Audit of Grade 3 Breast Cancer in New Zealand Women

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I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signed

Date: 30.11.18

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Abstract

Breast cancer is the most common cancer in New Zealand women, accounting for approximately 3000 new registrations per year, affecting one in nine women and resulting in more than 600 deaths annually. The survival rate for breast cancer is dependent on multiple factors. These can include patient factors, tumour biology and resource-related factors such as access to health interventions.

This study analysed data of selected prognostic factors of grade 3 tumours over a 5-year period from 1st January 2011 to 31st December 2015 from four Breast Cancer Registries (Auckland, Waikato, Christchurch, and Wellington).

The study of 2667 women found that subjects in the older age group of >70 years were at increased risk of five-year mortality. Of the ethnicity groups, the Pacific Islander group were at increased risk, whereas the Māori group were at decreased risk. Histology type showed no statistically significant difference, whereas the molecular subtypes HER2 enriched and TNBC subjects were at increased risk. The study also showed that NZ Europeans presented the largest proportion of HER2 enriched and TNBC and the subjects from these two molecular subtypes were at increased risk of five-year mortality. In addition, analysis of the hormonal receptors showed that ER-negative, PR positive group were at increased risk and in contrast, the ER/PR positive group were at decreased risk. Subjects from stages II, IV and X were at increased risk, however, subjects from stage III were approaching significance.

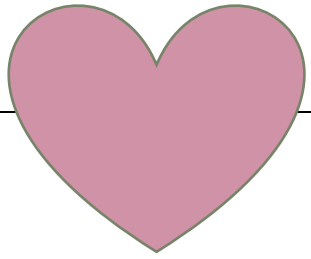
From the analysis, it can be noted that the survival rates for Grade 3 breast cancer vary across the selected prognostic factors and therefore it can be summarised that the survival of this disease is dependent on multiple factors. These factors can include patient factors, tumour biology and resource-related such as access to health interventions.

Grade 3 is heterogeneous cancer and this study has shown that despite being high grade, not every patient has a poor outcome. Therefore, survival has to be combined with other factors such as biological and potentially socioeconomic factors associated with this disease.

The results of this study make an initial contribution to the understanding of high-grade malignancy. The selected prognostic factors were used primarily as a preliminary study into the overall survival of this disease. The inclusion of other prognostic factors would potentiate further studies into this aggressive cancer. Such studies should be supported in order to gain better understanding and establishment of measures for the prediction of survival with grade 3 breast cancer in New Zealand women.

Chapter 1

General Introduction



1.1 Introduction

Breast cancer is the most common cancer for women worldwide and the disease has a considerable impact on our society.

Studying and finding new approaches to the treatment of breast cancer has been the focus of many researchers since the early 1900s. These new approaches include proteomic analysis of breast cancer and the use of nanotechnology in the treatment of this disease (Wulfkuhle et al. 2001; Yezhelyev et al. 2006). The benefits of research have helped more people survive from breast cancer now than ever before. Whilst in the 1970s, only a quarter of people survived, with recent improvements such as the use of tomosynthesis (digitally enhanced x-ray image) in detection and treatment in the field of breast cancer, more women survive for at least ten years (www.cancerresearchuk.org n.d).

New Zealand (NZ) is amongst the countries with high prevalence of breast cancer, as shown in Figure 1.3, with approximately 3000 new registrations per year, affecting one in nine women and resulting in more than 600 deaths annually ('Breast Cancer Aotearoa Coalition' 2018). It is of great value to understand the behavior of these often-aggressive cancers in order to establish an appropriate treatment and potentially improve the survival rate of these women.

This study seeks to analyse data of grade 3 breast cancer which is considered as a heterogeneous group of high-grade breast cancer from the New Zealand Breast Cancer Register (NZBCR) with an attempt to stratify its impact in NZ.

The results should make an initial contribution to the understanding of this selected heterogeneous high-grade group. A limited range of common prognostic factors deemed relevant for this thesis has been selected, primarily as a preliminary study understanding the behavior of this group. Whilst there are other prognostic factors which would be deemed just as relevant, its inclusion is beyond the scope of this thesis, but may form the scope of further studies into this aggressive cancer.

