-cause mortality and cancer recurrence. Kaplan-Meier survival curves were used to calculate 5-year crude breast cancer specific and disease free survival rates associated with high and sub-optimal adherence.

Results:

Median age of the cohort (n=1149) was 60 years (range 24-99). Median ages of NZ European and Māori were 62 (range 24-99) and 57 (range 28-89) years, respectively. Median follow-up duration was 51 months (inter-quartile range 32.1-73.0) months. There were a total of 131 (11.4%) cancer recurrences and 164 (14.3%) deaths, out of which 77 (47%) were due to breast cancer. Overall, 51% of women were followed up for at least 5 years or until death.

A total of 509 (42.2%) women were started on tamoxifen and 698 (57.8%) were started on an AI. Tamoxifen was the only endocrine therapy received by 269 (23.4%), while 521(45.3%) women received AIs alone. Sequential therapy with tamoxifen and AIs was received by 359 (31.2%) women.

Overall, a high level of adherence (MPR $\geq 80\%$) was observed in 809 (70.4%) of women over the total duration of therapy. Highest adherence was seen during the first year of therapy where 76.8% maintained a high level of adherence. This figure gradually declined to 73.5%, 71.4%, 66.3% and 59.3% over the second to fifth years of treatment, respectively. Māori women were observed to have a significantly lower adherence compared with NZ European women, overall (62.1% vs. 72.5%, p=0.004) and over each year of treatment (Figure 27). Rates of sub-optimal adherence were significantly higher (p<0.05) for Māori and Pacific women compared with NZ European women, in both univariate and multivariable models.

Figure 27: Annual rates of high level of adherence (MPR $\geq 80\%$) with adjuvant endocrine therapy for hormone receptor positive invasive breast cancer for NZ European and Māori women

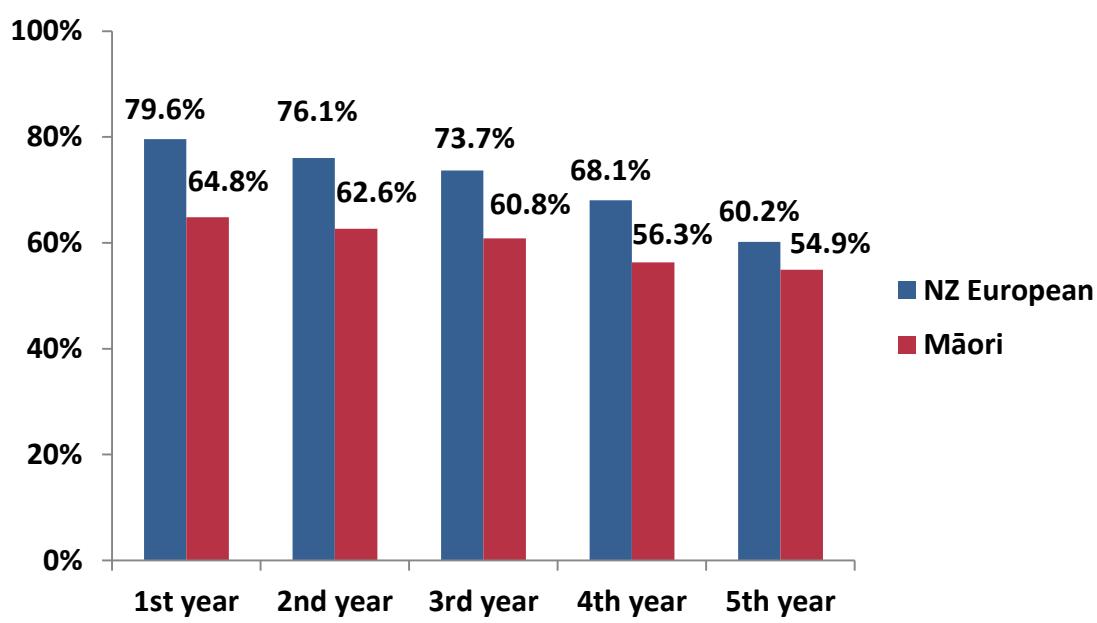


Table 33: Factors associated with adherence to adjuvant endocrine therapy for hormone receptor positive invasive breast cancer unadjusted and adjusted multivariable models

	Adherence		Unadjusted		Adjusted			
	$\geq 80\%$	<80%	OR	95% C.I.	p	OR	95% C.I.	p
n (%)	n (%)							
Ethnicity								
NZ European	665 (82.2)	252 (74.1)	1.00			1.00		
Māori	113 (14.0)	69 (20.3)	1.61	1.16-2.25	0.005	1.51	1.04-2.17	0.028
Other	21 (2.6)	5 (1.5)	0.63	0.23-1.68	0.356	0.55	0.20-1.54	0.256
Pacific	10 (1.2)	14 (4.1)	3.69	1.62-8.42	0.002	3.16	1.29-7.75	0.012
Age group (years)								
<40	23 (2.8)	30 (8.8)	2.17	1.18-4.01		2.22	1.16-4.27	
40-49	130 (16.1)	78 (22.9)	1.00		<0.001	1.00		0.015
50-59	203 (25.1)	95 (27.9)	0.78	0.54-1.13		0.85	0.51-1.40	
60-69	232 (28.7)	79 (23.2)	0.57	0.39-0.83		0.62	0.33-1.15	
70-79	121 (15.0)	34 (10.0)	0.47	0.29-0.75		0.52	0.26-1.06	
80+	100 (12.4)	24 (7.1)	0.40	0.24-0.68		0.37	0.17-0.83	
Deprivation decile								
Dep 1-2	99 (12.2)	34 (10.0)	1.00		0.422	1.00		0.814
Dep 3-4	81 (10.0)	31 (9.1)	1.11	0.63-1.97		0.88	0.48-1.62	
Dep 5-6	191 (23.6)	84 (24.7)	1.28	0.80-2.04		1.13	0.69-1.85	
Dep 7-8	249 (30.8)	96 (28.2)	1.12	0.71-1.77		1.02	0.62-1.67	
Dep 9-10	189 (23.4)	95 (27.9)	1.46	0.92-2.32		1.18	0.71-1.94	
Residence profile								
Urban	425 (52.5)	167 (49.1)	1.00		0.559	1.00		0.655
Semi-urban	318 (39.3)	142 (41.8)	1.14	0.87-1.48		1.15	0.86-1.54	
Rural	66 (8.2)	31 (9.1)	1.20	0.75-1.90		1.05	0.63-1.73	
Charlson score								
0	682 (84.3)	294 (86.5)	1.00		0.107	1.00		0.171
1-2	116 (14.3)	37 (10.9)	0.74	0.50-1.10		0.90	0.58-1.39	
3+	11 (1.4)	9 (2.6)	1.90	0.78-4.63		2.49	0.90-6.87	
Tumour stage								
T1	444 (54.9)	187 (55.0)	1.00		0.342	1.00		0.198
T2	303 (37.5)	116 (34.1)	0.91	0.69-1.20		1.02	0.73-1.42	

	T3	31 (3.8)	18 (5.3)	1.38	0.75-2.53	1.76	0.90-3.43
	T4	28 (3.5)	19 (5.6)	1.61	0.88-2.96	2.02	0.98-4.15
	Unknown	3 (0.4)	0				
Lymph node stage							
	N0	478 (59.1)	203 (59.7)	1.00		0.597	1.00
	N1	227 (28.1)	85 (25.0)	0.88	0.65-1.19	0.85	0.60-1.19
	N2	100 (12.4)	50 (14.7)	1.18	0.81-1.72	1.00	0.62-1.61
	Unknown	4 (0.5)	2 (0.6)				
Grade							
	I	205 (25.3)	110 (32.4)	1.00		0.082	1.00
	II	441 (54.5)	175 (51.5)	0.74	0.55-0.99	0.71	0.52-0.98
	III	134 (16.6)	46 (13.5)	0.64	0.43-0.96	0.55	0.34-0.89
	Unknown	29 (3.6)	9 (2.6)				
Therapeutic Surgery							
	No	36 (4.4)	14 (4.1)	1.00		0.801	1.00
	Yes	773 (95.6)	326 (95.9)	1.08	0.58-2.04	0.73	0.28-1.91
Chemotherapy							
	No	569 (70.3)	228 (67.1)	1.00		0.272	1.00
	Yes	240 (29.7)	112 (32.9)	1.16	0.89-1.53	0.81	0.53-1.23
Radiotherapy							
	No	246 (30.4)	95 (27.9)	1.00		0.404	1.00
	Yes	563 (69.6)	245 (72.1)	1.13	0.85-1.49	0.97	0.70-1.35

A significant trend ($p<0.001$) was observed between age and sub-optimal adherence with the lowest rate observed in women over the age of 80 years ($OR=0.37$, 95% CI 0.17-0.83) and the highest rate in women younger than 40 years ($OR=2.22$, 95% CI 1.16-4.27) (Table 33). There was a trend for higher rates of suboptimal adherence among women of higher deprivation categories, especially in the unadjusted model, which however was not statistically significant. Thirty-four (10%) and 43 (5.3%) breast cancer deaths were observed among women with sub-optimal ($n=340$) and high adherence ($n=809$), respectively. In both unadjusted and adjusted Cox regression models, sub-optimal adherence was associated with a significantly higher risk of breast cancer mortality ($HR=1.62$ and 1.77 , respectively) and breast cancer recurrence ($HR=1.90$ and 2.14 , respectively) (Table 34 & Table 35). Adjusting only for adherence

reduced the hazard ratio for breast cancer mortality for Māori from 1.44 (95% CI 0.82-2.55) to 1.36 (95% CI 0.77-2.42). Hazard ratios for overall mortality were also higher among sub-optimally adherent women (unadjusted HR=1.02, 95% CI 0.74-1.41, p=0.968, adjusted HR=1.17, 95% CI 0.81-1.69, p=0.401), although these were statistically non-significant.

Table 34: Adherence to adjuvant endocrine therapy and breast cancer mortality unadjusted and adjusted for age, comorbidity, deprivation, tumour factors (size, lymph node status, grade) and other treatment modalities (surgery, radiotherapy and chemotherapy)

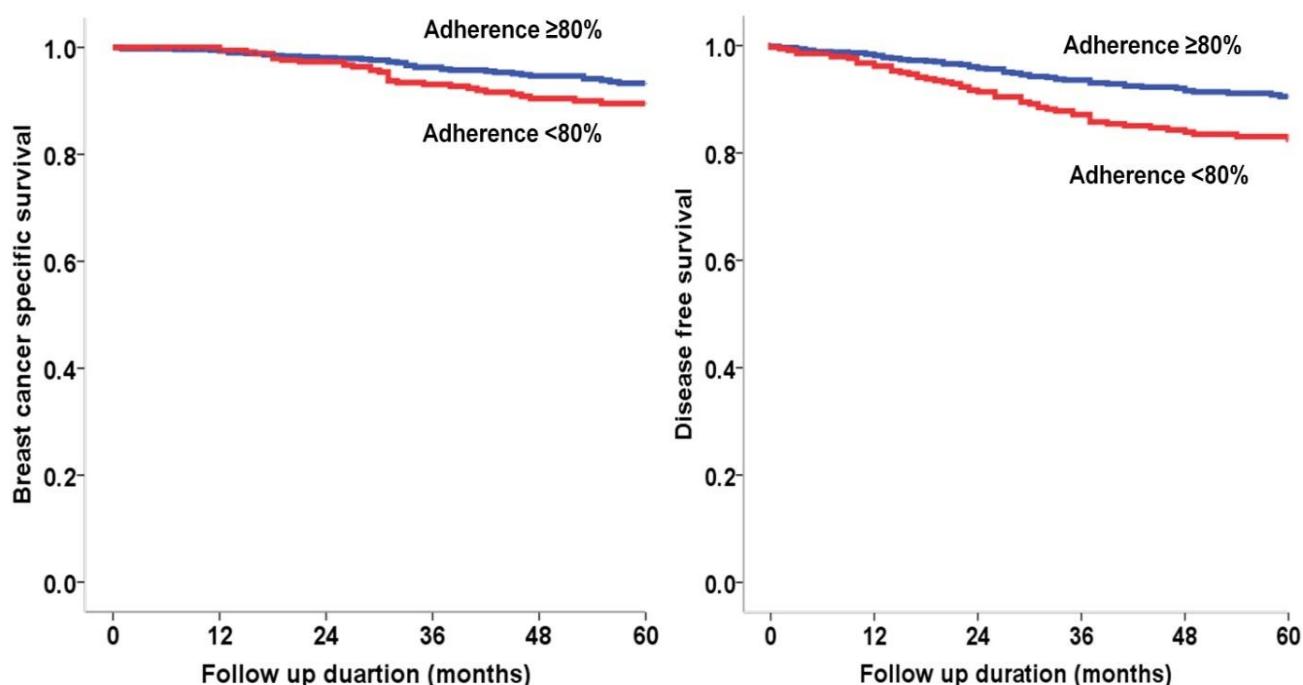
	Unadjusted			Adjusted		
	HR	95% C.I.	p	HR	95% C.I.	p
Adherence						
≥80%	1.00		0.036	1.00		0.033
<80%	1.62	1.03-2.54		1.77	1.05-2.99	
Ethnicity						
NZ European	1.00			1.00		
Māori	1.44	0.82-2.55	0.207	1.25	0.65-2.38	0.506
Other	0.66	0.09-4.79	0.684	0.60	0.08-4.53	0.620
Pacific	1.29	0.32-5.29	0.721	0.48	0.11-2.20	0.347

Table 35: Adherence to adjuvant endocrine therapy and breast cancer recurrence unadjusted and adjusted for age, comorbidity, deprivation, tumour factors (size, lymph node status, grade) and other treatment modalities (surgery, radiotherapy and chemotherapy)

	Unadjusted			Adjusted		
	HR	95% C.I.	p	HR	95% C.I.	p
Adherence						
≥80%	1.00		<0.001	1.00		<0.001
<80%	1.90	1.34-2.68		2.14	1.46-3.14	
Ethnicity						
NZ European	1.00			1.00		
Māori	1.27	0.80-1.99	0.309	0.99	0.61-1.63	0.979
Other	0.79	0.19-3.19	0.738	0.86	0.20-3.61	0.835
Pacific	1.15	0.36-3.61	0.817	0.42	0.12-1.40	0.158

Figure 28 shows Kaplan-Meier survival curves demonstrating crude 5-year breast cancer specific survival rates of 93.3% and 89.5% for women with high and sub-optimal adherence, respectively ($p=0.032$). Five year disease free survival rates were 86.8% for high and 77.2% for sub-optimally adherent women ($p=0.001$).

Figure 28: Kaplan-Meier survival curves for 5-year breast cancer specific and disease free survival by adherence to adjuvant endocrine therapy in Waikato, New Zealand 2005-2011



Discussion:

From this population-based cohort study we report that Indigenous Māori and Pacific women do have significantly higher rates of sub-optimal adherence to adjuvant endocrine therapy compared with NZ European women. This is important especially in light of our finding that risk of death and recurrence from breast cancer were significantly higher among women with sub-optimal adherence. This suggests that sub-optimal adherence to endocrine therapy may be a contributing factor to breast cancer mortality inequity between Māori and NZ European women, although this study was not able to prove it due to limitation of numbers. To our knowledge this is the first New Zealand study to investigate the impact of sub-optimal adherence to adjuvant endocrine therapy as a contributor for ethnic inequities in breast cancer survival.

Overall, the rate of optimum level of adherence to endocrine therapy seen in our study was comparable to other retrospective registry based studies (217, 220, 344), although much higher adherence rates are observed in endocrine therapy clinical trials (348). The rate of sub-optimal adherence was significantly higher among Māori women and included more than one third of Māori women. Even after adjusting for covariates, the odds of sub-optimal adherence for Māori women was more than 50% higher compared to NZ European women. Failure of these adjustments to adequately explain the observed lower adherence among Māori is most likely due to the impact of confounders such as barriers to accessing healthcare and health literacy (97), which were unmeasured in the present study.

Majority of women on endocrine therapy depend on general practitioners for follow up and regular endocrine therapy prescriptions, in between annual follow ups provided by specialist breast care clinics. Māori are known to experience more barriers and hence less access to primary health care providers compared with NZ European patients (97). This is an important issue since barriers that interfere with primary care may prevent general practitioner visits, which impact on continuation of endocrine therapy. In addition, although endocrine medications are fully funded by the government, women are required to pay a consultation or prescription fee of NZ \$15 to 50 which comes on top of travel costs, time off work and cost of care for dependents (349). Although was not statistically significant, higher rates of suboptimal adherence were seen among women of higher deprivation groups, and this further supports the association between cost affordability and adherence. Māori are more likely to be socioeconomically deprived and live in rural areas with less access to transport compared with NZ Europeans (34). As a result, Māori women are more likely to skip general practitioner visits which are a likely major contributor for sub-optimal adherence to endocrine therapy (350).

Good communication, regular advice and a good physician-patient relationship improve patient understanding and help maintain an optimum adherence with many medications including endocrine therapy (351). A good health literacy enables a patient to process and understand health information and promote better health decision making (103). Three out of four Māori females have poor health literacy skills, which is approximately 50% higher than NZ European women (106). Improving health literacy among women with breast cancer has the potential to improve adherence to endocrine therapy as well as to increase uptake and adherence with other adjuvant therapies, including chemotherapy and radiotherapy (352). Whilst low health literacy is a greater issue for Māori women and hence Māori are more likely

to benefit from any initiative aimed at improving health literacy, substantial proportions of women of other ethnicities may also benefit due to the widespread nature of both low adherence and low health literacy.

A limitation of our study design was the assumption that all prescribed medications were actually consumed by the patient. Despite that, this design has been shown to provide better estimates of adherence compared to other designs such as patient surveys or direct patient observation and has been validated by several previous studies (217, 220, 344). Although we managed to identify several associated factors for lower adherence, we were unable to identify specific underlying causes for lower adherence, as reasons for sub-optimal adherence were not available from our database. Moreover, the relatively short follow up of our study may have underestimated the actual survival benefit of good adherence, as the benefits of endocrine therapy are known to extend well beyond 10 years (49).

In conclusion, this study demonstrates that poor adherence to endocrine therapy is a significant factor for higher breast cancer mortality and recurrence, and may be a contributing factor towards breast cancer mortality inequity between Indigenous Māori and European women in New Zealand. Improving patient understanding of benefits of adjuvant endocrine therapy through better health literacy together with removal of existing barriers to access health care, especially for Māori women, need to be considered as possible avenues to improve adherence. These measures have the potential to improve adherence to care, not only for Indigenous Māori, but for all women with breast cancer in New Zealand.

5.9. Are there ethnic differences in the quality of surgical care provided for breast cancer?

Preface:

This chapter contains an abbreviated version of a manuscript Published in *ANZ Journal of Surgery*

- **Authors:** Seneviratne S, Scott N, Lawrenson R, Campbell I.
- **Title:** Ethnic differences in surgical treatment of breast cancer in New Zealand
- **Journal:** *ANZ Journal of Surgery*
- **Impact factor:** 1.12
- **Year of publication:** 2015
- **DOI:** 10.1111/ans.13011
- **Journal's aims and scope:** *ANZ Journal of Surgery*, established more than 70 years, is the leading surgical journal published in Australia, New Zealand and the South-East Asian region. The Journal is dedicated to the promotion of outstanding surgical practice and research of contemporary and international interest. *ANZ Journal of Surgery* publishes high-quality papers related to clinical practice and/or research in all fields of surgery and its related disciplines.