1.2 Purpose of this study

This study will analyse grade 3 breast cancer (as a stand-alone group) over the period 2011 to 2015, using data from the NZBCR. Linkage with limited follow up data will assess survival in this group of patients.

An analysis of breast cancer register data will not only increase insight into this often-aggressive group but also contribute to improved future patient management. The results from this study will also provide a basis for: 1. continuation and additional data fields studying grade 3 breast cancer register, 2. assist to assess the need to reshape treatments and 3. help identify specific factors for improved patient management of grade 3 breast cancer in NZ.

Survival rates for breast cancer are dependent on multiple factors. These can include patient factors, tumour biology and resource-related such as access to health interventions.

For this study, five prognostic factors that include, breast cancer subtype (molecular and histological) which includes hormone receptor markers, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factors 2, (HER2) status, stage at diagnosis, age at diagnosis and ethnicity will be examined. It is important to look at these factors in the NZ context and appraise similarities and differences internationally for treatment decisions.

A grade is a "score" that indicates how different the cancer cells' appearance and growth patterns are under a microscope when compared to those of normal breast cells. For breast cancer, the Nottingham modification of the Bloom-Richardson scale is most commonly used (Rakha et al. 2010). This grading scale looks at 3 different microscopic cell features and gives each of them a score from 1-3. The scores from each of these features are added up to give a total score, which indicates the tumour grade as shown in Table 1.1.

Table 1.1. Nottingham modification of the Bloom-Richardson scale used for grading breast cancer

Grade	Total Score	Description
1 (low)	3 to 5	The cancer cells are well differentiated. They look almost like normal cells.
2 (intermediate)	6 or 7	The cancer cells are moderately differentiated. They are between grades 1 and 3
3 (high)	8 or 9	The cancer cells are poorly differentiated or undifferentiated. They look less normal, or more abnormal than healthy cells.

Source: www.ccrcal.org

In general, a lower grade indicates slower-growing cancer and a higher grade indicates a faster-growing one.

Previous studies using NZBCR have analysed grade 3 breast cancer in conjunction with other grades and types but have not examined grade 3 breast cancer as a standalone group. Thus, this study will be unique in detailing chosen prognostic factors within grade 3 breast cancer highlighting their role in survival.

1.3 Overview of chapter 1

This chapter comprises of 4 subheadings. The introductory chapter outlines: 1. the purpose of this study, incidence/prevalence, and epidemiology, (survival rates), 2.a summary of normal and neoplastic breast histology (pathology), 3. ethnicity, (NZ context), 4. discussion of prognostic factors selected and the rationale behind this.

Incidence/Prevalence and Epidemiology

The origin of breast cancer can be traced back to ancient Egypt dating back 2500 B.C, with the earliest recorded case described in the Edwin Smith Papyrus. In its advanced state, breast cancer was obviously visible enough for the experts for that time to warrant a need to record it (Lakhtakia 2014). Since then, breast cancer has left its mark worldwide.

Breast cancer today is the most common cancer for women in 76% of the listed 184 countries worldwide and the third most common cancer overall, which makes this the only cancer that is common among women in all regions of the world (Ferlay et al. 2015; Globocan 2012).

On a global scale, estimates of breast cancer incidence have increased by more than 20% and the mortality has increased by 14%. According to epidemiological studies (Globocan 2012), approximately 1.67 million women were diagnosed with breast cancer with an estimated 522,000 related deaths in the vast majority of the countries worldwide. Approximately, 53% of new cases diagnosed occurred in economically developing countries, which represents about 82% of the world population. These numbers showed an increase in breast cancer incidence and related mortality by nearly 18 % from 2008 (Globocan 2012). According to the World Cancer Report, which is (the most comprehensive global examination of the disease to date), cancer rates could further increase by 50% to 15 million new cases in the year 2020. It has also been predicted using population forecasting and statistical methods, that the worldwide incidence of female breast cancer will reach approximately 3.2 million new cases per year by 2050 (Globocan 2012; Tao et al. 2015). Using the same prediction tools, the US alone is estimated to have a 50% increase and Australia/New Zealand has been predicted to have an increase by an estimated 44% by 2035 from 2012.

The data from (Globocan 2012) indicates that the burden of breast cancer worldwide may not be evenly distributed. There are large variations in the incidence, mortality, and survival between different countries and regions, including within specific regions as shown in Figure 1.1, Figure 1.2, and Figure 1.3.

As shown in Figure 1.1 and Figure 1.3, worldwide incidence and prevalence rates for breast cancer vary, high in Northern America, Australia/New Zealand, and Northern and Western Europe; intermediate in Central and Eastern Europe, Latin America, and the Caribbean; and low in most of Africa and Asia. The incidence rates vary by a factor of nearly 4 (Botha et al. 2003). Similarly, statistics show that rates (per 100,000) ranging from 27 cases in central Africa and in eastern Asia to 96 cases in Western Europe and the incidence ranges from 19.4 per 100,000 in East Africa to 89.7 per 100,000 in Western Europe (WHO 2015). Breast cancer incidence in developed countries is greater than in less developed countries, however, the mortality is greater in less developed countries (Ghoncheh et al, 2016).

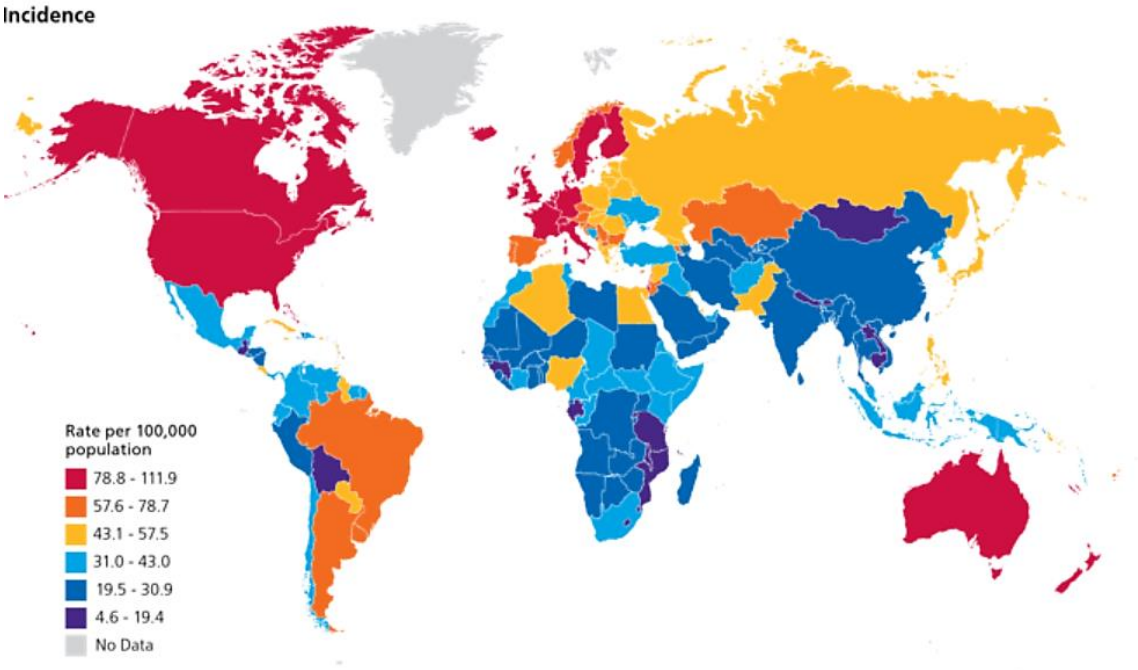


Figure 1.1. Breast Cancer global incidence. Per 100,000, age-standardized to the World Standard Population. Source: Globocan 2012 (IARC)

Similarly, there is variation in mortality rates worldwide as shown in Figure 1.2 and Figure 1.3. Variation may be seen due to better survival in the (high-incidence) developed regions (Globocan 2012).

Breast cancer is a leading cause of cancer death predominantly in less developed countries potentially related to a lack of screening, health resources, and to clinical advances in treatment not available to women (Botha et al. 2003; Clegg et al. 2009; Donnelly 2006; Ferlay et al. 2015; Ghoncheh, Pournamdar, and Salehiniya 2016). In contrast, developed countries have shown a decrease in breast cancer mortality (Ferlay et al. 2010; Jemal, Ward, and Thun 2007; Torre et al. 2015).This could be potentially related to earlier detection, screening, available resources, and improved therapy.