Abstract:

Background:

Indigenous Māori are known to experience inferior quality cancer care compared with non-Indigenous Europeans in New Zealand. However, limited data are available on ethnic/socioeconomic differences in surgical treatment of breast cancer, or reasons for such variations within the local context. We investigated ethnic/socioeconomic differences in rates of mastectomy, sentinel node biopsy (SNB), post-mastectomy breast reconstruction and definitive local therapy for breast cancer in New Zealand.

Methods:

A retrospective review of prospective data in the Waikato Breast Cancer Register for women diagnosed during 1999-2012 was performed. Differences in rates of mastectomy (for stage I/II, T1/T2 cancers), SNB (for stage I/II, T1/T2, cN0 cancers), post-mastectomy breast reconstruction (for non-metastatic cancers in women <70 years) and definitive local therapy (for stage I/II cancers) were analysed in univariate and multivariate regression models, adjusting for covariates.

Results:

Significantly lower mastectomy and higher reconstruction rates were associated with younger age, private compared with public hospital care and screen compared with non-screen detection. Compared with NZ Europeans, Māori (41% vs. 33%, p=0.025) were significantly more likely to undergo mastectomy for cancers which were potentially amenable for breast conserving surgery, but were significantly less likely to undergo post-mastectomy breast reconstruction (12% vs. 35%, p<0.001). No significant ethnic or socioeconomic differences were observed in rates of SNB or definitive local therapy.

Conclusions:

This study has demonstrated lower rates of breast conserving surgery and reconstructions in Māori compared with NZ European women, and highlight the need for future research to focus on understanding the reasons behind these findings.

Background:

In 1990, a Consensus Statement from the US National Institute of Health recommended that either breast conserving surgery (BCS) followed by whole breast irradiation or total mastectomy as local therapies of equal oncological efficacy for early stage breast cancer (353). The efficacy and safety of sentinel lymph node biopsy (SNB) based management for clinically node negative early breast cancer have been well established for more than a decade, and were absolutely confirmed with the publication of the large NSABP randomised trial in 2010 (354). SNB has been formally recommended in Australia and New Zealand for women with unifocal breast cancers less than 3cm in size since 2008 (355) and has gained wide acceptance as the standard of care for those women (356). A majority of breast cancers nowadays are diagnosed in early stage, and hence, are suitable for BCS and/or SNB based management, resulting not only in better cosmetic outcomes, but also in lower physical and psychological morbidity for a majority of women (357, 358). Even for the minority of women requiring mastectomy due to oncological reasons, advances and wider availability of cosmetic and reconstructive surgery have seen a steady increase in rates of post-mastectomy breast reconstructions (359).

Many non-tumour related factors including age, comorbidity, patient/surgeon preference, and availability and access to healthcare services have been shown to influence the decision on type of surgical treatment for breast cancer (360-363). Many of these factors also contribute to ethnic, socioeconomic and geographic variations in quality and type of surgical care, which are well documented from many countries (361, 364-366). These variations include lower rates of BCS, SNB, post-mastectomy breast reconstruction and definitive local therapy among women of minority/Indigenous ethnicity, lower socioeconomic status and rural residency (364-366).

At present limited data are available on quality or types of surgical treatment received by women with breast cancer in New Zealand (197) or possible ethnic differences in such treatment. We investigated differences in rates of BCS, SNB, post-mastectomy breast reconstruction and definitive local therapy for breast cancer by ethnicity among a cohort of women with invasive breast cancer in New Zealand. We also investigated tumour and socio-demographic factors associated with these differences, and time trends in disparities in surgical care between Māori and NZ European women.

Methods:

Study population:

All women with newly diagnosed primary invasive breast cancer between 1999 and 2012 were identified (N=2848) from the WBCR.

Eligibility criteria:

Different inclusion criteria were used to identify women eligible for separate analyses.

1. Breast conserving surgery (BCS) versus mastectomy - all women with early stage (stages I & II), T1 or T2 tumours undergoing a primary surgical intervention for breast cancer (n=2140).
2. SNB versus non-SNB based management of the axilla - women with early stage (stage I and II) T1 or T2 tumours with clinically node negative axillae (cN0), undergoing an axillary surgical intervention (n=1910).
3. Post-mastectomy breast reconstruction (immediate or delayed) versus no reconstruction - all women younger than 70 years with non-metastatic invasive breast cancer undergoing mastectomy (primary or following failed BCS) as surgical intervention for the ipsilateral breast (n=888).
4. Completed definitive local therapy (i.e. BCS with radiotherapy or mastectomy with or without radiotherapy) versus non-completed definitive local therapy - all women with stage I & II breast cancer (n=2245).

Outcome variables:

Women undergoing simple/total mastectomy, radical/modified radical mastectomy and skin/nipple sparing mastectomy were considered to have received a mastectomy. Any operation that was less than a mastectomy (i.e. excision biopsy, lumpectomy, wide local excision, partial mastectomy, sector resection or quadrantectomy) was considered as a BCS. SNB based management of the axilla was defined as all instances where a radio-isotope or a blue dye or both were used to identify first axillary lymph node/s draining the ipsilateral breast or the tumour/s. All other situations where the axilla was treated surgically (i.e. primary axillary lymph node dissection or axillary node sampling) were considered as non-SNB based management. Any woman undergoing immediate or delayed reconstruction of the ipsilateral breast after a total mastectomy using autologous tissue, implants or both, was considered to

have undergone a breast reconstruction. Definitive local therapy was defined as undergoing either BCS followed by whole breast radiation or any form of mastectomy as defined above.

Statistical analysis:

Chi squared (χ^2) tests for trend were used to test for univariate differences, and multivariable logistic regression models were used to test for multivariate differences in distribution of factors associated with BCS versus mastectomy, SNB versus non-SNB based management of the axilla, post-mastectomy breast reconstruction versus non-reconstruction and completed versus incomplete definitive local therapy. As some of the variables included of missing data, analyses were repeated using only cases with complete data for all variables. The results were almost identical to the full dataset, and are not presented in this report. Imputation of missing values was not undertaken due to the similarity of these results.

Results:

Breast Conserving Surgery (BCS) versus Mastectomy:

Of a total of 2140 women with early stage T1 and T2 tumours undergoing a primary surgical treatment for the ipsilateral breast, 751 (35.1%) underwent primary mastectomy and 1389 (64.9%) underwent primary BCS. Māori compared with NZ European ethnicity (OR=1.45, 95% CI 1.07-1.95), a distance of >50km from surgical treatment facility (OR=1.48, 95% CI 1.13-1.93), age above 70 years (OR=1.66, 95% CI 1.19-2.34), non-screen detection (OR=1.79, 95 % CI 1.42-2.28), T2 primary tumour (OR=2.30, 95% CI 1.86-2.84), lobular histology (OR=1.64, 95% CI 1.19-2.28), multi-focality (OR=2.75, 95% CI 2.11-3.58), treatment in a public hospital (OR=1.26, 95% CI 1.01-1.60) and a comorbidity score ≥ 1 (OR=1.48, 95% CI 1.12-1.93) were significantly associated with mastectomy rather than BCS as primary surgical treatment in the multivariable logistic regression model (Table 1). Peak rate of primary mastectomy (40.7%) was observed during 2003-2006, which since has declined gradually to just under 30% during 2010-2012. As Māori women had a higher proportion of T2 cancers compared with NZ European women (42.9% vs. 35.1%), rates of mastectomy were analysed separately for T1 and T2 cancers between these two groups. Higher rates of mastectomy were observed in Māori women for both T1 (31.7% vs. 25.2%) and T2 (55.3% vs. 49.7%) tumours.

Table 36: Characteristics associated with mastectomy versus breast conserving surgery for women with T1 & T2 breast cancers undergoing surgery in the Waikato 1999-2012

Characteristic	Total (N=2140) n (%)	Mastectomy (%)	Unadjusted			Adjusted		
			OR	95% CI	p	OR	95% CI	p
Ethnicity								
NZ European	1774 (82.9)	599 (33.8)	Ref			Ref		
Māori	287 (13.4)	120 (41.8)	1.41	1.09-1.82	0.008	1.45	1.07-1.95	0.015
Pacific	30 (1.4)	12 (40.0)	1.31	0.63-2.73	0.476	1.19	0.54-2.64	0.660
Other	49 (2.3)	20 (40.8)	1.35	0.76-2.41	0.306	1.67	0.88-3.15	0.115
Age (yrs.)								
<40	85 (4.0)	40 (47.1)	1.64	1.02-2.63		1.50	0.91-2.48	
40-59	996 (46.6)	322 (32.3)	Ref		<0.001	Ref		<0.001
60-79	897 (41.9)	303 (33.8)	0.98	0.78-1.14		1.03	0.81-1.32	
80+	162 (7.6)	86 (53.1)	2.09	1.44-3.02		1.72	1.14-2.67	
Deprivation								
Dep 1-2	226 (10.6)	81 (35.8)	Ref		0.733	Ref		0.811
Dep 3-4	232 (10.8)	73 (31.5)	0.82	0.56-1.21		0.80	0.52-1.22	
Dep 5-6	544 (25.4)	187 (34.4)	0.94	0.68-1.30		0.83	0.58-1.19	
Dep 7-8	608 (28.4)	217 (35.7)	0.99	0.72-1.37		0.86	0.59-1.26	
Dep 9-10	530 (24.8)	193 (36.4)	1.03	0.74-1.42		0.80	0.54-1.18	
Distance								
<10km	661 (30.9)	214 (32.4)	Ref		0.163	Ref		0.045
10-50km	843 (39.4)	294 (34.9)	1.12	0.90-1.39		1.14	0.86-1.55	
>50km	636 (29.7)	210 (39.8)	1.31	1.04-1.67		1.48	1.13-1.93	
Screening status								
Screen	935 (43.7)	213 (22.8)	Ref		<0.001	Ref		<0.001
Non-screen	1205 (56.3)	538 (44.6)	2.73	2.26-3.31		1.79	1.42-2.28	
Hospital type								
Private	672 (31.4)	221 (32.9)	Ref		0.148	Ref		0.048
Public	1468 (68.6)	530 (36.1)	1.15	0.95-1.40		1.26	1.01-1.60	

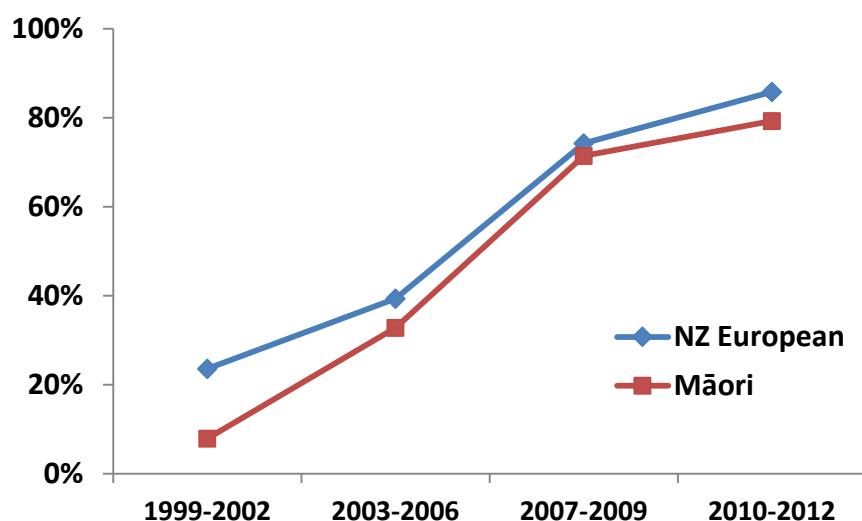
Diagnosis year						
1999-2002	473 (22.1)	165 (34.9)	Ref	<0.001	Ref	<0.001
2003-2006	649 (30.3)	264 (40.7)	1.28	1.00-1.64	1.54	1.14-2.06
2007-2009	485 (22.7)	168 (34.6)	0.99	0.76-1.29	1.07	0.75-1.52
2010-2012	533 (24.9)	154 (28.9)	0.76	0.58-0.99	0.79	0.56-1.13
Grade						
Grade I	584 (27.3)	157 (26.9)	Ref	<0.001	Ref	0.831
Grade II	1100 (51.4)	407 (37.0)	1.60	1.28-1.99	1.11	0.86-1.43
Grade III	419 (19.6)	174 (41.5)	1.93	1.48-2.52	1.15	0.82-1.61
Unknown	37 (1.7)	13 (35.1)				
ER/PR status						
ER/PR +	1817 (84.9)	617 (34.0)	Ref	0.012	Ref	0.089
ER & PR -	302 (14.1)	125 (41.4)	1.37	1.07-1.76	1.31	0.94-1.78
Unknown	21 (1.0)	9 (42.9)				
HER-2 status						
Negative	1171 (54.7)	382 (50.9)	Ref	0.004		0.136
Equivocal	135 (6.3)	54 (7.2)	1.38	0.96-1.98	1.25	0.82-1.95
Positive	244 (11.4)	108 (14.4)	1.64	1.24-2.17	1.41	1.03-1.91
Unknown	590 (27.6)	207 (27.6)				
Histology type						
Ductal	1772 (82.8)	603 (34.0)	Ref		Ref	0.005
Lobular	216 (10.1)	102 (47.2)	1.73	1.30-2.31	0.000	1.64
Other	152 (7.1)	46 (30.3)	0.84	0.59-1.21	0.346	0.82
Multi-focality						
No	1813 (84.7)	580 (32.0)	Ref	<0.001	Ref	<0.001
Yes	327 (15.3)	171 (52.3)	2.33	1.84-2.96	2.75	2.11-3.58
T stage						
T1	1356 (63.3)	353 (26.0)	Ref	<0.001	Ref	<0.001
T2	784 (36.7)	398 (50.8)	2.93	2.43-3.53	2.30	1.86-2.84
Charlson score						
0	1790 (83.6)	591 (33.0)	Ref	<0.001	Ref	0.015
≥1	350 (16.3)	160 (45.7)	1.65	1.29-2.09	1.48	1.12-1.93

Of women who underwent primary mastectomy (n=751), details of decision process for mastectomy (surgeon recommendation versus patient preference) was documented for 600 (79.9%) women. Of these, 139 (23.2%) mastectomies were due to patient preference. Compared with NZ European women (21.5%), a higher proportion of mastectomies in Māori (24.7%) was due to patient preference, although this difference was statistically not significant ($p=0.560$). No significant differences in tumour or socio-demographic characteristics were observed between women for whom the decision was documented compared with women for whom it was not (Appendix 8).

SNB versus non-SNB based management of the axilla:

The rate of SNB for early stage T1 and T2 cancers has increased by four-fold over the study period from, 21.3% during 1999-2002 to 84.7% during 2010-2012. Overall rates of SNB between Māori and NZ European women were similar (55.1% and 55.4%, respectively, $p=0.921$) and similar increasing trends in SNB rates were observed for Māori (from 7.9% to 79.3%) and NZ European women (from 23.5% to 85.9%) over the study period (Figure 29). Multivariable regression model adjusting for socio-demographic and tumour characteristics also did not show a significant difference in rate of SNB (OR=1.16, 95% CI 0.96-1.54) between Māori and NZ European women (Appendix 9).

Figure 29: Trends in rate of sentinel lymph node biopsy for women with early stage (stage I & II), T1-2, cN0 tumours undergoing an axillary surgical intervention by ethnicity



Breast reconstruction following mastectomy

Unadjusted and adjusted rates of post-mastectomy breast reconstruction for non-metastatic breast cancer in women younger than 70 years are shown in Table 37. Overall, 263 (29.6%)

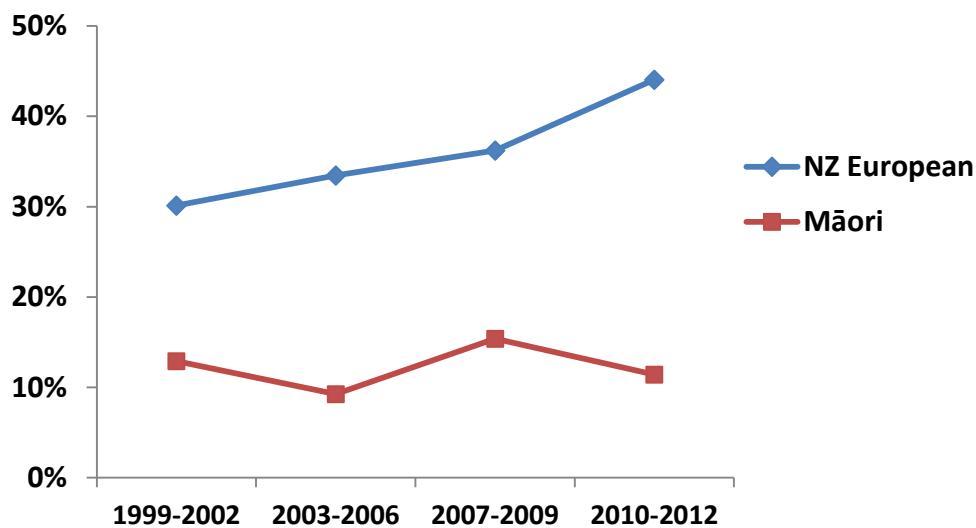
women had received a post-mastectomy reconstruction of which 237 (90.1%) were immediate and 26 (9.9%) were delayed reconstructions. Māori compared with NZ European ethnicity (OR=0.38, 95% CI 0.18-0.64), age above 50 years (OR=0.56, 95% CI 0.38-0.82), public hospital care (OR=0.56, 95% CI 0.39-0.81), primary tumour larger than T2 (OR=0.52, 95% CI 0.36-0.76) and comorbidity (OR=0.46, 95% CI 0.26-0.84) were significant predictors of not receiving a breast reconstruction, in the multivariable model. Higher body mass index (BMI) was also associated with lower reconstruction rates, but was statistically significant only for women with a BMI ≥ 35 (OR=0.37, 95% CI 0.14-0.99) in the multivariable model. The Māori cohort who underwent mastectomy tended to be younger than their NZ European counterparts (mean age 51.6 vs. 52.5 years, p=0.457) and compared with NZ Europeans, higher proportions of Māori women were observed to be obese (57.7% vs. 25.3%, p<0.001), smokers (59.6% vs. 30.4%, p<0.001), belonged to the two highest deprivation quintiles (70.3% vs. 48.4%, p<0.001) and a lower proportion (11% vs. 37.9%, p<0.001) had received surgery in the private sector. Adjusting for these factors resulted only in a marginal change in the odds of breast reconstruction for Māori women. The rate of reconstruction for Māori has not changed substantially over the study period (varying between 10 and 15%), while a 50% increase in the rate of breast reconstruction was observed for NZ European women (Figure 30).