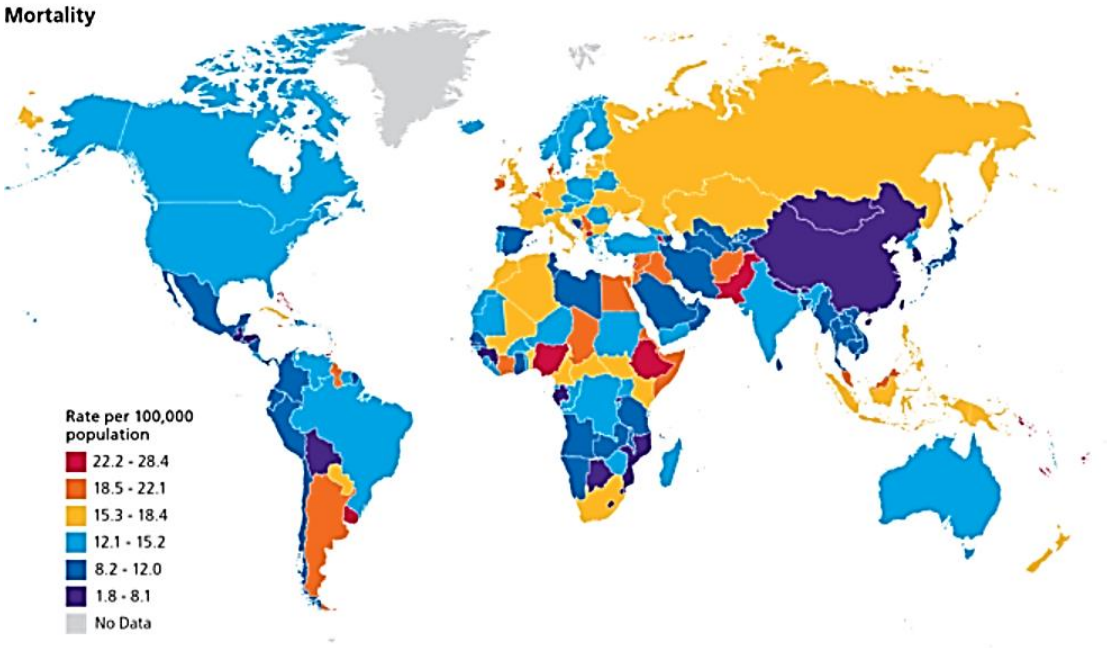


Figure 1.2. Breast Cancer global mortality. Per 100,000, age-standardized to the World Standard Population. Source: Globocan 2012(IARC)