Table 37: Characteristics associated with women undergoing major breast reconstruction following mastectomy for breast cancer in Waikato 1999-2012 ^a

Characteristic	Total (N=888)	Reconstruction (N=263)	Unadjusted			Adjusted				
			n (%)	n (%)	OR	95% CI	p	OR	95% CI	p
Ethnicity										
NZ European	659 (74.2)	233 (35.4)			Ref			Ref		
Māori	172 (19.4)	21 (12.2)	0.25	0.16-0.41	<0.001	0.38	0.18-0.64	<0.001		
Pacific	24 (2.7)	5 (20.8)	0.48	0.18-1.31	0.151	0.48	0.16-1.50	0.217		
Other	33 (3.7)	4 (12.1)	0.25	0.09-0.73	0.011	0.16	0.05-0.49	0.001		
Age (years)										
<40	82 (9.2)	42 (51.2)	1.52	0.93-2.50		1.81	1.03-3.18			
40-49	267 (30.1)	109 (40.8)	Ref		<0.001	Ref		<0.001		
50-59	299 (33.7)	93 (31.1)	0.65	0.46-0.92		0.56	0.38-0.82			
60-69	240 (27.0)	19 (7.9)	0.12	0.07-0.21		0.11	0.06-0.18			

Deprivation							
Dep 1-2	89 (10.0)	41 (46.1)	Ref	0.004	Ref		0.576
Dep 3-4	95 (10.7)	28 (29.5)	0.49	0.27-0.90	0.56	0.28-1.13	
Dep 5-6	232 (26.1)	73 (31.5)	0.54	0.33-0.89	0.68	0.38-1.22	
Dep 7-8	239 (26.9)	65 (27.2)	0.44	0.26-0.72	0.71	0.39-1.28	
Dep 9-10	233 (26.2)	56 (24.0)	0.37	0.22-0.62	0.76	0.41-1.39	
Hospital type							
Private	280 (31.5)	118 (42.1)	Ref	<0.001	Ref		0.002
Public	608 (68.5)	145 (23.8)	0.43	0.32-0.58	0.56	0.39-0.81	
Year of diagnosis							
1999-2002	196 (22.1)	53 (27.0)	Ref	0.290	Ref		0.035
2003-2006	310 (34.9)	88 (28.4)	1.07	0.72-1.60	1.06	0.67-1.67	
2007-2009	201 (22.6)	58 (28.9)	1.09	0.71-1.70	1.66	0.99-2.76	
2010-2012	181 (20.4)	64 (35.4)	1.48	0.95-2.29	1.80	1.08-2.98	
T stage							
T1	349 (39.3)	127 (36.4)	Ref	0.004	Ref		0.001
T2	416 (46.8)	109 (26.2)	0.62	0.46-0.85	0.52	0.36-0.76	
T3	75 (8.4)	18 (24.0)	0.55	0.31-0.98	0.48	0.25-0.92	
T4	47 (5.3)	9 (19.1)	0.41	0.19-0.88	0.29	0.13-0.68	
Charlson score							
0	761 (85.7)	250 (32.9)	Ref	<0.001	Ref		0.018
≥1	127 (14.3)	13 (10.2)	0.25	0.14-0.45	0.46	0.26-0.84	
BMI category							
<20	39 (4.4)	14 (35.9)	Ref	<0.001	Ref		0.058
20-30	471 (53)	165 (35.0)	0.98	0.48-1.98	1.07	0.48-2.42	
30-35	141 (15.9)	40 (28.4)	0.75	0.33-1.50	1.13	0.48-2.68	
>35	107 (12.0)	13 (12.1)	0.25	0.10-0.59	0.37	0.14-0.99	
Unknown	130 (14.6)	31 (28.3)	0.56	0.26-1.21	0.86	0.36-2.08	
Smoking status							
Never smoked	536 (60.4)	170(31.7)	Ref	0.045	Ref		0.312
Smoker	295 (33.2)	77 (26.1)	0.70	0.49-0.99	0.80	0.53-1.23	
Unknown	57 (6.4)	16 (28.1)	0.84	0.46-1.54	0.89	0.44-1.44	

^a non-metastatic breast cancer among women <70 years

Figure 30: Trends in the rates of post-mastectomy breast reconstruction by ethnicity**Definitive local therapy for early stage (stage I & II) breast cancer**

Overall, 89.5% of NZ European and 91.1% of Māori women had completed definitive local therapy ($p=0.324$) over the study period. Age older than 70 years ($OR=0.46$, 95% CI 0.26-0.82), higher tumour grade ($OR=1.56$, 95% CI 1.06-2.24) and comorbidity ($OR=0.55$, 95% CI 0.38-0.80) were significantly associated with non-completed definitive local therapy in the multivariable logistic regression model (Table 38).

Table 38: Characteristics associated with women completing definitive local therapy for early (stage I & II) breast cancer in Waikato 1999-2012

Characteristic	Total (N=2245)	Definitive local therapy completed		Unadjusted		Adjusted			
		n (%)	n (%)	OR	95% CI	p	OR	95% CI	p
Ethnicity									
NZ European	1858 (82.8)	1662 (89.5)	Ref				Ref		
Māori	305 (13.6)	278 (91.1)	1.21	0.80-1.85	0.367	0.88	0.54-1.44	0.608	
Pacific	32 (1.4)	28 (87.5)	0.83	0.29-2.38	0.722	0.76	0.19-3.12	0.708	
Other	50 (2.2)	48 (96.0)	2.83	0.68-11.7	0.152	1.23	0.29-5.33	0.778	

Ethnic differences in breast cancer outcomes in Aotearoa New Zealand

Age (yrs.)							
<40	88 (3.9)	88 (100)	-	-	-	-	-
40-49	410 (18.3)	388 (94.6)	Ref		<0.001	Ref	<0.001
50-59	603 (26.8)	569 (94.4)	0.95	0.55-1.65		1.01	0.57-1.80
60-69	583 (25.9)	540 (92.6)	0.71	0.42-1.21		0.82	0.47-1.44
70-79	343 (15.3)	299 (87.2)	0.39	0.23-0.66		0.46	0.26-0.82
80+	218 (9.7)	132 (60.6)	0.09	0.05-0.15		0.16	0.09-0.29
Deprivation							
Dep 1-2	231 (10.3)	217 (93.9)	Ref		0.114	Ref	0.172
Dep 3-4	245 (10.9)	213 (86.9)	0.43	0.22-0.83		0.39	0.18-0.86
Dep 5-6	572 (25.5)	519 (90.7)	0.63	0.34-1.16		0.57	0.27-1.18
Dep 7-8	641 (28.5)	573 (89.4)	0.54	0.30-0.99		0.57	0.28-1.17
Dep 9-10	556 (24.8)	494 (88.8)	0.51	0.28-0.94		0.47	0.22-0.97
Diagnosis year							
1999-2002	494 (22.0)	432 (87.4)	Ref		0.144	Ref	0.210
2003-2006	679 (30.2)	615 (90.6)	1.38	0.95-1.99		1.49	0.95-2.32
2007-2009	513 (22.8)	470 (91.6)	1.57	1.04-2.36		1.37	0.84-2.21
2010-2012	559 (24.9)	499 (89.3)	1.19	0.82-1.74		1.03	0.66-1.61
Grade							
Grade I	589 (26.2)	529 (89.8)	Ref		<0.001	Ref	<0.001
Grade II	1124 (50.1)	1041 (92.6)	1.42	1.01-2.02		1.54	1.06-2.24
Grade III	436 (19.4)	411 (94.3)	1.86	1.15-3.03		1.79	1.01-3.17
Unknown	96 (4.3)	35 (36.5)					
ER/PR status							
ER &/or PR +	1874 (83.5)	1686 (90.0)	Ref		0.048	Ref	0.705
ER & PR -	335 (14.9)	313 (93.4)	1.59	1.01-2.51		0.90	0.52-1.05
Unknown	36 (1.6)	17 (47.2)					
T stage							
T1	1378 (61.4)	1257 (91.2)	Ref		0.004	Ref	0.424
T2	829 (36.9)	733 (88.4)	0.79	0.59-1.06		1.08	0.76-1.53
T3	38 (1.7)	28 (73.7)	0.29	0.13-0.62		0.56	0.21-1.50
Charlson score							
0	1838 (81.9)	1707 (92.9)	Ref		Ref		<0.001
≥1	407 (18.1)	309 (75.9)	0.30	0.22-0.41		0.55	0.38-0.80

Discussion:

This study has shown that Indigenous Māori women were significantly more likely to undergo primary mastectomy for breast cancers which were potentially amenable for BCS, but were significantly less likely to receive a post-mastectomy breast reconstruction. Rates of SNB and definitive local therapy did not differ significantly between Māori and NZ European women. Overall, the rates of BCS, SNB, breast reconstruction and definitive local therapy were acceptable and comparable to rates reported from countries with similar health care systems (367, 368).

Mastectomy versus BCS:

Patients' preference for mastectomy over BCS appears to have been a major contributor, while surgeon preference may also have contributed for higher rates of mastectomy observed in Māori compared with NZ European women. Although details of mastectomy decision process was available for only 80% of women, this explanation is likely to be valid as no significant differences in tumour or socio-demographic characteristics were observed between women for whom details of decision process was available and the rest.

As expected, tumour size and multi-focality influenced mastectomy, but no significant associations were observed between tumour biological characteristics which are known to be associated with higher risks of local or systemic failure, and the rate of mastectomy. The association between aggressive tumour characteristics and higher mastectomy rate is well documented (361), and is due to the belief among some surgeons that BCS is an oncologically inferior operation to mastectomy, especially for more aggressive cancers (361). The absence of this observation indicates widespread acceptance of BCS for all early breast cancers among surgeons in the region, and adherence to treatment guidelines (44).

Several factors are known to influence a woman's decision towards mastectomy over BCS, for a cancer that is technically suitable for BCS. These include; the belief that mastectomy is "safer", to avoid radiotherapy due to fear of its long term complications or due to difficulties in accessing radiotherapy services (such as living some distance from a treatment centre) and to avoid potential re-operations (360, 369-372). Women of low socioeconomic backgrounds and rural women have been documented to have significantly higher rates of mastectomy compared with socioeconomically affluent and urban women, respectively as they are more likely to experience difficulties in accessing radiotherapy services (80, 361, 373). Consistent with this, a significantly higher mastectomy rate was observed among rural compared with

urban dwelling women. However, no similar association was observed between socioeconomic deprivation and rates of mastectomy. Lack of this association in the present study might have been influenced at least to some extent, by the use of an area based deprivation system to measure socioeconomic status. A significantly lower rate of mastectomy among women treated in private versus public hospitals was also observed. This, though indirectly, supports the association between higher mastectomy rates with lower socioeconomic status.

Post-mastectomy breast reconstruction:

A significantly higher rate of breast reconstruction was observed among NZ European women compared with Māori women. However, whether this difference was contributed by patient or surgeon decision process could not be evaluated as this information was not available from the WBCR database. Regardless, we observed several factors which appear to have contributed to this disparity including higher socioeconomic deprivation, obesity, smoking and lower likelihood of private sector treatment in Māori compared with NZ European women. The difference in rates of reconstruction between public and private seems to have had a major impact on difference in rates of reconstruction between Māori and NZ European as only 10% of Māori received treatment in private sector compared with 38% of NZ European women. Higher socioeconomic deprivation in Māori compared with NZ European women seems to have contributed to this disparity as women of more affluent backgrounds were more likely to receive treatment from the private sector. Seeking reconstruction from the private sector might also have been influenced by lack of availability and/or longer wait lists for breast reconstruction in public sector. It is likely that at least for some women, who could not afford private sector reconstructions, these delays would have prompted to forgo reconstruction.

Lower uptakes of breast reconstruction in minority ethnic women have been documented in the USA, which were contributed by several reasons including cultural, educational and financial factors (366, 374). It is unclear whether cultural factors and possible differences in attitudes towards body image have contributed to differences in rates of BCS and reconstruction between Māori and NZ European women.

SNB and definitive local therapy:

There were no differences in rates of SNB and definitive local therapy by either ethnicity or socioeconomic deprivation. Rates of SNB have steadily increased over the study period as SNB gained recognition as standard of care for women with clinically node negative early

breast cancer. However, the safety of SNB for early breast cancers >3cm in diameter or for multifocal cancers has not been proven by randomised trial yet, and women with likely involved nodes on imaging or clinically, are not offered SNB. These are the likely reasons for the SNB rate plateauing at 80% during 2010-2012.

Overall, from this study, it appears that interventions which are associated with cancer outcomes (i.e. definitive local therapy) and morbidity (i.e. SNB) have been provided and taken up by women of diverse ethnic and socioeconomic groups at almost similar rates, while major differences were observed for interventions that improve cosmetic outcomes (i.e. BCS and reconstruction). Breast cancer surgery is no longer considered an oncological intervention aimed only at cancer cure, but also as an intervention aimed at providing best quality of life for a woman, by preserving a near normal breast or by creating a new breast through reconstruction. Therefore, it is important that all women are provided with the option of reconstruction, unless it is contraindicated due to patient or tumour factors. However this needs to be provided in a manner that is acceptable to women of different ethnic, cultural and socioeconomic backgrounds, and perhaps more importantly in a way that it would not compromise long term cancer outcomes, for instance by adding longer treatment delays.

There were a few limitations in this study. Despite the WBCR being a comprehensive database that captures all surgical treatment in detail, some of the delayed reconstructions, especially the ones performed outside the Waikato region may have been omitted. However such numbers are expected to be minimal and the undercounting resulted from this bias is unlikely to influence the final results of this study.

In conclusion, a majority of study women were observed to have received high quality surgical care for breast cancer on par with accepted guidelines. However, significant disparities in quality of surgical care for breast cancer by ethnicity and geographic location were observed with Māori and rural women receiving fewer BCS and reconstructions compared with NZ European and urban women, respectively. Many socio-demographic and healthcare services related factors likely to have contributed to these observed differences. However, exact mechanisms and their contributions towards lower rates of BCS and breast reconstructions in Māori compared with NZ European women are unclear at present. Future research focussing on understanding underlying mechanisms for these differences is needed which may help develop measures to reduce disparities.

5.10. How things add up: quantitative impact of factors on ethnic inequity

Preface:

This chapter contains an abbreviated version of a manuscript submitted for publication in *Cancer Causes and Control*

- **Authors:** Seneviratne S, Campbell I, Scott N, Shirley R, Peni T, Lawrenson R.
- **Title:** Ethnic differences in breast cancer survival in New Zealand:
Contributions of differences in screening, treatment, tumour biology,
demographics and comorbidities
- **Journal:** *Cancer Causes & Control*
- **Impact factor:** 2.96

Journal's aims and scope: *Cancer Causes & Control* is an international refereed journal that both reports and stimulates new avenues of investigation into the causes, control, and subsequent prevention of cancer. Its multidisciplinary and multinational approach draws together information published in a diverse range of journals.

Coverage of the journal extends to variation in cancer distribution within and between populations; factors associated with cancer risk; preventive and therapeutic interventions on a population scale; economic, demographic, and health-policy implications of cancer; and related methodological issues.

Abstract:

Introduction:

Underlying reasons for ethnic inequities in breast cancer outcomes are complex and poorly understood. We investigated the breast cancer survival inequity between Indigenous Māori and European women, and quantified relative contributions of patient, tumour and healthcare system factors towards this inequity.

Methods:

All women with newly diagnosed invasive breast cancer between 1999 and 2012 were identified from the WBCR. Cancer specific survival between Māori and NZ European women was compared using Kaplan-Meier survival curves while contributions of different factors towards the survival disparity were quantified with Cox proportional hazard modelling.

Results:

Of the total of 2791 women included in this study, 2260 (80.1%) were NZ European and 419 (15%) were Māori. Compared with NZ European women, Māori had a significantly higher age adjusted cancer specific mortality ($HR = 2.02$, 95% CI, 1.59-2.58) with significantly lower 5-year (86.8% vs. 76.1%, $p < 0.001$) and 10-year (79.9% vs. 66.9%, $p < 0.001$) crude cancer-specific survival rates. Stage at diagnosis explained approximately 40% while screening, treatment and patient factors (i.e. comorbidity, obesity and smoking) contributed by approximately 15% each towards the survival disparity. The final model accounted for almost all of the cancer survival disparity between Māori and NZ European women ($HR = 1.07$, 95% CI, 0.80-1.44).

Conclusions:

Māori women experience an age-adjusted risk of death from breast cancer, which is more than twice that for NZ European women. Lower screening coverage, delay in diagnosis, inferior quality of treatment and greater patient comorbidity appear to be important factors contributing to survival disparity between Māori and NZ European women.

Introduction:

Ethnic disparities in cancer survivals are well documented for a range of cancers among many different ethnic populations.

The underlying factors for ethnic disparities in cancer survival are complex, poorly understood and vary widely among different countries and populations (96, 375). Causes of inequities in cancer survival between ethnic and socioeconomic groups can be categorized broadly into healthcare system, patient, and tumour related factors. Patient level factors include access to the determinants of health such as income, healthy housing, education and a healthy environment. Inequities in access to these determinants of health cause inequities in patient level factors such as comorbidities, smoking and obesity. Only a few studies to date have reported on the impact of comorbidities, smoking and obesity on breast cancer survival disparity. Many studies on cancer survival rely on routinely collected data sets such as national cancer registries, and data on these variables are not available from routine datasets. (146). The impact of tumour biological characteristics has been studied in great detail, especially in the USA, where Black African women are known to have breast cancers with biological characteristics associated with worse outcomes (166). Healthcare system contributes to survival disparity through differences in barriers to access care (135) and once gained access, through institutional factors including discrimination, lower use and inferior quality cancer treatment provided for Indigenous/ethnic minority patients (307, 316).

This study was aimed at investigating the breast cancer survival disparity between Māori and NZ Europeans in a regional cohort of New Zealand women, and to quantify the relative contributions of patient, tumour and healthcare system factors towards the survival disparity.

Methods:***Data sources:***

Data were obtained from the WBCR and the WBCR data were linked with the National Mortality Collection, the National Breast Cancer Screening Database and the National Minimum Dataset (NMDS) using National Health Index number.

Study population:

A total of 2791 women with newly diagnosed breast cancer (2848 cancers) over a 14-year period from 01/01/1999 to 31/12/2012 were identified from the WBCR. For women with more than one episode of invasive cancer, data from the first episode were included for analysis.

Study covariates:

Breast cancer treatment

Breast cancer treatment was broadly considered under local and systemic modalities. Definitive local therapy was defined as receipt of breast conserving surgery (BCS) followed by radiation therapy or receipt of mastectomy that was performed with curative intent. BCS without radiation, palliative mastectomy or no surgical treatment was considered as incomplete definitive local therapy. Receipt of chemotherapy, radiotherapy and hormonal therapy were considered under systemic breast cancer treatment. Delays in initiating treatment beyond proven clinically significant thresholds were considered as treatment delays. These included a 60-day threshold from diagnosis to first surgical intervention (206), a 60-day threshold from first surgery to chemotherapy (207, 208) and for radiotherapy, a 90-day threshold from first surgery, where chemotherapy was not given, or from the date of completing chemotherapy, where chemotherapy was given (209).

Outcome variables:

Date and cause of death for all deceased women (censored at 31/12/2013) were identified from the WBCR and the National Mortality Collection. Follow up duration was calculated from the date of diagnosis to date of death, or to the date of the last known follow up (censored at 31/12/2013).