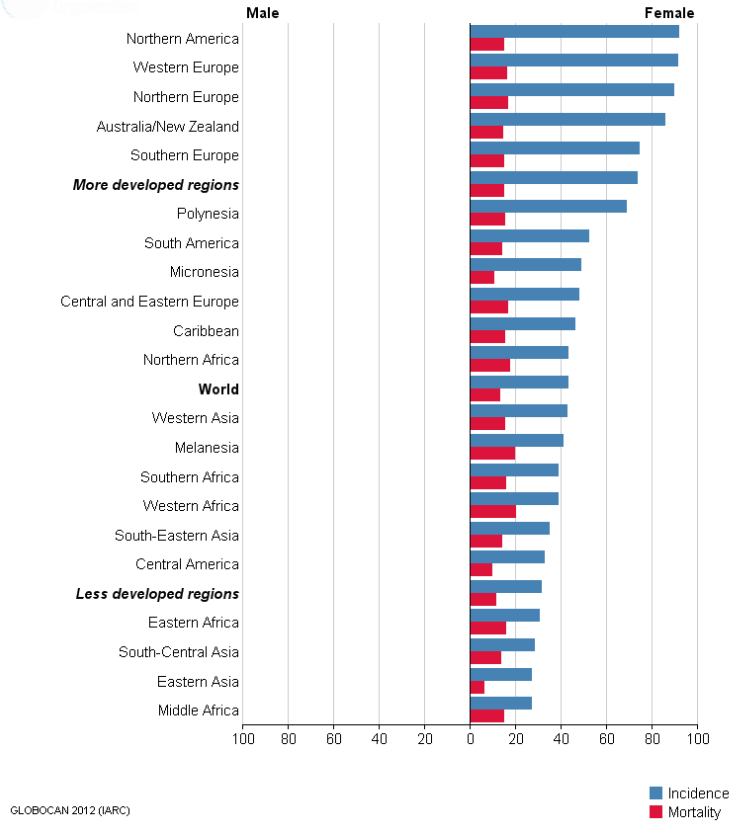


Figure 1.3. Breast cancer Incidence and Mortality rates by world area (Globocan 2012)

In the general US population, based on 2012-2014 data, there is a 12.4% lifetime risk of women developing cancer at some point during their lifetime (Hortobagyi et al. 2005; SEER Cancer Statistics Review). The risk of women developing breast cancer increases with age where 5% of all breast cancers occur in women under 40 years of age (Han and Kang 2010). This will be further discussed in chapters 1 and 2.

In NZ, breast cancer is the most common cancer for women resulting in more than 600 deaths per year (Ministry of Health 2015). According to recent surveys, approximately 3000 breast cancer cases are diagnosed each year, of which less than 1% are in males. In NZ, breast cancer incidence affects 1 in 9 women over their lifetime. In 2014 alone, 23,023 new cancer registrations were recorded of which 3020 were breast cancer (www.breastcancer.org.nz n.d). The 5-year survival (the probability for an individual surviving at 5 years from the date of diagnosis), is better if cancer is detected early, but unfortunately, approximately 600 will die every year.

There are multiple factors that underlie variations in incidence, prevalence, and mortality. These include age at diagnosis, ethnicity, lifestyle, geography, socioeconomic status, hereditary risk factors, disease grade, and stage, and access to high-quality care (Hortobagyi et al. 2005). Due to the limitations of this thesis format, only a small number of prognostic factors have been selected to be discussed: For example; cancer subtype (molecular and histological differentiation) including hormone receptor marker status, (ER, PR, immunohistochemistry HER2) protein expression, stage of disease, age at diagnosis and ethnicity will be discussed/evaluated.

1.3.1 Anatomy of the breast

The breast (as shown in Figure 1.4) is an organ that functions to produce milk for lactation. There are two main components that make up the breast structure: the epithelial and stromal components.

The epithelial component consists of ducts and lobules. In an adult female breast, there are 15-20 lobes in each breast and each lobe has 20-40 lobules. The lobular cells have a secretory function to produce milk. Milk secretions are transported from the lobules to the nipple via a series of ducts. These ducts increase in caliber incrementally from the lobules to the nipple.

The stromal component is for support. It is made up of fat, breast tissue, along with nerves, veins, arteries, and connective tissue.

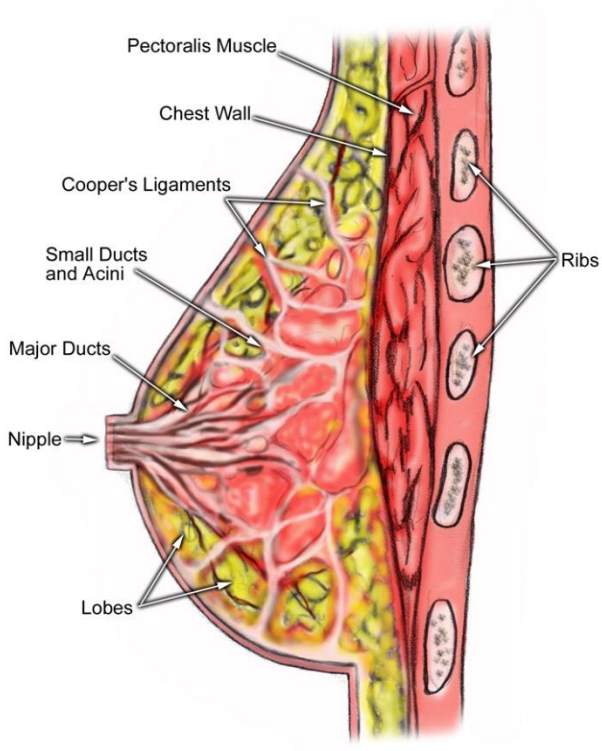


Figure 1.4. Anatomy of the breast showing the location of ducts and lobules
Source: (Gabriel 2016)

Cancer in the breast can arise as monophasic tumours from the epithelial and stromal components or as biphasic tumours, with the former being most common. The cancers arising from the epithelial components are categorized as carcinomas. These carcinomas develop because of genetic or epigenetic mutations of the genes responsible for regulating the normal growth of glandular cells.

The tumours are classified into '*in-situ*' (defined to the luminal space) or 'invasive' (extending into surrounding stroma as depicted in the diagram in Figure 1.5).

The most common subtype's of carcinomas of the breast are ductal or lobular, originally on the basis of the site of origin, but now are based on morphology and biologic characteristics.

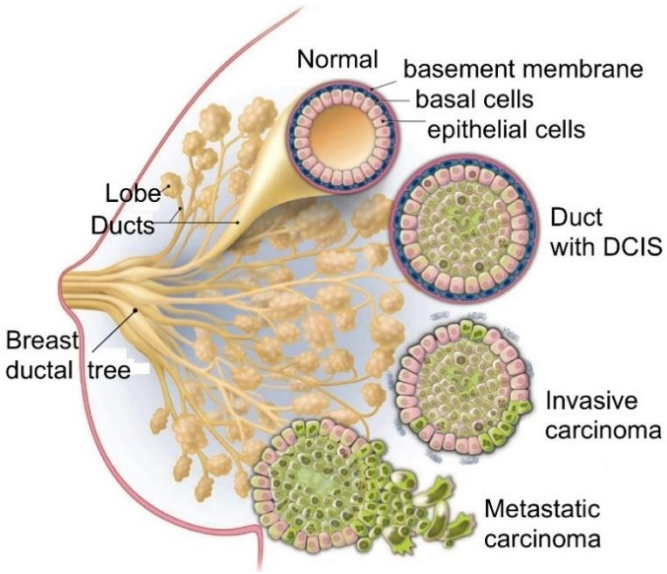


Figure 1.5. Anatomy of breast showing *in situ* and invasive carcinoma
Source: (CapeRay 2018)

Infiltrating ductal carcinoma (IDC) is the most common subtype accounting for 70-80% of all invasive lesions (Bleiweiss, Chagpar, and Duda 2013; Malhotra et al. 2010), followed by lobular carcinoma accounting for 10-15%, (Arpino et al. 2004; Lakhani et al. 2012). Ductal carcinoma differs from lobular carcinoma with regard to biologic behavior, cell morphology, and architecture pattern, growth and radiologic features (Deici et al. 2014). There are other less frequent histologic subtypes such as papillary, medullary, apocrine, mucinous, tubular and phyllodes carcinomas, which will not be discussed in this thesis. The distinctions between these two types of carcinomas are primarily based on the growth pattern and the adhesion molecules of the lesions (Bleiweiss, Chagpar, and Duda 2013). The purpose of identifying the histologic type is to predict the likely behavior of its response to therapy.

The analysis for this study will only report on ductal and lobular carcinomas and other carcinoma subtypes will not form part of this study.

1.3.2 Prognostic factors

The selected prognostic factors such as; 1. Molecular subtype, 2. Estrogen receptor positive/negative breast cancer (luminal subtype), 3. Progesterone receptor positive/negative breast cancer (luminal subtype), 4. HER2 positive/negative breast cancer, 5. Triple negative breast cancer (TNBC), 6. Stage at diagnosis, 7. Age at diagnosis, 8. Ethnicity will be briefly introduced in this chapter. However, they will be discussed in detail in chapter 2.

1.3.2.1 Molecular subtype

Breast carcinomas constitute a heterogeneous group of lesions (Corban 2013). Their microscopic appearance, biological behavior, and responsiveness to therapy differ. The biologic behavior characterized by variation in the gene expression pattern when using DNA microarrays, provide a distinctive molecular portrait of cancer (Perou et al. 2000). Thus, tumours are classified into

subtypes distinguished by the difference in their gene expression pattern. The molecular subtypes of breast cancer may be therefore useful in treatment strategies and developing new therapies.