Statistical analysis:

Multivariable Cox proportional hazard models were used to calculate breast cancer specific mortality hazard ratios with 95% confidence intervals for Māori compared with NZ European women, stratifying into tumour stage at diagnosis (I/II and III/IV). Kaplan-Meier survival curves were created for crude breast cancer specific mortality for Māori and NZ European women. Due to small numbers, Pacific and Other ethnic group women were excluded from these analyses.

The initial base model calculated hazard ratios for breast cancer specific mortality controlling only for age and year of diagnosis. Additional variables were introduced sequentially, starting with breast cancer screening followed by cancer stage at diagnosis, biological characteristics, cancer treatment, comorbidities and healthcare access factors. We also performed a separate model with a different sequential introduction as we felt that healthcare access factors could influence stage at diagnosis, as well as cancer treatment. For the second model, healthcare access factors were introduced first, followed by other factors, in same sequence as the first model.

As some of the variables included high numbers of missing data, survival analysis was repeated using only cases with complete data for all variables. Results were almost similar to those obtained from the Kaplan-Meier and Cox proportional hazards regression models, and these data are not presented in this report. Imputation of missing values was not undertaken due to the similarity of these results.

Results

Of the 2791 women included in this study, 419 (15%) were Māori, 2260 (80.9%) were NZ European, 51 (1.8%) were Pacific and 61 (2.2%) were of Other ethnicity. A minimum follow up of five years or up to death was available for 255 (60.8%) Māori and 1527 (67.6%) NZ European women. Median follow up was 43 months for Māori women (mean 54.5 months, SD=41) and 61 months for NZ European women (mean 68.9 months, SD=45). A total of 131 (31.3%) deaths were observed for Māori and 544 (24.1%) for NZ European women of which 87 (66.4%) for Māori and 312 (57.4%) for NZ European women were due to breast cancer.

The Māori cohort was significantly younger than the NZ European cohort (Table 39), in keeping with the younger age structure of Māori population in New Zealand (31). Māori were significantly more likely to be diagnosed with more advanced breast cancer, and were around two and a half times more likely to be diagnosed with metastatic disease than NZ European women (11% vs. 4.6%). Māori women had a significantly higher prevalence of medical comorbidities (27.9% vs. 17.3%, p<0.001), obesity (52% vs. 28%, p<0.001), smoking (59% vs. 25%, p<0.001) and were significantly more likely to live in more deprived areas (p<0.001) compared with NZ European women. Māori women were significantly less likely to be diagnosed through mammographic screening (29.8% vs. 36.9%, p<0.001) and were less than a

third as likely as NZ European women to have had surgical treatment from a private facility (9.3% vs. 31.9%, p<0.001).

Māori women had generally higher graded cancers; fewer grade I and more grade II tumours, and a higher rate of HER-2 positive cancers (21.9% vs. 17.2%, p<0.001) compared with NZ European women. Māori were significantly more likely to undergo mastectomy than breast conserving surgery and were significantly less likely to complete definitive local therapy compared with NZ European women (79.8% vs. 83.5%, p=0.021). Māori women were significantly more likely to have received chemotherapy (36.8% vs. 31.6%, p=0.038), but were less likely, albeit non-significantly, to have received adjuvant endocrine therapy (67.1% vs. 71.6%, p=0.058).

Table 39: Patient, tumour treatment and healthcare access characteristics of the study cohort by Māori and NZ European ethnicity

Characteristic	Total (N=2791)		NZ European (N=2260)		Māori (N=419)		p
	n (%)		n (%)		n (%)		
Age (mean +/- SD)	60.5 +/-13.8		61.4 +/-13.9		55.6 +/-12.2		<0.001
Diagnosis year							<0.001
1999-2002	597	21.4	502	22.2	73	17.4	
2003-2006	853	30.6	727	32.2	99	23.6	
2007-2009	652	23.4	497	22.0	117	27.9	
2010-2012	689	24.7	534	23.6	130	31.0	
Stage							<0.001
I	1112	39.8	943	41.7	139	33.2	
II	1087	38.9	880	38.9	159	37.9	
III	433	15.5	332	14.7	75	17.9	
IV	159	5.7	105	4.6	46	11.0	
Deprivation							<0.001
Dep 1-2	284	10.2	261	11.5	13	2.1	
Dep 3-4	289	10.4	248	11.0	29	6.9	
Dep 5-6	678	24.3	581	25.7	73	17.4	
Dep 7-8	813	29.1	655	29.0	128	30.5	
Dep 9-10	727	26.0	515	22.8	176	40.2	

Urban rural status							0.008
Urban	1493	53.5	1215	53.8	201	48.0	
Semi-urban	786	28.2	615	27.2	145	34.6	
Rural	512	18.3	430	19.0	73	17.4	
Screening status							0.006
Screen detected	988	35.4	833	36.9	125	29.8	
No-screen detected	1803	64.6	1427	63.1	294	70.2	
Hospital type							<0.001
Private	781	28.0	722	31.9	39	9.3	
Public	2010	72.1	1538	68.0	380	90.7	
Charlson score							<0.001
0	2264	81.1	1869	82.7	302	72.1	
1-2	478	17.1	357	15.8	103	24.6	
3+	49	1.8	34	1.5	14	3.3	
Smoking							<0.001
Non smoker	1802	69.9	1558	75.0	163	40.8	
Ex-smoker	260	10.1	204	9.8	52	13.0	
Current smoker	517	20.0	315	15.2	184	46.1	
Unknown	(212)		(183)		(20)		
BMI							<0.001
<20	113	5.6	96	6.1	13	3.9	
20-25	594	29.5	501	31.6	66	19.9	
25-30	650	32.3	543	34.2	79	23.8	
>30	655	32.6	446	28.1	174	52.4	
Unknown	(780)		(674)		(87)		
Grade							0.007
Grade I	615	23.7	529	25.1	68	17.8	
Grade II	1365	52.6	1095	52.0	221	58.0	
Grade III	613	23.6	482	22.9	92	24.1	
Unknown	(198)		(154)		(38)		
ER/PR status							0.153
ER &/or PR +	2298	84.1	1873	84.8	335	81.3	
ER & PR -	434	15.9	336	15.2	77	18.7	
Unknown	(59)		(51)		(7)		

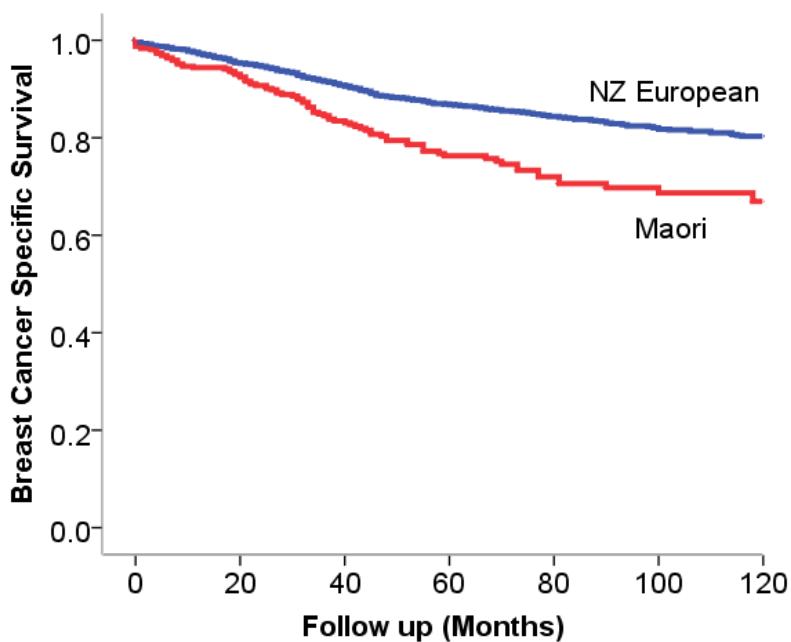
HER-2							<0.001
Negative	1517	73.6	1214	74.7	251	72.3	
Equivocal	156	7.6	131	8.1	20	5.8	
Positive	384	18.7	280	17.2	76	21.9	
Unknown	(734)		(635)		(72)		
Loco-regional treatment							<0.001
BCS + Radiotherapy	1257	45.0	1064	47.1	149	35.6	
Mastectomy	1065	38.2	830	36.7	183	43.7	
BCS without radiotherapy	228	8.2	192	8.5	30	7.2	
No primary surgery	241	8.6	174	7.7	57	13.6	
Chemotherapy							0.038
Yes	924	33.1	714	31.6	154	36.8	
No	1867	66.9	1546	68.4	265	63.2	
Endocrine therapy							0.058
Yes	1974	70.7	1619	71.6	281	67.1	
No	817	29.3	641	28.4	138	32.9	
Delay in surgery ^a							0.001
No	2220	87.1	1841	88.3	295	81.5	
Yes	330	12.9	245	11.7	67	18.5	
No surgery	(241)		(174)		(57)		
Delay in chemotherapy ^b							0.103
No	621	67.4	494	69.5	96	62.7	
Yes	301	32.6	217	30.5	57	37.3	
No chemotherapy	(1869)		(1549)		(266)		
Delay in radiotherapy ^c							0.045
No	677	68.0	592	69.4	68	60.2	
Yes	319	32.0	261	30.6	45	39.8	
No radiotherapy	(1795)		(1407)		(306)		

^a delay in surgery longer than 60 days from date of diagnosis, ^b delay in adjuvant chemotherapy longer than 60 days from date of first surgery, ^c delay in radiotherapy longer than 90 days from first surgery if no chemotherapy was given or from completion of chemotherapy if chemotherapy was given

Breast cancer survival

Māori had a significantly lower crude cancer-specific survival than NZ European women ($p<0.001$) (Figure 31). The crude five and 10-year cancer-specific survival rates were 86.8% and 79.9% respectively, for NZ European and 76.1% and 66.9% respectively, for Māori women. An improvement in 5-year survival rates were observed for both Māori and NZ European women over time, which was greater for Māori than NZ European women. For instance, 5-year survival increased from 73% to 79% for Māori from 1999-2005 to 2006-2012 while an increase from 87% to 89% was observed for NZ European women over the same time periods (Appendix 11).

Figure 31: Kaplan-Meier survival curves for breast cancer specific survival (unadjusted) for Māori and NZ European cohorts



Hazards ratios (HR) for breast cancer mortality for selected characteristics from the multivariable Cox proportional model are shown in Table 40. Non-screen detection compared with screen detection, advanced cancer stage, ER/PR negativity, higher grade, not completing definitive local therapy and higher comorbidity index were significantly associated with higher risks of breast cancer mortality.

Table 40: Breast cancer specific mortality hazard ratios for selected variables from final Cox proportional hazard model

Characteristic		HR	95% CI
Ethnicity	NZ European	Ref	
	Māori	1.07	0.80-1.44
Mode of diagnosis	Screen detected	Ref	
	Non-Screen	1.44	1.05-1.96
T stage	1	Ref	
	2	1.72	1.30-2.28
	3	3.06	2.07-4.52
	4	2.63	1.80-3.83
N stage	0	Ref	
	1	1.68	1.28-2.20
	2+	2.77	1.98-3.85
M stage	0	Ref	
	1	2.97	2.12-4.16
Grade	I	Ref	
	II	3.15	1.80-5.51
	III	6.10	3.41-10.9
ER/PR	Positive	Ref	
	Negative	1.47	1.10-2.01
HER-2	Negative	Ref	
	Equivocal	0.92	0.53-1.59
	Positive	0.98	0.74-1.29
Definitive local therapy	Yes	Ref	
	No	2.07	1.49-2.88
Chemotherapy	Yes	Ref	
	No	1.17	0.86-1.56
Endocrine therapy	Yes	Ref	
	No	1.16	0.87-1.56
Delay in surgery	Yes	Ref	
	No	1.07	0.79-1.47
Delay in adjuvant therapy	Yes	Ref	
	No	0.97	0.74-1.27

Charlson score	0	Ref	
	1-2	1.33	1.04-1.72
	3+	1.29	0.66-2.51
Smoking status	Non-smoker	Ref	
	Ex-smoker	1.25	0.90-1.75
	Current smoker	1.10	0.84-1.45
Facility type	Public	Ref	
	Private	0.87	0.67-1.13
Deprivation	Dep 1-2	Ref	
	Dep 3-4	1.69	1.02-2.80
	Dep 5-6	1.55	0.99-2.44
	Dep 7-8	1.54	0.98-2.43
	Dep 9-10	1.50	0.95-2.36
Residence	Urban	Ref	
	Semi-urban	0.87	0.68-1.11
	Rural	0.83	0.63-1.10

Hazard ratios for breast cancer-specific mortality with sequential adjustments for factors of interest are provided in Table 41. The baseline model is adjusted for age and year of diagnosis, whereas the fully adjusted model adjusts for mode of diagnosis, tumour characteristics, treatment including delays, comorbidities, and demographics. Results are presented for all stages of disease and then stratified by stage I/II and III/IV.

All stages

When all invasive cancers are considered, Māori women had a significantly higher hazard of death, which was more than double that for NZ European women at baseline (HR=2.02; 95% 95% CI, 1.59–2.58); but was explained almost fully, and was no longer significant (HR=1.07; 95% CI, 0.80-1.44) after full adjustment.

Table 41: Hazard ratios for breast cancer-specific mortality risk in Māori compared with NZ European women with stepwise adjustment for demographics, screening status, disease factors, treatment factors, patient factors and healthcare access

Characteristics	Overall	Stage I & II	Stage III & IV
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted	1.81 (1.43-2.30)	0.99 (0.62-1.58)	1.96 (1.47-2.61)
Model A (Baseline - adjusted for age and year of diagnosis)	2.02 (1.59-2.58)	1.20 (0.75-1.93)	2.09 (1.56-2.80)
Model B (Model A + Screening status)	1.86 (1.46-2.37)	1.14 (0.71-1.93)	2.00 (1.49-2.67)
Model C (Model B + Cancer stage at diagnosis [TNM])	1.48 (1.15-1.93)	1.08 (0.67-1.74)	1.67 (1.23-2.27)
Model D (Model C + Cancer biological factors)			
ER/PR, Grade & HER-2	1.40 (1.09-1.81)	1.15 (0.71-1.88)	1.49 (1.09-2.05)
Model E (Model D + Treatment)			
Completion of definitive local therapy	1.31 (1.01-1.69)	1.18 (0.72-1.92)	1.40 (1.02-1.93)
Use of systemic therapy ^a	1.26 (0.97-1.64)	1.12 (0.69-1.83)	1.35 (0.98-1.87)
Delay in surgery or adjuvant therapy ^b	1.25 (0.96-1.63)	1.13 (0.69-1.85)	1.41 (1.01-1.95)
Model F (Model E + Patient factors)			
Comorbidity index score	1.20 (0.92-1.57)	1.08 (0.66-1.78)	1.33 (0.95-1.86)
Smoking	1.16 (0.88-1.53)	1.10 (0.66-1.85)	1.24 (0.88-1.76)
BMI	1.11 (0.83-1.48)	1.12 (0.66-1.90)	1.16 (0.81-1.66)
Model G (Model F + Healthcare access factors)			
Socioeconomic deprivation	1.10 (0.83-1.47)	1.07 (0.63-1.84)	1.16 (0.81-1.67)
Urban / rural residency	1.09 (0.82-1.46)	1.08 (0.63-1.84)	1.16 (0.80-1.67)
Public / private treatment	1.07 (0.80-1.44)	1.12 (0.65-1.93)	1.11 (0.77-1.61)

^a chemotherapy and endocrine therapy, ^b delay in surgery or delay in initiating chemotherapy or radiation therapy

Differences in mode of diagnosis (screen vs. non-screen) contributed approximately 15% of the survival disparity. Cancer stage at diagnosis accounted for approximately a third of the survival disparity between Māori and NZ European women, with adjustments for tumour, lymph node and metastatic status reducing the hazard ratio from 1.86 to 1.48 (Table 40). The contribution from cancer biological characteristics was relatively small at approximately seven percent. Differences in treatment including use of definitive local therapy, systemic therapy, and delays in treatment contributed approximately 15% to the total survival disparity, with a reduction in hazard ratio from 1.40 to 1.25. Patient characteristics including medical comorbidities, smoking and BMI contributed a further 15% to the survival disparity. In this model, contributions from healthcare access factors were minimal (approximately 2-3%) after adjusting for patient, tumour and treatment factors. Factors included in this final model (Table 41) together accounted for approximately 95% of the observed survival disparity between Māori and NZ European women, and Māori women were only 7% more likely to die from their breast cancer in the fully adjusted model.

A second model was performed with a different sequence of variable introduction (Appendix 10). For this model, healthcare access characteristics were introduced first to the baseline model, followed by rest in the same sequence. In this model, healthcare access factors contributed approximately 20% to the survival disparity (reduction in hazard ratio from 2.02 to 1.80). Screen-detection explained approximately 20% (HR reduction from 1.80 to 1.60) and stage at diagnosis 25% (HR reduction from 1.60 to 1.35) of the survival disparity. No substantial differences in hazard ratio reductions were observed for patient factors (15% vs. 16%), tumour biology (7% vs. 8%) or treatment (15% vs. 14%) between the two models.

Stage specific

In the fully adjusted model for stage I/II, Māori women had a higher hazard ratio for breast cancer mortality ($HR=1.20$), which however, was substantially lower than the hazard ratio for all cancers. Adjustments for patient, tumour, treatment and healthcare access factors resulted only in a reduction of approximately 40% (HR reduction from 1.20 to 1.12), which was proportionately a much smaller reduction than for all cancers.

Compared with early stage cancers, the survival disparity for Māori compared with NZ European women for advanced staged cancers (stage III/IV) was approximately five-times higher, at a baseline hazard ratio of 2.09. Similar to the model for all stages, adjustments for

patient, tumour, treatment and access to healthcare factors resulted in approximately a 90% reduction in survival disparity with a hazard ratio decline from 2.09 to 1.11. Compared with the overall model, greater contributions were observed for tumour biology and patient factors (approximately 15% each), while smaller contributions were seen for screening and treatment (approximately 8% and 1% respectively).

Discussion:

In this population based cohort study of New Zealand women with breast cancer, Māori women were observed to have a significantly poor cancer specific survival rate, and an age adjusted risk of death from breast cancer, which was more than double that for NZ European women. More advanced stage at diagnosis appeared to be the major factor contributing to excess breast cancer mortality in Māori, while other factors including comorbidities, smoking, obesity and differences in treatment made significant contributions. Differences in cancer biological characteristics contributed minimally to the survival disparity overall and for early stage cancer, while for advanced cancer a substantial contribution was observed. Together these factors explained almost all the observed breast cancer survival disparity between Māori and NZ European women.

Most causes of inequity in breast cancer survival between Māori and NZ European women are due to health service inequities including differential access to screening, and access, timeliness and quality of breast cancer treatment. Access to screening is the likely main determinant of inequities in stage at diagnosis between Māori and NZ European women which was responsible for about 40% of the survival inequity. Despite the gradual improvement in mammographic breast cancer screening coverage over the last decade, coverage for eligible Māori women continues to be significantly lower than that of NZ European women, and the target coverage of 70% (39). In addition, women with screen detected cancers in this study appeared to have a significantly better survival even after adjusting for stage and tumour biological characteristics. Higher likelihood of cancers with a relatively favourable prognosis among screen detected women might explain some of it, but other confounders including less variation in access, timeliness and quality of breast cancer care for screen versus symptomatic pathways of care might also have contributed.

A greater survival disparity was observed between Māori and NZ European women with advanced staged cancer ($HR=2.09$) than for early staged cancer ($HR=1.20$). It seems that

advanced stage at diagnosis for Māori women was associated with poorer survival not only through the advanced nature of the disease itself, but also through other associated adverse healthcare, patient and tumour characteristics. Greater levels of comorbidity, high BMI and smoking for Māori versus NZ European women accounted for a quarter of the survival disparity between Māori and NZ European women with advanced disease, while for early stage disease the contribution was less than 15%. The greater impact of comorbidity on reduced survival in Māori than in NZ European women for more advanced cancer indicates that Māori women with advanced cancer may be more likely to receive sub-optimal treatment. This theory is further supported by a previous study on colon cancer where comorbidity was reported to be a major risk factor for sub-optimal therapy in Māori compared with non-Māori patients (156).

Inequities comorbidities, obesity and smoking result from differential access to determinants of health such as income, education and housing as well as access to timely, high quality health care (376). While health care services can only play a small part in eliminating unfair social determinants of health, they can mitigate the effects of poverty as a determinant of access to transport to health care, timely access to health professionals, access to pharmaceuticals, and access to social welfare.

Overall, differences in tumour biological characteristics appeared to be contributing minimally to the survival disparity. However, for advanced stage cancers the contribution was substantially greater than for early staged cancers (7% vs. 15%). This indicates that some of the more advanced cancers diagnosed in Māori women might have been due to biologically more aggressive nature and rapid growth of these cancers (e.g. higher grade and HER-2 positive). Ethnic differences in cancer biological characteristics and their contributions towards ethnic differences in breast cancer outcomes have been studied previously (11, 166). For example African American women are about 50% more likely to have more aggressive breast cancers (86, 377), and these differences have been shown to be responsible for approximately 15-25% of the breast cancer survival disparity between African and White American women (83). Although biological differences in breast cancer between Māori and NZ European women seem to be contributing to survival disparity, its impact appears to be much smaller, and nature of biological differences seem to differ from the USA (80, 166).

Reasons for ethnic differences in breast cancer biology are largely unknown (301). It is unlikely that there are innate genetic differences between ethnic groups resulting in more aggressive breast cancers for some groups. Ethnic groups are not always from discrete

ancestry groups. For example, NZ European and Māori women descend from a wide range of ancestry groups and each group shares common ancestry groups. It is likely that socio-environmental factors put minority, Indigenous and other socially disadvantaged women at risk of having more aggressive breast cancers than privileged ethnic groups (302).

Barriers to accessing healthcare and inferior quality of care received by Māori compared with NZ Europeans have been shown to be an important mediator for poor outcomes in Māori for many medical conditions, including cancer (67, 102, 182, 378). For instance, Māori have been shown to be less likely than NZ European counterparts to undergo coronary revascularization for ischaemic heart disease (183), to receive surgery for operable lung cancer (182), and were less likely to have received a curative resection for operated colon cancer (67). Higher prevalence of markers of poor healthcare access factors for Māori including poor socioeconomic status, lack of health insurance and rural residency might have contributed to these disparities (12, 235). Furthermore, there is evidence that Māori receive inferior quality healthcare within healthcare institutions for instance with lower use of adjuvant therapy or with longer delays for treatment (67). The New Zealand healthcare system is expected to provide a high quality equitable care for all citizens (28). However, it seems that healthcare structure, delivery of health services and possible institutional racism have contributed to a relatively inferior cancer treatment being delivered to Māori compared with NZ European patients (35, 67).

The New Zealand Cancer Control Strategy has identified decreasing inequalities in cancer outcomes as a key objective alongside the objective of improving outcomes for the total population (275). There are arguments for prioritizing equity over total population goals but the policy does not reflect this sentiment in its strategies. Although the actions arising from the New Zealand Cancer Control Strategy have seen some tangible improvements in cancer outcomes for Māori (379), much work is still needs to be done, as breast cancer disparities exist at multiple levels from screening to gaining access to healthcare through to treatment (39, 123). In an attempt to standardize care for all women with breast cancer, the Ministry of Health recently published standards of service provision for women with breast cancer (59), which is expected not only to provide standards of care but also tools to measure and audit quality of care. Monitoring and reporting care by ethnicity against these standards will provide valuable feedback to identify deficiencies, so remedial action through equity focussed quality improvement can be targeted at ‘inequity hotspots’ along the breast cancer care pathway.

Although majority of the key variables used in this study had complete data, a few included significant proportions of missing data. However, an analysis performed including only complete datasets yielded results much similar to results shown, and hence unlikely to have significantly affected the reported findings. Although regional variations in healthcare services may have impacted on some of the observed differences, overall findings were comparable with similar research on ethnic disparities in other cancers in New Zealand (67, 182). Hence, our study findings are likely to be representative of the ethnic differences of breast cancer in New Zealand.

In conclusion, this study has reconfirmed significantly worse breast cancer outcomes in Indigenous Māori compared with NZ European women. Several healthcare access and treatment patient, tumour, factors appeared to be contributing to this disparity. Equity focused improvements to healthcare, including increasing mammographic screening coverage for Māori women and providing equitable high quality and timely cancer care has the potential to significantly improve the survival disparity between Māori and NZ European women.

Chapter 6. Discussion and Conclusions

6.1. Interpretation of results

Key findings of this study could be broadly categorized into differences observed in relation to patient characteristics, tumour factors, treatment differences and differences in breast cancer survival.

1. *Socio-demographic and patient characteristics* – Māori patients were significantly different from NZ European patients in relation to healthcare access characteristics and patient characteristics that included levels of comorbidity, smoking and obesity
2. *Cancers* – breast cancers in Māori were significantly more likely to be advance staged at diagnosis and were more likely to carry some of the prognostic characteristics associated with worse cancer outcomes. Further, Māori women (overall and within screening age) were significantly less likely to have been diagnosed through screening compared with NZ European women.
3. *Treatment* – Māori were significantly less likely to receive certain forms of cancer treatments and were more likely to experience longer delays to receive cancer treatment than NZ European patients. Once started on treatment, Māori were more likely to be sub-optimally adherent with treatment.
4. *Outcomes* – Māori women were approximately 100% more likely to die from their breast cancer (age adjusted) compared with NZ European women. Delay in diagnosis due to lack of healthcare access and lower screening participation were responsible for about a half of this disparity while comorbidity and treatment differences made substantial contributions.

This section tries to bring together findings from studies mentioned under results chapter and summarises key findings of this study. Study findings are discussed in the context of existing literature on breast cancer survival disparities in New Zealand.

6.1.1 Differences between Māori and NZ European women with breast cancer

Significant socio-demographic, tumour and treatment differences were observed between Māori and NZ European women with breast cancer included in this study. All these factors appeared to be contributing at varying degrees towards the final survival inequity.

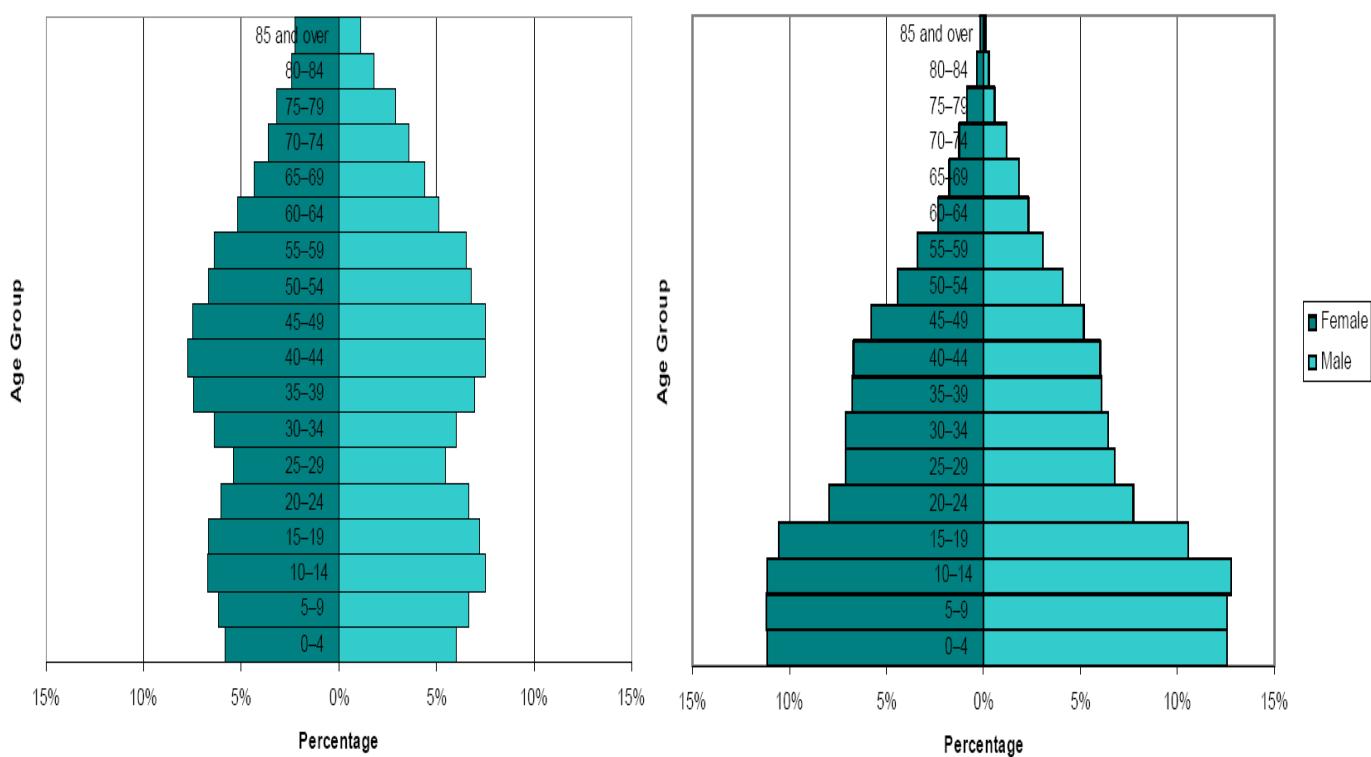
Differences in socio-demographic and patient characteristics

Demographics

Average age of Māori women with breast cancer was approximately six years lower compared with NZ European women. This finding was compatible with age structures of Māori and NZ European populations within the region and in New Zealand (Figure 32) (41).

Considering the age distribution pattern, Māori women are expected to have a lower crude breast cancer mortality rate than NZ European women. However, the crude mortality rate was approximately 80% higher for Māori, and age adjustment increased this disparity further, to just over 100%.

Figure 32: Age structure for Māori and non-Māori populations in Waikato in 2006 (*Source: Census 2006, Statistics, New Zealand*)



The number of breast cancers diagnosed per year has increased for both groups in the Waikato; number of cancers per year has approximately doubled for NZ Europeans (from 100 to 200 per year approximately) while the number has approximately tripled for Māori women (from 15 to 50 per year approximately). This has resulted in a gradual increase in the proportion of Māori breast cancers, which has increased from 12% to 19% compared with a comparative reduction from 84% to 77% for NZ European women from 1999-2002 to 2010-2012. Expansion of Māori population at a rate faster than NZ Europeans, and a gradual increase in life expectancy in Māori which has resulted in a shift in the population age structure of Māori would explain some of this increase in breast cancer incidence for Māori (41).

Where relevant, all comparisons between Māori and NZ Europeans have been adjusted for age/age category at diagnosis and year/year category of diagnosis.

Cancer stage

Stage at diagnosis was significantly more advanced in Māori compared with NZ European women, which was consistent with previous literature (4, 9). However, the rate of metastatic cancer in Māori was found to be more than twice that for NZ European women, which was significantly higher than reported in previous literature (4). Under-staging of metastatic cancer, which is more common in Māori, was the major reason for this difference between publications based on the NZCR and the present study.

More advanced cancer at diagnosis in Māori seemed to be contributed both by a delay in diagnosis due to delay in presentation to a healthcare facility and a due to a lower rate of screen detected cancer compared with NZ European women. The actual proportional contribution of these two factors (and the added provider delays) towards more advanced cancer at diagnosis could not be analysed in this study due to the unavailability of data on primary care consultations.

Patient factors

Rates of medical comorbidities, smoking and obesity were significantly higher in Māori compared with NZ European women. These findings were comparable with published rates for Māori and NZ European women (33). These patient factors were significant contributors

towards overall worse breast cancer survival in Māori. Poorly controlled medical comorbidities, smoking and obesity are likely to be higher in women of lower socioeconomic groups, in women with a low health literacy as well as in Māori (31). As there is a significant overlap among these three categories, identifying the independent effect of ethnicity is complex. Irrespective of the origin, the root cause for these disparities lie in the differential access to determinants of health and differential access to quality healthcare.

Differences in tumour characteristics

Tumour biology was an area where there were significant myths and controversies. Lack of proper local data, and hence trying to extrapolate based on findings from countries including the USA has created a myth among some physicians that Māori have an inherently worse tumour biology compared with NZ European women. A study based on the Auckland Breast Cancer Register by Weston and colleagues have supported this theory, while others including McKenzie et al and Dachs et al have refuted such claims (70, 74, 169). Our observation was that Māori do have significantly higher rates of certain biological characteristics (e.g. HER-2 positive cancers), but not others (e.g. triple negative cancer) associated with worse outcomes. Regardless, the overall contribution of these differences to the mortality disparity was minimal, in the region of approximately 5%.

Differences in treatment – provision and adherence

Assessment of quality of treatment is complex. Some of the areas of quality are highly subjective. Some include several steps during each treatment pathway which are difficult to capture and hence are not documented. Only a few selected key areas of treatment were used for analysis of treatment disparities and their contribution towards the survival disparity. These parameters included timeliness and use of and adherence with (endocrine therapy only) treatment. Other areas of treatment including referral for adjuvant therapy, oncology decision process, and adherence with and completion of radiotherapy and chemotherapy were not analysed. It is likely that similar disparities do exist in those areas which might have contributed to the survival disparity. Although all these characteristics were not included, the key parameters used in this study are expected to have captured most of the key treatment differences contributing to the survival inequity.

Overall, Māori women appeared to have received an inferior quality of breast cancer care compared with NZ European women. Longer delays were observed for receipt of primary surgery as well as for adjuvant therapy. Māori were significantly more likely to have undergone mastectomy for cancers that were suitable for breast conservation, but the rate of post-mastectomy reconstruction was only a third that of NZ European women. Use of radiotherapy and endocrine therapy were lower for eligible Māori compared with NZ European women, although no such difference was observed for chemotherapy. Once started, adherence to treatment was significantly lower in Māori than NZ European women, as observed with lower adherence to adjuvant endocrine therapy. Although patient choice seems to have been a contributory factor for some of these differences (e.g. higher mastectomy rate in Māori), most of these inequities appeared to have been driven by healthcare access, including lack of access to private healthcare for Māori, and healthcare delivery process.

Outcome differences

The risk of mortality from breast cancer in Māori was twice that for NZ European women after adjusting for age and year of diagnosis. Survival disparity was significantly smaller for early staged cancer (20%) compared with advanced staged cancer (109%).

Lower screening coverage and more advanced stage at diagnosis

As discussed previously, Māori women had significantly more advanced breast cancer at diagnosis compared with NZ European women. This disparity contributed to approximately 40% of the overall survival disparity between Māori and NZ European women. Lower proportion of screen detected cancer contributed an additional 15% to the survival disparity which appeared to be independent of the stage at diagnosis. Inclusion of a higher proportion of cancers with better prognosis including over diagnosis of clinically indolent low grade cancers with screening mammography might have been responsible for some of this difference. Access to healthcare and levels of health literacy are likely to have been better for women who participated in screening and these might also have contributed to relatively better prognosis for women with screen detected cancer. This is further supported by the lack of a survival disparity observed for screen versus non-screen cancer between Māori and NZ European women. Perhaps more importantly, this shows that Māori women with breast cancer do as well

as, if not better than NZ European women provided that they are diagnosed early and provided with equitable quality of care.

Stage at diagnosis contributed by a third towards the survival disparity seen for both early staged (stage I/II) and advanced staged cancer (stage III/IV) between Māori and NZ European women. Differences in rates of screen detected cancer contributed another third towards survival disparity for early staged, but was less than 10% for advanced cancers. However, only a small proportion of advance staged cancers were included under screen detected category.

Comorbidity, obesity and smoking

Patient factors contributed approximately 15% towards the survival disparity. This contribution was much greater for advanced stage cancers compared with early staged cancers (25% versus <5%). Other adverse characteristics including lower health literacy and lower socioeconomic state which are more common among these patients might have contributed for this greater contribution seen for women with advanced staged cancer.

Quality of healthcare –provision, delays and adherence

Treatment disparities appeared to be contributing to approximately 15% of the survival disparity between Māori and NZ European women. As only a few key areas of treatment disparities were analysed, we may have underestimated the actual contribution. However, the underestimation, if there is one, is likely to be minimal as key parameters used in the analysis probably would have captured effects of some of the unmeasured parameters (e.g., use of chemotherapy and radiotherapy are likely to have captured differences in rates of referral, though we have not analysed differences in referrals for oncology treatment).

6.2. Why do these disparities exist?

Results from this study has shown that almost all, if not all, breast cancer survival inequity between Māori and NZ European women is due to modifiable risk factors, of which the most important was differences in timely access to quality healthcare. These findings are largely comparable with previously reported survival disparities for bowel and lung cancers in New Zealand (67, 182). Cancer survival disparities observed between Indigenous/ethnic minority and other populations are not unique to New Zealand. Many other countries including Australia and the USA experience similar or sometimes worse cancer survival disparities (80, 81, 380).

Why do Māori have less access to timely and quality healthcare? Finding an answer to this question is complex as these disparities are brought about by a series of patient and healthcare service characteristics, as well as due to certain incompatibilities between the two. It is further complicated by other covariates including lower socioeconomic status, geographical location and health literacy which also contribute to health inequities.

As discussed in the literature review these factors could be categorized broadly into healthcare system, healthcare process and patient characteristics for ease of understanding, despite the significant overlaps observed among these categories.

6.2.1 Provider and healthcare system characteristics

Structural aspects of healthcare delivery appeared to be the main driver of Māori – NZ European healthcare inequities. While some of these inequities are due to direct effects, additional effects are mediated through socioeconomic and geographical differences between Māori and NZ European women.

Findings from this study have highlighted some of the areas where the healthcare system has failed to provide an acceptable and equitable level of cancer care for Māori compared with NZ European patients. Māori were observed to experience inferior quality of care at almost each step of the cancer care pathway, and this indicates the widespread nature of disparities throughout the health service. As Māori tended to be diagnosed with more advance staged disease compared with NZ European women, inferior quality of care including longer delays likely have had a significant impact on the survival inequity.

Population groups who bear the burden of health services inequity enter the health system with additional disadvantage of inequities in determinants of health such as income, education, healthy housing, healthy employment and living in safe communities. For non-dominant or Indigenous ethnic groups, inequities in access to social determinants of health and to quality health care are compounded by a much greater exposure to racism. This is a major risk factor for poor health as it impacts on access, timeliness and quality of health care.

The role of health services in creating and maintaining health inequities is well known (381). An increase in inequities while increasing ‘health for all’ is a well-documented unintended consequence of interventions aimed at improving population health (382). A strategic approach that is equity focussed is imperative if the dual goals of achieving equity and improving health for all are to be realised. A focus on improving total population health can result in improved health overall while at the same time increasing inequities. This is because total population health can improve even when there is a large growth in health inequities between a majority and a minority population. The adoption of evidence based approaches for achieving equity in cancer mortality by New Zealand health services has been inconsistent, not well monitored and not prioritised over improving total population health. As a result, major inequities continue to exist for a spectrum of medical conditions both by ethnicity and socioeconomic status.

As with other national systems and institutions, the New Zealand healthcare system also is designed by and follows the European pattern. Although recent changes to the healthcare structure and system have incorporated some Māori governance and values, these remain relatively minor. Cancer specialist services are exclusively available through mainstream health services dominated by a European culture, by providers with European values and beliefs. Such a system might neither be completely acceptable nor comfortable for Māori patients, and might have created a barrier for Māori to access optimum level of cancer care.

Cultural differences between healthcare system and patients, interfering with optimum cancer treatment has to be recognized as different from culture, values or belief of a patient group restricting optimum cancer care (96, 191). For instance, certain beliefs among some ethnic/cultural groups may prevent these patients from accessing readily available healthcare services. All ethnic groups carry a cultural identity and will be at ease receiving healthcare from a culturally compatible healthcare system, similar to what NZ Europeans experience in New Zealand healthcare system which largely follows a European pattern. On the other hand,

the healthcare system that is designed and functions along values of Europeans may create an environment that differs from expectations of Māori patients.

Many local and international researches have reported on the influence of cultural and/or ethnic identity of patients towards physician decision making processes (96, 191). These may be driven on at times by discrimination, or perhaps more commonly due to a lack of understanding of values of a particular culture or ethnicity. In the context of public healthcare system, there is an unequal distribution of power between clinicians and patients, in favour of clinicians. This may influence physicians to provide an inferior quality of care for patients who belong to minority ethnic or cultural groups. In the fee levying private health system, such disparities are less likely to exist as the physician patient relationship is driven primarily through remuneration. However, only a small proportion of Māori are able to afford private sector care and this has made them more vulnerable as they have to depend almost entirely on public healthcare system for healthcare needs.

This study did not include details of physician decision making processes or patient-physician interactions. Hence, possible differences of these characteristic between Māori and NZ Europeans were extrapolated as possible reasons for observed disparities in cancer care, supported through existing local and international literature (96, 191). For instance, Hill and colleagues have reported that for stage III colon cancer, Māori and non-Māori patients are referred at equal rates for chemotherapy (181). Yet, chances of chemotherapy being offered for Māori for these cancers were significantly lower than for non-Māori. This suggests that physicians are less inclined to recommend chemotherapy for Māori, possibly due to a belief that Māori are less likely to benefit from chemotherapy or due to the belief that Māori are less suitable for chemotherapy. It is unclear whether such discrepancies were existent for breast cancer in the Waikato as we did not observe significant differences in rates of chemotherapy between Māori and NZ European women. However, we did not have adequate data to ascertain possible ethnic differences in rates of referral or being offered with chemotherapy.

6.2.2 Patient factors including socioeconomic factors

This study observed that rates of medical comorbidities, smoking and obesity were significantly higher in Māori compared with NZ European women with breast cancer. All these are factors well-known to be associated with an increase in breast cancer mortality (146, 377, 383). As expected, these factors were found to be contributing to approximately 15% of

the survival inequity. These patient related factors appeared to be contributing to higher breast cancer mortality mostly through interfering with optimum cancer treatment.

Higher levels of comorbidity, smoking and obesity, as mentioned previously, arise as a result of poor health literacy and differential access to determinants of healthcare including primary and preventative healthcare services. These very same markers also contribute to delays in diagnosis, lower rates of acceptance and adherence with treatment, which further increase likelihoods of poorer breast cancer outcomes for these women.

There were some instances of patient choice influencing differences in treatment between Māori and NZ Europeans. For instance Māori were more likely to opt for a mastectomy for a cancer suitable for breast conservation. However, this is a scenario of two treatment options of equal efficacy, and this difference is likely to have been driven by other factors including difficulties in accessing radiotherapy after breast conservation. Equal rates of definitive local therapy observed for early breast cancer between Māori and NZ European women further support this. We did not have information to identify the impact of patient choice on use of other treatment including chemotherapy and radiotherapy. It is unclear whether patient choice has been a reason, especially in light of previous conflicting reports published based on lung and bowel cancer. Patients declining treatment was a major factor for differences in surgical treatment for lung cancer while patient choice had no impact on treatment differences observed for colon cancer (67, 182).

Both Māori ethnicity and lower socioeconomic state appeared to be associated with poor access to healthcare, an inferior quality of treatment and ultimately, with poor breast cancer outcomes. Treatment and outcome disparities between Māori – NZ European groups tended to be significantly greater than disparities observed between affluent and deprived socioeconomic groups. This pattern of breast cancer treatment and outcome disparities associated with ethnicity and socioeconomic status are compatible with treatment and outcome disparities for breast and many other cancers reported from New Zealand and internationally (4, 82). Underlying reasons associated with these inequities appear to be barriers to access healthcare and inferior quality of care experienced by Māori and women of lower socioeconomic groups. Lower socioeconomic status in Māori patients was a strong driver for lower access and poor quality healthcare, but explained only part of the inequity. This is further supported by the disparities observed within the same socioeconomic category between Māori and NZ European women.

6.3. How can we provide Māori women with better and equitable healthcare?

As the extent of breast cancer outcome inequity between Māori and NZ European women, and some of the key drivers behind inequities have been ascertained, the following section attempts to discuss ways to correct such disparities.

6.3.1 Identifying the problem and its underlying reasons

Breast cancer survival inequity between Māori and NZ European women was well known for over three decades and some of the underlying causes including delay in diagnosis were also known during this time (4). Current study has added to this knowledge base, first by confirming the validity of previous findings and second, by shedding light on previously unknown disparities, including disparities in breast cancer treatment. Many of the objective differences in cancer care and cancer outcomes identified in this study, as well as in many previous studies, were due to cumulative effects of many subjective and objective factors acting throughout the cancer care pathway. Some of these factors are difficult or impossible to measure. Hence, many of the proposed changes are based not only on findings from the present and previous New Zealand studies, but also from personal experiences of clinicians and research findings from other countries.

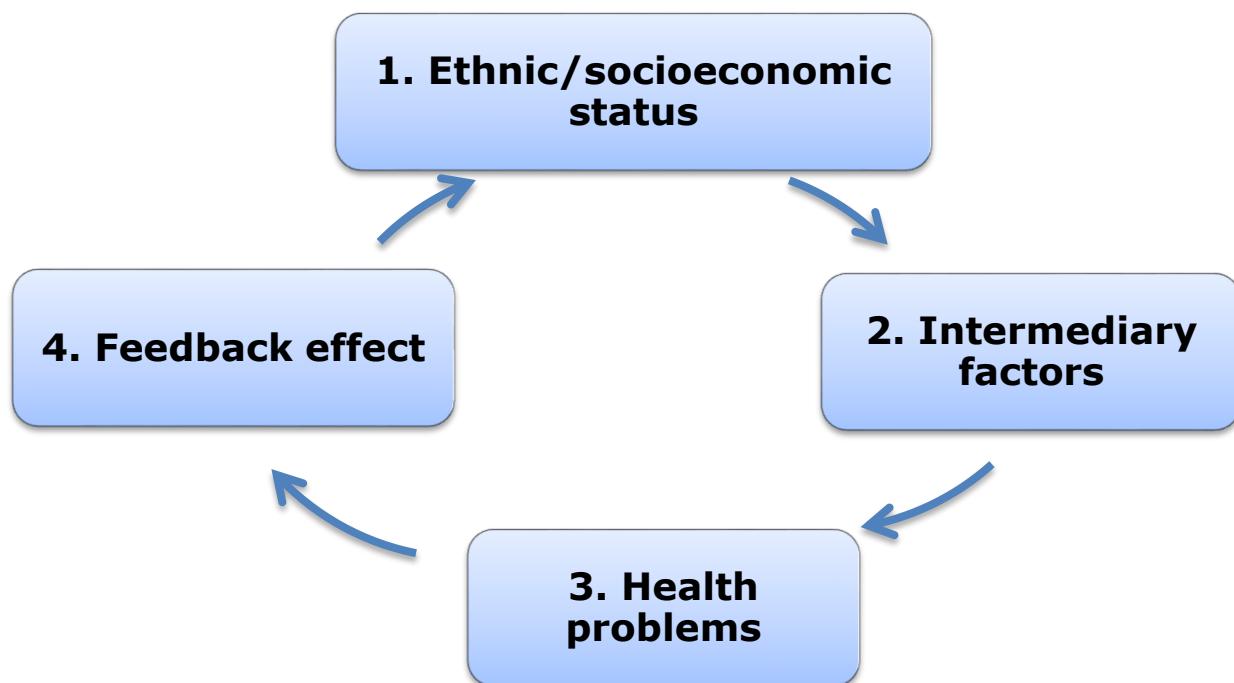
6.3.2 Providing equitable and acceptable care

Addressing the issue of providing an equitable quality of healthcare for disadvantaged populations including Māori and low socioeconomic groups requires changes in several aspects of the healthcare system. First, it requires a strong focus on providing equitable care. Second, those strategies that have been shown to be effective locally as well as internationally need to be recognized, and implemented in a manner that suits the local context. Finally, the performance of implemented strategies needs to be evaluated and monitored by ethnicity to identify effectiveness and deficiencies.

In this regard, Mackenbach has described four possible targets to intervene in order to reduce ethnic and/or socioeconomic inequalities in health (384). In this framework (Figure 33) health inequalities may be reduced by targeting:

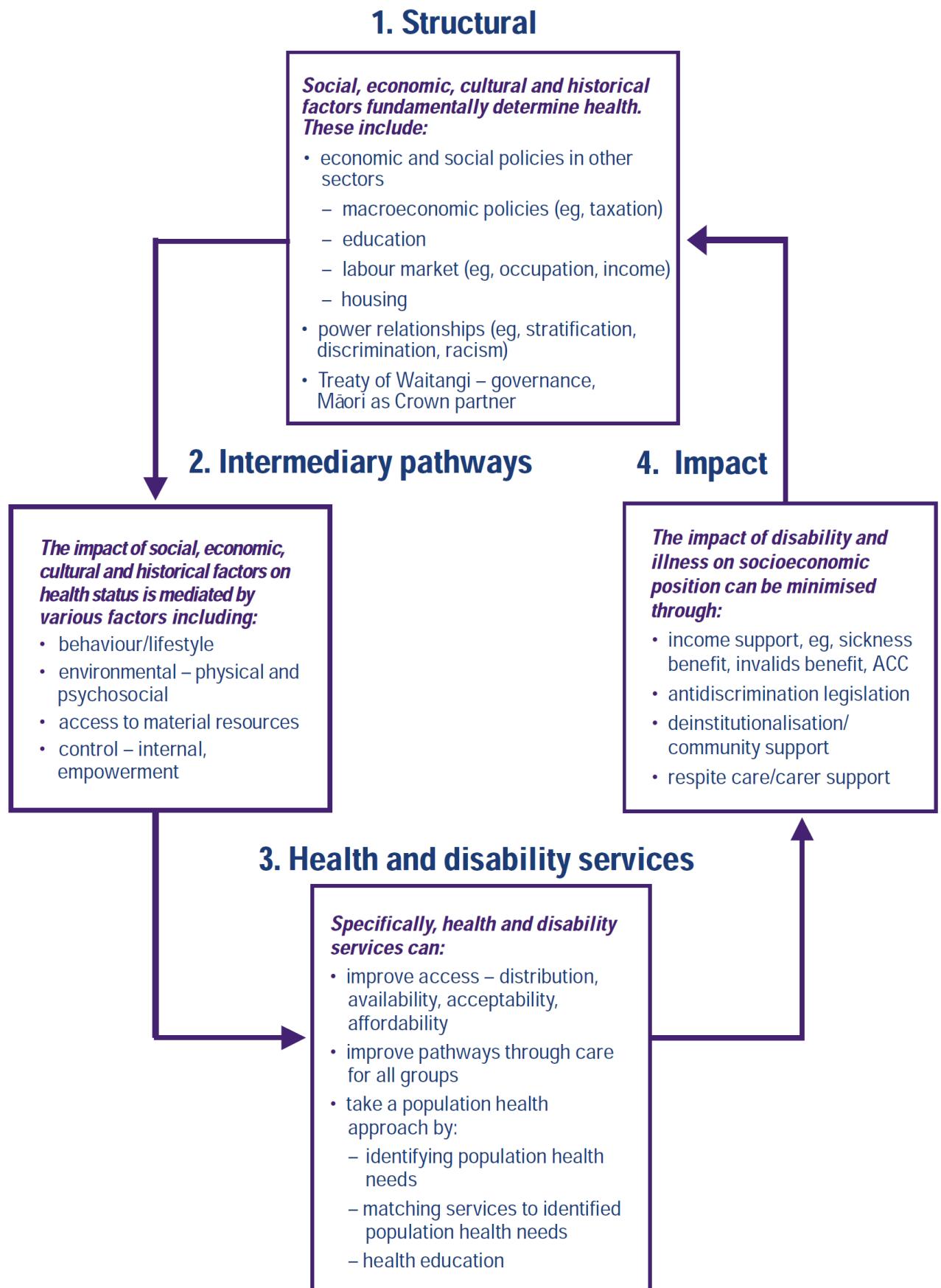
1. Underlying social and economic determinants of health
2. Factors that are intermediate between socioeconomic determinants and health, such as behaviour, environment and material resources
3. Health and disability support services
4. The feedback effect of ill health on socioeconomic position.

Figure 33: Four possible targets for interventions to reduce ethnic/socioeconomic inequalities in health
(Adapted from Mackenbach *et al.*)



Based on the Mackenbach model, the Ministry of Health has developed an intervention framework model (Figure 34) which provides a guide for the development and implementation of comprehensive strategies to improve health and reduce health inequalities. Step three of this framework has direct relevance to interventions that are proposed based on the current study. In broad terms, these include improving access to care, improving care pathways and targeting to improve health through a population approach. Further, the New Zealand Cancer Control Strategy has also identified reducing ethnic inequalities in cancer outcomes as one of its two main objectives (275). Together, these provide the necessary policy support at governmental and ministerial level to reduce ethnic inequalities in cancer outcomes. Within this context, a strong focus on equity should be established and maintained at all levels of cancer including cancer prevention and treatment which may help reduce cancer inequalities between Māori and NZ Europeans.

Figure 34: Intervention framework to improve health and reduce inequalities (Source: Ministry of Health)



Increasing the participation of Māori in healthcare provision is one of the recognised effective strategies to reduce ethnic inequalities. Māori involvement should be targeted at all levels of cancer care including cancer prevention, control and care of established cancer. Not only that, participation of Māori in policy decision processes will ensure that healthcare policies are acceptable for Māori, which would result in greater levels of acceptance and access to healthcare in Māori. However, under-availability of suitable and qualified Māori personnel has been a significant restriction hindering attempts at improving Māori participation within the healthcare sector. Providing more opportunities for Māori for healthcare sector related training and employments should be targeted to achieve greater Māori participation.

A regular evaluation of different policies, programmes and interventions will help identify the performance of these strategies and where changes are required to achieve better performances. Available frameworks such as Health Equity Assessment Tool (HEAT) could help anticipate and address likely gaps in services and programmes (385) while guidance tools such as the Medical Research Council of the UK guidance on Evaluating Complex Interventions would help measure performances against objective tools (386). Evaluation of performance against objective criteria allows for comparison of performance of different strategies and same strategy within different contexts and healthcare institutions. This potentially would allow deficiencies to be readily recognized and to rectify deficiencies through a feedback process. Finally, this will also provide accountability for the system and the providers to achieve equity in healthcare services.

Health system

Health service funding policies have direct impacts on health inequalities. For instance, this study has shown that the proportion of Māori receiving cancer care from the private sector was only a quarter that of NZ Europeans. Hence any changes to health policy that reduces public sector healthcare funding would likely further exacerbate health inequalities between Māori and NZ European women. Healthcare expenditure has been increasing exponentially, especially over the last decade, and it is unrealistic to place the complete responsibility on the government to provide best quality cancer care for all citizens. On the other hand, a better developed private healthcare sector could help to reduce existing workload and congestion in the public sector which could help public sector to provide better quality and timely cancer care, within existing funding caps. Although a balance between the two may be difficult to

achieve, it could potentially create a better environment for delivery of optimum of cancer care for a majority, if not all cancer patients.

Changes to the workforce development should target greater Māori provider participation and providing training for all healthcare providers to create awareness on issues relating to equity of care and cultural safety. Such changes will improve the understanding of healthcare providers on needs and expectations of Māori patients who seek care from mainstream healthcare services.

As discussed several times the importance of increasing breast cancer screening coverage for Māori women cannot be over-emphasized. Several factors including higher background incidence and higher rates of obesity means that Māori women stand a greater chance of benefitting from a greater screening coverage, more than NZ European women (40). To this end, commendable efforts and the dedication of the BSA programme has resulted in an increase in Māori coverage by over 50% during the last decade. However, the existing ethnic and regional variations in screening rates highlight the need for further efforts, and perhaps use of novel strategies to increase screening coverage. These changes will be especially beneficial to regions such as the Midland region that includes the Waikato, which consistently has reported the lowest screening coverage in Māori (39). Increasing screening coverage in the Midland region poses greater difficulties due to remoteness of many regions, general lower socioeconomic status of its population and higher than average Māori population (41). Greater area coverage and increasing the frequency of mammographic screening provided through mobile screening units are some of the strategies which have shown to be effective, and hence have the potential to increase rates of screening. Further, greater Māori provider participation in the BSA programme should be targeted which has shown to improve communication and make screening participation more acceptable for Māori women (143). Significant quality variations in process of invitation for screening are another issue that need addressing (387). Improving and standardizing the process of invitation appears to be an area with a greater potential to improve rates of screening for Māori. For instance a personal letter or a personal phone call or a personal invitation through the general practitioner has been shown to significantly increase the screening participation compared with the common invitation letter which is presently used by the BSA programme (388).

Improving the geographical accessibility of cancer care services is another issue that was observed to have significant effects not only for Māori, but also for all rural dwelling women. Recent changes to the health policy and cost cutting measures have seen many cancer services

being confined to centralized tertiary care units (37). Although it is logistically impossible to provide all specialist cancer care through regional units, increasing the distribution and frequency of oncology outreach clinics could improve access and acceptance of cancer therapy for many rural women. Implementation of such a strategy in the Waikato area is likely have a greater impact where oncology services are focused at a central unit that covers needs of cancer patients spread over an area of over 20,000 square kilometres.

Although many of the key factors contributing to ethnic disparity in breast cancer mortality has been documented several key areas remain unexplored. These include understanding the mechanisms of observed disparities and identifying the efficacy and cost effectiveness of different strategies to correct identified disparities in cancer care.

Healthcare processes

Structural organizations of healthcare services create the necessary background while healthcare process further promotes ethnic inequities in cancer. Women with breast cancer are required to go through a complex diagnostic and treatment processes which may extend well over a few years. Complexities of these processes combined together with social, economic and psychological impacts of cancer could result in many women being unable to complete these treatment processes in a manner that enable them to achieve optimum outcomes (389). A better healthcare delivery process could minimize complexities of care and should provide support for women with cancer for them to deal with social, economic and psychological issues through the treatment process.

Coordinated care and patient navigation are some of more recently introduced strategies that have shown to help women navigate through the complex cancer care pathway (229, 390). Although we could not directly show the impact of Cancer Care Coordinators (CCC) in this study, it is likely that a major portion of the reduction in treatment disparities observed over last 3-year period of the study is attributed to their work. Still, care provided through two CCC's appeared to be inadequate, as any given point of time, over 100 women with breast cancer are undergoing active treatment in the Waikato. The government has recognized the importance of care provided by the CCC's and has provided funding to all DHB's to recruit CCC's to manage common cancers in New Zealand (229). Although these efforts should be commended, there is a greater need for CCC's especially for breast cancer as the numbers are greater and treatment is likely to be more complicated and protracted.

Providing support for women to deal with psycho-social issues during the treatment processes will be of greater benefit for Māori as they are more likely to be socioeconomically deprived, hence more likely to encounter greater social and financial barriers. Further, many Māori women expect to be with their whānau during the process of treatment. As such, provision of transport and temporary accommodation may have to include whānau members. At present some of these services are available, but many Māori women seem to be unaware of the availability. Hence, there should be an active approach to inform women of the availability of these services and process of obtaining such services. CCC's who are expected to act as the single point of contact for these women has the potential to provide such services, but as mentioned above, means an additional workload and may require an increase in staff.

As discussed previously, provision of training for all healthcare staff on values and expectations of Māori patients and maintaining cultural safety will develop a better relationship between Māori patients and healthcare providers. Dedicated Māori social workers could supplement better communication through trust and better relationship building between healthcare services and Māori patients. This will have a significant impact not only on routine cancer treatment processes, but also on palliative care where there has been a greater reluctance in Māori to accept care in a mainstream setup away from their whānau (391).

Patient factors

Breast cancer outcome inequalities are driven primarily by health system and healthcare processes which are either not provided, or provided in a manner that is not acceptable or comfortable to a patient group. Lack of access, especially for determinants of healthcare would manifest as higher rates of smoking, obesity and comorbidities as was observed among Māori in this study. Equal access for healthcare services could reduce rates of poorly controlled comorbidity, smoking and obesity in these women. Further, impact of many of these conditions on breast cancer mortality could be minimized by better control of comorbidities or by giving up smoking after the diagnosis of cancer (392). However, these interventions require time and effort from the healthcare providers which at times could be quite daunting.

On a broader context, minimizing the impact of these factors on outcomes from breast and other cancers require a better access for determinants of health for Māori women. This includes better education and health literacy, through which many healthcare improvements could be achieved for the whole Māori population.

6.4. Strengths and Limitations – How valid are the findings?

The validity of a research is dependent upon its design (appropriate to answer the study question), its conduct and analysis. Next section looks at key strengths and key limitations of this study and discusses the possible errors that have been induced through bias, confounding and chance.

In summary, the key strengths of this study include the completeness of the study sample, comprehensiveness of the data and relatively long follow up. Limited sample size that restricted study power of some the analysis, impact of unmeasured/under-measured confounders and missing data were identified as key limitations.

6.4.1 Study design

Completeness of the population based sample of women included in this study, richness of the data which were collected prospectively (i.e. the WBCR data) or through a manual review of patient clinical records (i.e. retrospectively collected data) and the high proportion of Māori and rural women included (compared with rest of New Zealand) are the primary strengths of this study. This allowed for comprehensive comparisons of socio-demographic tumour and treatment characteristics by ethnicity, and to analyse for impacts of these differences on breast cancer outcome inequities between Māori and NZ European women. A further strength is the relatively long follow up of women included in this study, which has provided data for a robust survival analysis. Proportional hazard modelling provided the opportunity of identifying the impact of each factor of interest on final outcome disparity between Māori and NZ European women.

The major limitation of this study was the limited sample size. Although this study included data for all women with breast cancer diagnosed in the Waikato over a period of 14 years, the Māori sample size was relatively small with only 429 invasive cancers. This number is small especially compared with previous studies carried out with routinely collected administrative data which included many thousands of patients (4, 9, 13, 70). Although the inclusion of women diagnosed over a 14-year period provided a relatively larger sample size and a longer follow up, it has also introduced a degree of heterogeneity. This heterogeneity appeared to be greatest for breast cancer treatment, where significant and major changes were observed during this period.

Pacific women in NZ have also experienced an upward trend in both breast cancer incidence as well as mortality, especially over the last two decades (7, 73). However, as Pacific women made up only about 2% of the Waikato cohort of women with breast cancer, meaningful analysis of association of factors and outcomes in this group was practically impossible. Hence, all ethnic comparisons were performed between Māori and NZ European women and Pacific women were excluded from those analysis. This was another significant limitation of the present study.

Study data

The data included in this study were derived either from the WBCR or through a retrospective manual clinical notes review. Both these processes included a thorough review of all clinical information relating to breast cancer from several sources including prospectively collected data forms, clinical records and pathology reports. Further, an audit process of completed records in the database helped to minimize errors in data entry, and to maintain accuracy and uniformity of data entry. As mentioned previously, this process has enabled the WBCR to become the most complete and comprehensive breast cancer registry in New Zealand at present (259, 260). For instance, a comparison of data included in this study versus the NZCR identified that 12.3% of breast cancers in the NZCR to be unstaged compared with less than 1% in this study.

Review of medical records also provided the opportunity of assessing the full breast cancer care pathway from the point of first clinical assessment through diagnosis and treatment to the final breast cancer outcome. This information enabled us to analyse differences in the use and timeliness of different treatments among groups of women of interest and to identify their impacts on cancer survival.

Study power

Power of this study is restricted by the limited sample size of Māori included in the study. Although approximately 20% of the population in the Waikato are Māori, only about 15% of the breast cancers were in Māori due to younger age distribution in Māori compared with NZ European women (Figure 1).

There were several other options for increasing the Māori sample size and increasing the study power. These included increasing the eligibility time limit (include women diagnosed prior to 1999) or to include women with breast cancer diagnosed outside the Waikato region.

Increasing the time limit would probably have reduced the quality of data and increased the proportion of missing data and heterogeneity. For example many women prior to 1999 did not have hormone receptor status or tumour grade recorded in pathology reports. Further, BSA programme was initiated in 1999 and inclusion of women diagnosed prior to 1999 would have resulted in a significant shift in the proportions of screen versus non-screen detected breast cancers further increasing sample heterogeneity.

Although the inclusion strategy used in the present study was not the most efficient to detect Māori - NZ European differences due to unequal proportions of Māori and NZ European, it has helped to minimize possible selection bias that would have included with a smaller NZ European sample. Further, overall larger study sample allowed to identify impact of various socio-demographic, cancer and treatment characteristics on breast cancer outcomes in the complete cohort, and to generate some conclusions based on differences in distribution of those characteristics between Māori and NZ European women. This was important as in some analyses the study power was not adequate to demonstrate a statistically significant difference induced by these characteristics on the mortality inequity between Māori and NZ European women.

Misclassification of cause of death

Cause of death was derived based on information gathered from patient clinical record and was supplemented with data from the National Mortality Collection. The New Zealand Mortality Collection has a rigorous process to assign cause of death for individuals and is known to be highly accurate, especially when compared with mortality records of many other developed countries, including Australia and the USA (393).

For a majority of women included in this study (approximately 80%), there was sufficient information available from clinical records to ascertain definitive cause of death. For these patients the concordance of cause of death based on clinical records and the Mortality collection was over 90% and, was over 95% when cause of death was categorized into breast cancer non-breast cancer. For those 20% of women where the cause of death could not be

ascertained based on clinical record data (for example for a death of a woman who has not had any healthcare service contact for several years), we had to use cause of death assigned by the Mortality Collection. This would have included some degree of misclassification bias to causes of death, but is likely to be relatively minor. Further we expect this bias to have influenced both Māori and NZ European women in a non-differential manner, further reducing the likelihood of a bias that could substantially influence final results of this study.

6.4.2 Internal validity / Bias

Misclassification of ethnicity

Misclassification of ethnicity, which is the primary exposure variable in this study is the most significant possible misclassification. Ethnicity classification procedures included in this study and the rationale for use of such procedures has been described previously. There were a number of possibilities for misclassification of ethnicity as discussed below.

Inaccurate documentation of self-identified ethnicity was the first possibility. This error was less likely for the WBCR patients as the patients themselves record ethnicity during the consent process. However, misunderstanding of the question or mis-documentation of the response might still have happened, though unlikely. Inaccurate documentation was more likely for retrospective data collection as ethnicity was assigned primarily based on ethnicity data collected by healthcare worker/s during hospital admission/s. Wide variations in wording of the question related to ethnicity and the way in which this question was asked from the patient have been reported to have led to significant undercounting of Māori (5). Further, on many occasions the healthcare workers are known to assign ethnicity based on their assumption of patients' ethnicity without actually asking this question from the patient (394).

Second, a patient may opt not to reveal their true ethnic identity or select an ethnicity that is different from their true ethnicity depending on the circumstance. It is known that some patients who identify themselves as Māori within the Māori community, identify themselves as NZ European when comes into contact with the healthcare system (395). Previous literature on undercounting of Māori based on healthcare records has estimated the undercounting to be as high as 30% (5, 396). However, recent improvements in ethnicity data collection has been shown to have reduced the Māori undercounting rates significantly (179). Further, we have

used ‘ever-Māori’ approach for ethnicity assignment for retrospective data which would likely have further minimized possible undercounting of Māori in this study.

Selection bias

Selection bias in this study is likely to have been minimal due to the complete nature of the study sample. Data from seven women with post-mortem diagnosis of breast cancer and a further 31 women with breast cancer diagnosed during 1999-2004 were unavailable, and were not included in the study. This provided a participation rate of 98.6%. For the missing 31 women, cancer data or ethnicity was unavailable. Therefore it is impossible to ascertain whether the proportional distribution of ethnicity or breast cancer outcomes for these women were different from the complete study sample.

Information bias

Information biases applicable to this study include ethnicity, clinical information and outcomes. Possible impacts of misclassification of ethnicity have already been discussed. Bias in relation to misclassification of clinical details and outcomes are discussed next.

Misclassification of clinical details:

There is potential for misclassification of data included for patient and tumour clinical characteristics, treatment and outcomes.

The majority of patient and clinical characteristics were collected through prospective data collection forms and patient clinical records, which were filled by the attending physicians. These data were further cross referred (for example with breast screening or oncology records) where possible to improve accuracy. Still, it is likely that there might have been under-documentation (e.g. comorbidities) or mis-documentation of some data. However, such under- or mis-documentations were less likely for treatment and pathology information as these were invariably discussed and reconfirmed at the multi-disciplinary meetings and were documented at multiple sites and time points during patient management.

Misclassification of outcomes / death

Misclassification of outcomes could have affected this study in two main ways. First, is the fact of death (i.e. whether a particular woman is alive or deceased). Second is the cause of death for women who are deceased.

Fact of death is likely to be misclassified for women who have migrated out of the country after the diagnosis of breast cancer. The numbers who have migrated out of New Zealand totalled 12 based on available records which unlikely to have influenced the results of this study significantly irrespective of their outcomes. Misclassifying a living person as deceased is another scenario, but the risk is expected to be negligible as details of all deceased women were analysed individually.

As discussed above, based on our estimations, a small proportion of deceased women would have had the cause of death misclassified. However this is likely to have impacted both Māori and NZ European women in a non-differential manner. This likely would have had a minimal impact on observed mortality inequity.

Ascertainment of disease recurrence to determine disease free survival is likely to have included a greater bias. This can arise due to several reasons. First, disease recurrence is a process rather than a discrete event as death. Hence some women might have lived with disease recurrence without coming into contact with the health system. Some women with recurrent disease might have migrated out of the area. Unlike death, it is practically impossible to capture details of recurrence, especially if the woman was detected with recurrence in private sector or in a different region. We used disease free survival as a secondary outcome measure only for a few studies due to its higher risk of bias as discussed here and, interpretations of such results are appropriately cautioned.

6.4.3 Confounding and estimating effects

Analyses of differences between Māori and NZ European women in relation to tumour, treatment and outcomes were adjusted for a number of covariates. These included some direct confounders (e.g. age) and others which were mediators of tumour characteristics or outcomes (e.g. socioeconomic deprivation).

Confounders

Age and year of diagnosis were the only pure confounders influencing tumour characteristics and outcomes in this study. All analyses were adjusted for these two variables (e.g. odds ratios, hazard ratios) except for situations where it was necessary to use unadjusted variable values (e.g. Kaplan-Meier survival curves). Adjusting for year of diagnosis made only minor changes to Māori and NZ European odds and hazard ratio estimates. However age had a major impact on these estimates due to the younger age distribution of Māori (Figure 1) compared with NZ European women (e.g. breast cancer mortality hazard ratio increased from 1.81 to 2.02 after adjusting to age).

Other covariates / mediating variables

Other covariates or mediating variables are factors that were associated with both ethnicity and, tumour characteristics and breast cancer outcomes. These factors represent a causal pathway between ethnicity and outcomes of interest. Appropriate adjustments for these factors were undertaken for the purpose of assessing their contribution to Māori and NZ European disparities.

The actual contribution of each mediating variable might have been imperfectly or imprecisely measured resulting in residual confounding/mediation. Misclassification or residual variation within measured categories might have imparted a degree of residual variation.

Residual confounding was a likely factor in all scenarios where the NZDep 2006 was used as a measure of socioeconomic status. The NZDep 2006 is an area based system of socioeconomic deprivation, and use of this system in the current study to measure socioeconomic state would likely have misclassified deprivation for some individuals resulting in residual confounding. However, at a population level NZDep 2006 has been shown to be a valid proxy measure of socioeconomic deprivation (397). Further, the associations observed in this study between breast cancer outcomes and socioeconomic status was compatible with associations reported previously and this further confirms the validity of NZDep as a measure of socioeconomic deprivation.

Cancer stage at diagnosis is another instance where residual variation might have had an influence. Almost all analyses were performed using either TNM stage groups or T and N categories separately. However within each stage category or within each T or N stage, one

group might have had more advanced cancers. Although use of sub-stage categories (e.g. stage IA, IB, etc.) was one option available to get over this issue, small numbers of Māori within each sub-category meant that estimates of odds or hazard ratios were highly variable with large confidence intervals making data interpretations difficult.

Unmeasured confounders / mediating variables

There were several unmeasured confounders / mediating variables in this study which are known to influence outcomes of interest. Most of these confounders were factors related to socio-demographics. For example no details of patient education, health literacy or insurance status were available, and hence were not included in analyses. Patient education and health literacy are known to impact several health related issues including recognition of symptoms, health seeking behaviours, acceptance and adherence with treatment and follow up (11, 80). Some of these factors were likely reasons for persisting large difference between Māori and NZ European women after adjusting for available covariates (e.g. adherence to endocrine therapy in Māori was 50% lower after adjusting for available covariates).

Estimating survival effects

Final survival analysis included a model to quantify impacts of different covariates on observed Māori - NZ European mortality disparity. Covariates included in this model explained about 95% of the observed disparity. However this model included several limitations and hence interpretations based on this model needs caution. First, previously described errors of misclassification and confounding were included in this model which might have led to some degree of imprecision of estimates. Second, based on the sequence of introduction, significant differences were observed on impacts of different covariates. For example, when healthcare access related factors were introduced into this model before the stage at diagnosis or treatment, the impact was approximately 10%, while the impact was reduced to 2% when it was introduced into the model after stage at diagnosis and treatment.

Potential effects of misclassification, confounding and residual mediation are complex, and are difficult to overcome. Adjusting for covariates, sub-group analyses, analyses only of complete data and sensitivity analyses to a certain extent have helped to minimize or to estimate the impact of these factors on final results. Presence of confounding, mediating variables and

misclassification do not invalidate the data or the results of this study; rather they point to areas where one needs to be cautious and to interpret results within the correct context.

6.4.4 Chance and variability

This study included a limited sample size for Māori. This resulted in limited precision of estimates with large confidence intervals which were more evident in sub-group analyses. Low precision and lack of significance of subgroup analyses were dealt in most situations by using multivariable logistic regression models with sub-groups included as covariates. As most of the outcomes of interest included in this study had a large number of covariates, this resulted in complex statistical calculations which might have led to a degree of imprecision, albeit with tight confidence intervals. Every attempt has been made to minimize this imprecision by using sub-group analyses where possible, by selecting only the minimum number of covariates for multivariable models and by performing stepwise regression analyses.

Limited sample size has the risk of including a Type II error; that is, not detecting a difference when one exists. There were several situation where differences between Māori and NZ European women were observed but were not statistically significant (e.g. age adjusted HER-2 positivity rate was higher in Māori [20.7%] compared with NZ European [16.3%], but the difference was statistically not significant). However, these differences are proportionately small and are unlikely to be clinically significant.

6.4.5 External validity

This study was conducted using a regional cohort of women with the objective of identifying differences in breast cancer characteristics and outcomes between Māori and NZ European women in New Zealand. Therefore, the validity of study results and its generalizability to the general New Zealand population requires a thorough evaluation.

There were some factors and outcomes which were clearly due to regional variations. For example, longer delays in treatment (radiotherapy and chemotherapy) observed during 2003-2005 time period was due to shortage of oncologists and other oncology staff in the Waikato DHB. Yet, a pattern that was similar to other time periods was observed where more Māori experiencing longer delays. Therefore, although the absolute values of these variables might

not be applicable to the whole country, trends and patterns observed are likely to be valid and applicable.

Further, distribution of some socio-demographic characteristics of the study population was different from rest of the country. The Waikato DHB includes more rural areas compared with other DHBs and breast screening coverage rate within the Midland region (that includes the Waikato DHB) has persistently been the lowest in the country (39). Although these factors might have limited the generalizability of the study results, they have also provided the opportunity of demonstrating differences in outcomes in relation to these factors. For example, the high rural population and women residing more than 100km from the tertiary centre in the Waikato DHB area allowed the demonstration of statistically significant lower coverage and longer radiotherapy delay for these women.

When all above facts are considered, this study appears to be fairly representative of the New Zealand population and likely to be valid for general New Zealand population of women with breast cancer over the study period.

Findings from this study on breast cancer inequalities are likely to be applicable to many other cancers and other chronic conditions within their contexts and with limitations. For example, similar disparities in treatment and outcomes have been shown for bowel and lung cancer (181, 182). However there were significant differences between those cancers and breast cancer (e.g. there was no difference between stage at presentation for bowel cancer between Māori and non-Māori). Although there seem to be general trends in cancer disparities between Māori and NZ European, substantial and significant differences do seem to exist which are unique to each cancer.

Applicability and relevance of this study data to inequities between Indigenous/ethnic minority women with breast cancer in other countries should be interpreted within their contexts and differences unique to each country. Where possible, results of this study have been compared with similar studies from other countries. Although there were several similarities, some significant differences were observed. For example African American women in the USA have been documented to have breast cancers with significantly worse tumour biology which was not observed in Māori women.

6.5. Conclusions

This study has shown that Māori women with breast cancer are almost twice as likely as NZ European women to die from their disease. This survival inequity appeared to be due to differential access to determinants of health (i.e., obesity, smoking, comorbidity) and cancer care services for Māori compared with NZ European women. Such a concept is supported by this study and many others who have shown the existence of persistent patient, physician, and healthcare system barriers to accessing quality cancer care for Māori patients with cancer in general, and for breast cancer (31, 34, 67, 97, 182). The central barriers that act at patient level include low socioeconomic status, low health literacy and possible culturally mediated attitudes that may contribute towards key final pathways that mediate poor cancer outcomes observed in Māori women (34, 398). At provider level, gaps in training in patient-physician communication could also constitute an unaddressed barrier to cancer care (99).

Achieving equity in breast cancer survival between Māori and NZ European women will require a concerted effort by health care providers, with central leadership from the Minister of Health to prioritise equity over improving the health of the total population. Reducing the influence of non-clinical factors on the receipt of cancer treatment may provide an important means of reducing ethnic inequities in cancer outcomes. Many interventions to improve access to cancer services for Indigenous/ethnic minority populations have been developed targeting one or more of the domains that drive inequities in access to quality cancer care. For instance, educational strategies and behavioural models have been used successfully to overcome low health literacy or attitudinal barriers, and to increase mammography screening rates (385). Similarly, interventions targeted to physicians that rely on behavioural cues (e.g. reminders) and education have been used to increase breast cancer screening rates (96). Māori provider organizations and cultural safety education are some of the local examples of initiatives that have emerged not in isolation but, rather, within a context of government policies that have been shown to promote health status of Indigenous Māori populations (99, 100). A greater integration of Māori providers into the healthcare service has shown not only to reduce cultural barriers to access care but also to reduce possible institutional discrimination towards Māori cancer patients (100).

This study has provided data on many previously unknown or lesser known areas contributing to breast cancer survival inequity by ethnicity in New Zealand. Yet, many other areas remain inadequately researched or completely unexplored. For example, breast cancer in Pacific women in New Zealand has hardly been researched, although the breast cancer mortality rate

is known to be even worse than Māori. New data resources and improved study methodologies are needed to better identify and quantify the full spectrum of all non-clinical factors contributing to the mortality inequity and to develop strategies to facilitate appropriate cancer care for all women with breast cancer. To date, there also is limited research on patient based or physician-based interventions focussed on early diagnosis of cancer or cancer treatment, and still fewer research based on interventions at the healthcare system or process level. Interventions designed to enhance access also needs to be evaluated systematically to ensure that patient outcomes are improved for all patients, but with a greater focus on disadvantaged groups including Māori, in the most cost-efficient manner. Together, future research and interventions hold the promise of eliminating the current ethnic inequalities in access to cancer care and cancer outcomes in New Zealand.

Appendices

Appendix 1

Multivariable **logistic** regression model for unstaged versus staged cancer in the New Zealand Cancer Register

Characteristic		OR	95% CI	p
Age category (years)	<40	Ref		<0.001
	40-59	0.99	0.50-1.99	
	60-79	1.06	0.53-2.15	
	80+	3.32	1.59-6.97	
Ethnicity	NZ European	Ref		0.664
	Māori	1.09	0.75-1.59	
Deprivation	1-2	Ref		0.704
	3-4	1.08	0.65-2.16	
	5-6	1.07	0.64-1.81	
	7-8	1.04	0.64-01.71	
	9-10	0.86	0.51-1.45	
Charlson score ^a	0	Ref		0.001
	1-2	1.71	1.24-2.36	
	3+	1.96	1.09-3.51	
Therapeutic surgery	Yes	Ref		<0.001
	No	6.85	4.90-9.58	

(OR – Odds ratio, CI – Confidence interval, ^a Charlson Comorbidity Score)

Appendix 2

Characteristics of women associated with stage at diagnosis and, univariate and multivariate logistic regression analyses for factors associated with early^a versus advanced^b stage for screening age^c women with newly diagnosed breast cancer

Characteristic	Total (N=1846)		Early ^a		Advanced ^b		Unadjusted			Adjusted		
	n	(%)	n	(%)	n	(%)	OR	95% CI	p	OR	95% CI	p
Screening status												
Screen detected	1064	(57.6)	766	(72.0)	298	(28.0)	Ref		<0.001	Ref		<0.001
Non-screen	782	(13.1)	251	(32.1)	531	(67.9)	5.41	4.42-6.63		5.30	4.32-6.49	
Ethnicity												
NZ European	1459	(29.3)	835	(57.2)	624	(42.8)	Ref			Ref		
Māori	311	(79.0)	146	(46.9)	165	(53.1)	1.51	1.18-1.93	0.001	1.26	0.97-1.65	0.085
Pacific	26	(16.8)	8	(30.8)	18	(69.2)	3.01	1.30-6.97	0.010	2.32	0.94-5.73	0.068
Other	50	(1.4)	28	(56.0)	22	(44.0)	1.05	0.60-1.86	0.863	0.94	0.50-1.73	0.831

(^a early stage = in-situ & stage I, ^b advanced stage = stages II, III & IV, ^c only cancers diagnosed from July 2004 onwards are included)

Appendix 3

Characteristics of women associated with stage at diagnosis and, univariate and multivariate logistic regression analyses for factors associated with early^a versus advanced^b stage for screening age^c women with newly diagnosed *invasive* breast cancer

Characteristic	Total (N=1548)		Early ^a		Advanced ^b		Unadjusted			Adjusted ^d		
	n	(%)	n	(%)	n	(%)	OR	95% CI	p	OR	95% CI	p
Screening status												
Screen detected	858	(55.4)	538	(62.7)	320	(37.3)	Ref		<0.001	Ref		<0.001
Non-screen	690	(44.6)	181	(73.8)	59	(26.2)	4.72	3.79-5.88		4.54	3.63-5.68	
Ethnicity												
NZ European	1220	(78.8)	596	(48.9)	624	(51.1)	Ref			Ref		
Māori	268	(17.3)	103	(38.4)	165	(61.6)	1.53	1.16-2.00	0.002	1.29	0.96-1.74	0.091
Pacific	24	(1.6)	6	(25.0)	18	(75.0)	2.86	1.13-7.26	0.027	2.24	0.84-6.01	0.101
Other	36	(2.3)	14	(38.9)	22	(61.1)	1.50	0.76-2.96	0.241	1.23	0.58-2.57	0.584

(^a early stage = stage I, ^b advanced stage = stages II, III & IV, ^c only cancers diagnosed from July 2004 onwards are included, d adjusted for age category, deprivation and residential status)

Appendix 4

Age and breast cancer biological characteristics at diagnosis compared between NZ European and Māori women.

Characteristic	NZ European (N=2304)		Māori (N=429)		p
	n (crude %)	<i>Age adjusted %</i>	n (crude %)	<i>Age adjusted %</i>	
ER/PR					
ER+	1884 (83.7)	84.5	334 (79.1)	80.6	0.011
ER-	366 (16.3)	15.5	88 (21.9)	19.4	
ER Unknown	54		7		

Appendix 5

Cox regression model for factors associated with breast cancer specific mortality

Characteristic	Univariate			Multivariate			Multivariate (Post 2005 only)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Ethnicity^a									
NZ European	Ref		<0.001	Ref		0.007			0.102
Māori	1.98	1.55-2.54		1.41	1.09-1.82		1.41	0.93-2.14	
T stage									
T1	Ref		<0.001	Ref		<0.001			<0.001
T2	3.33	2.56-4.33		2.21	1.67-2.92		3.91	2.11-7.23	
T3	8.68	6.01-12.5		3.99	2.68-5.94		5.35	2.51-11.4	
T4	18.6	13.8-25.1		4.60	3.17-6.65		5.94	2.93-12.1	
N stage									
N0	Ref		<0.001			<0.001			<0.001
N1	2.03	1.58-2.60		1.49	1.15-1.93		1.75	1.12-2.72	
N2+	4.04	3.01-5.42		3.03	2.41-3.92		3.42	2.41-5.26	
M Stage									
M0	Ref		<0.001			<0.001			<0.001
M1	15.4	12.2-19.4		5.04	3.09-6.71		5.32	3.55-8.01	
Mode of detection									
Non-screen	Ref		<0.001			<0.001			0.017
Screen	0.26	0.20-0.35		0.57	0.43-0.78		0.46	0.25-0.87	

Appendix 6

Multivariable model for factors associated with delay in chemotherapy longer than 90 days ^a

Delay in chemotherapy >90 days			
	OR	95% CI	p
Ethnicity			
NZ European	Ref		
Māori	1.41	0.66-3.03	0.291
Pacific	1.10	0.22-5.58	0.908
Other	0.82	0.10-6.78	0.853
Year of diagnosis ^b	1.37	1.11-1.61	<0.001
Re-excision	3.96	1.93-7.70	0.001
Surgical facility type	4.89	1.78-11.3	0.001
Distance from hospital	1.16	0.90-1.49	0.245

^a Adjusted for age, tumour stage, socioeconomic deprivation and comorbidity score, ^b Year categories as in Table 26.

Appendix 7

Multivariable logistic regression analysis for factors associated with use of adjuvant chemotherapy for invasive breast cancer.

Characteristic	OR	95% CI	p
Māori ethnicity	1.25	0.85-1.87	0.258
Age ^a	0.88	0.79-0.99	0.031
Year of diagnosis ^b	0.92	0.79-1.09	0.351
ER and/or PR positive	0.43	0.28-0.65	<0.001
Deprivation	0.96	0.85-1.28	0.527
Charlson score	0.30	0.20-0.45	<0.001
Hospital type	0.81	0.58-1.13	0.217
T stage	1.24	0.99-1.56	0.058
N stage	2.01	1.64-2.48	<0.001
Grade	2.24	1.70-2.93	<0.001
LVI	1.74	1.24-2.45	0.001
HER-2	1.27	1.11-1.45	<0.001

^a age categories as in Table 29, ^b year categories as in Table 29

Appendix 8

Characteristics associated with women undergoing mastectomy for whom details of decision process was available versus women for whom this information was unavailable

Characteristic	Total (N=751) n (%)	Decision known (N=600) n (%)	Decision not known (N=151) n (%)	p
Ethnicity				0.535
NZ European	599	474 (79.1)	125 (20.9)	
Māori	120	101 (84.2)	19 (15.8)	
Age (years)				0.113
<40	40	31 (77.5)	9 (22.5)	
40-49	142	115 (81.0)	27 (19.0)	
50-59	180	136 (75.6)	44 (24.4)	
60-69	148	118 (79.7)	30 (20.3)	
70-80	155	130 (83.9)	25 (16.1)	
80+	86	70 (81.4)	16 (18.6)	
Deprivation				0.392
Dep 1-2	81	71 (87.3)	10 (12.3)	
Dep 3-4	73	59 (80.8)	14 (19.2)	
Dep 5-6	187	150 (80.2)	37 (19.8)	
Dep 7-8	217	172 (79.3)	45 (20.7)	
Dep 9-10	193	148 (76.7)	45 (23.3)	
Hospital type				0.549
Public	530	427 (80.6)	103 (19.4)	
Private	221	173 (78.3)	48 (21.7)	
T stage				0.654
T1	353	285 (80.7)	68 (19.3)	
T2	398	315 (79.1)	83 (20.9)	
Charlson score				0.311
0	591	466 (78.8)	125 (21.2)	
≥1	160	134 (83.8)	26 (16.2)	

Appendix 9

Characteristics associated with women undergoing major breast reconstruction following mastectomy for breast cancer in Waikato 1999-2012 ^a

Characteristic	Total	Sentinel node biopsy	Adjusted		
	(N=1910)	(N=263)	OR	95% CI	p
n (%)	n (%)				
Ethnicity					
NZ European	1584 (83.0)	873 (55.2)	Ref		
Māori	258 (13.4)	143 (55.4)	0.81	0.57-1.14	0.237
Pacific	24 (1.3)	9 (37.5)	0.38	0.18-1.14	0.060
Other	44 (2.3)	22 (50.0)	0.53	0.25-1.11	0.094
Age (years)					
<40	78 (4.1)	34 (43.6)	0.63	0.35-1.15	
40-49	369 (19.3)	211 (57.2)	Ref		<0.001
50-59	545 (28.5)	313 (57.4)	1.18	0.85-1.64	
60-69	525 (27.6)	323 (61.3)	1.04	0.74-1.45	
70-80	281 (14.7)	127 (45.4)	0.59	0.40-0.90	
80+	112 (5.9)	41 (36.6)	0.38	0.22-0.68	
Deprivation					
Dep 1-2	200 (10.5)	123 (61.5)	Ref		0.552
Dep 3-4	209 (11.0)	108 (51.7)	0.70	0.42-1.15	
Dep 5-6	479 (25.1)	271 (56.7)	0.92	0.61-1.39	
Dep 7-8	554 (29.0)	297 (53.7)	0.85	0.55-1.24	
Dep 9-10	468 (24.5)	248 (53.0)	0.93	0.61-1.44	
Hospital type					
Public	1306 (68.3)	680 (52.1)	Ref		<0.001
Private	604 (31.7)	367 (60.8)	1.82	1.42-2.35	
Year of diagnosis					
1999-2002	394 (20.6)	84 (21.3)	Ref		<0.001
2003-2006	574 (30.0)	219 (38.2)	2.27	1.66-3.11	
2007-2009	453 (23.7)	330 (73.0)	13.9	9.81-19.8	
2010-2012	489 (25.6)	414 (84.7)	35.3	21.9-47.6	

T stage					
T1	1232 (64.5)	785 (63.8)	Ref		<0.001
T2	678 (35.5)	262 (38.6)	0.26	0.20-0.32	
Charlson score					
0	1626 (85.2)	918 (56.5)	Ref		
≥1	284 (14.2)	139 (48.9)	0.76	0.53-10.5	0.101

Appendix 10

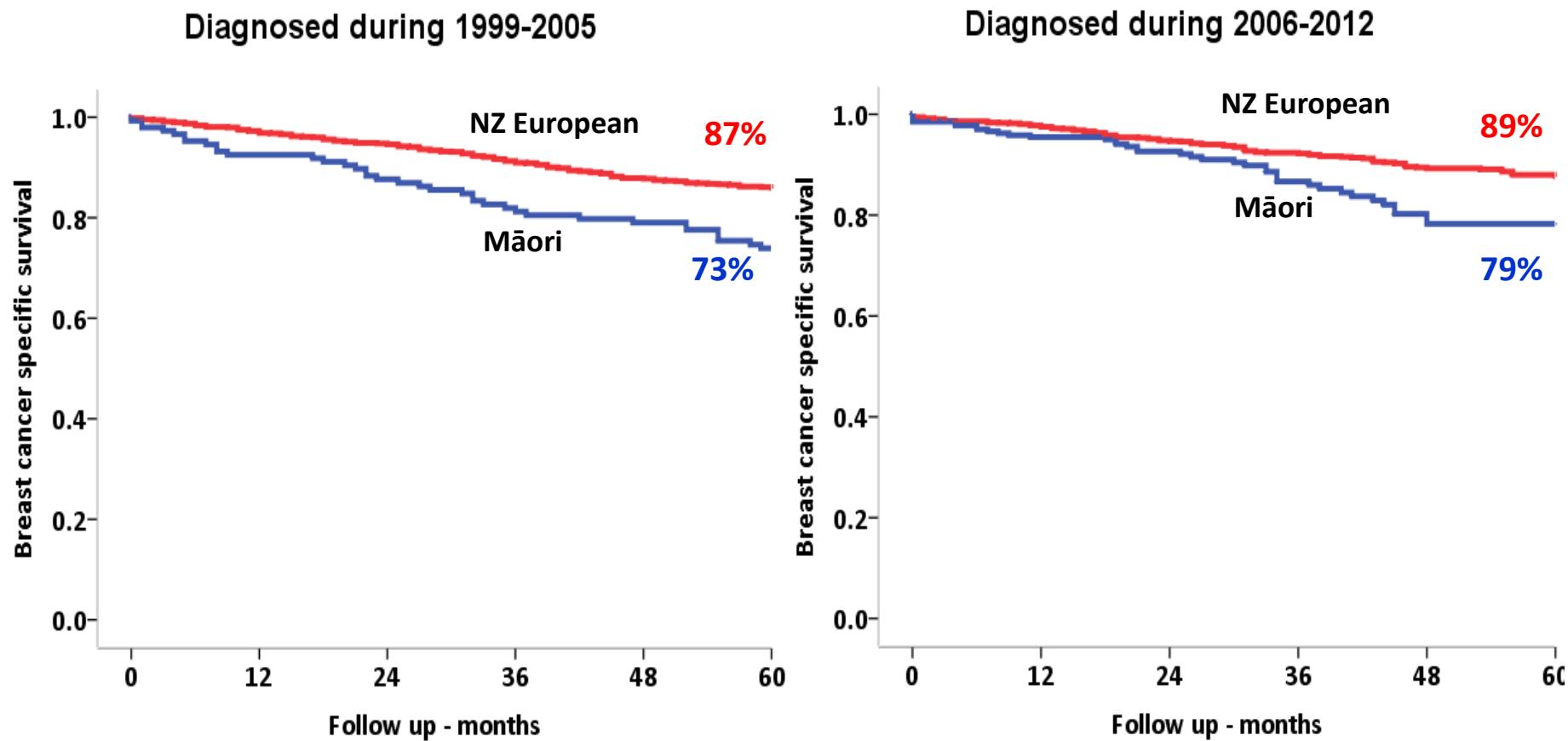
Hazard ratios for breast cancer-specific mortality risk in Māori compared with NZ European women with stepwise adjustment for demographics, screening status, disease factors, treatment factors, patient factors and healthcare access.

Characteristics	Overall HR (95% CI)
Unadjusted	1.81 (1.43-2.30)
Model A (Baseline - adjusted for age and year of diagnosis)	2.02 (1.59-2.58)
Model B (Model A + Healthcare access factors)	
Socioeconomic deprivation	1.91 (1.49-2.46)
Urban / rural residency	1.92 (1.49-2.46)
Public / private treatment	1.80 (1.39-2.32)
Model C (Model B + Screening status)	1.60 (1.24-1.98)
Model D (Model C + Cancer stage at diagnosis [TNM])	1.36 (1.04-1.78)
Model E (Model D + Cancer biological factors)	
ER/PR, Grade & HER-2	1.31 (1.01-1.71)
Model F (Model E + Treatment)	
Completion of definitive local therapy	1.24 (0.94-1.63)
Use of systemic therapy ^a	1.21 (0.92-1.60)
Delay in surgery or adjuvant therapy ^b	1.19 (0.91-1.51)
Model G (Model F + Patient factors)	
Comorbidity index score	1.16 (0.88-1.48)
Smoking	1.12 (0.84-1.46)
BMI	1.07 (0.81-1.41)

^a chemotherapy and endocrine therapy, ^b delay in surgery or delays in initiating chemotherapy or radiation therapy

Appendix 11

Time trends in 5-year breast cancer survival rates by ethnicity during 1999-2012



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