The four major molecular subtypes in breast cancer have been determined by gene profiling, and these include: 1. Luminal A, 2. Luminal B, 3. Triple negative/basal-like and, 4. HER2 type. Biomarkers including Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Receptor 2 (HER2) can be used as a surrogate to classify breast cancer. The status of these biomarkers is established by the amount i.e. the percentage (%) and the expression or intensity of the nuclear staining with its appropriate antibody using Immunohistochemistry (IHC) studies (detecting antigen with antibodies on cancer tissue samples).

The effect of each of these subtypes along with other prognostic factors on survival will be discussed in this chapter. The other less common subtypes however will not form part of this discussion.

1.3.2.2 Estrogen receptor positive/ negative breast cancer (Luminal subtype)

The growth, development, and regulation of the female breast are dependent on estrogen hormone. Normal breast ductal and lobular cells contain estrogen receptors to bind the hormone. There are four major naturally occurring estrogens in women; estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). Estradiol is the predominant estrogen during reproductive years and in this research we will refer to Estradiol as estrogen. It also plays a vital role in the pathogenesis and development of breast cancer. The risk of the disease is linked to the duration of exposure to the endogenous (produced within body cells) and exogenous (outside source such as hormone replacement therapy) estrogen (Morgan, Refalo, and Cheung 2011b).

Since the recognition of the role of estrogen in breast cancer, studies have shown that ER status is the most important predictive and prognostic biomarker (Bouchard-Fortier et al. 2017). ER has been used to establish the degree of differentiation of breast cancer and hence it provides a rationale for the observed differences in the biological behavior (response of disease to estrogen therapy) between the ER-positive and ER-negative breast cancers (Morgan, Refalo, and Cheung 2011a).

The hormone receptors are proteins that are expressed both in the epithelium and in breast stroma which bind to circulating hormones which then mediate their cellular effects (Polyak 2011). These receptors are tested on cancer tissue samples using immunohistochemistry (IHC) techniques and the status is determined by percentage (%) of positive or negative staining (of the brown colored nuclear/membrane), shown in Figure 1.6).

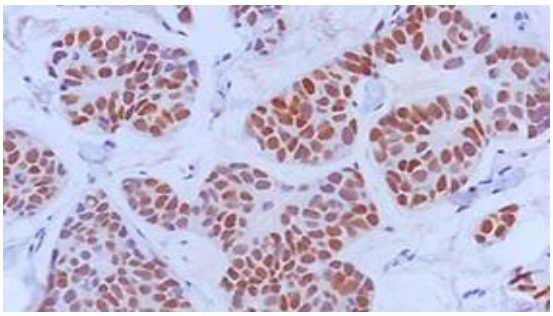


Figure 1.6. ER-positive cells – nuclear staining

About two-thirds of breast cancers are ER-positive and one third are ER-negative. ER-positive breast cancer is the most common subtype of breast cancer. Both subtypes are heterogeneous regarding their clinical behavior (progression of the disease) and response to therapies, (Loi et al. 2008; Turner et al. 2017).

Estrogen receptor positive breast cancers have shown to be predictive factors for response to endocrine therapy and are associated with a survival benefit (Bouchard-Fortier et al. 2017; Morgan, Refalo, and Cheung 2011a). There is a current disparity surrounding ER-negative tumours, especially when both the hormones status of ER and PR are compared (Shen et al. 2015), therefore it is important to have an understanding of this.

Of the luminal subtype, luminal A is the most common subtype which represents 50-60% of all breast cancers. This subtype is defined as ER-positive and/or PR-positive with negative HER2. These cancers often are low grade and have a good prognosis. They are characterized by high levels of ER and low levels of proliferating genes, hence the treatment is mainly based on hormonal therapy (Guarneri and Conte 2009; Kennecke et al. 2010). Of the four subtypes, luminal A cancers tend to have the best prognosis, with fairly high survival rates and low recurrence rates (Carey et al. 2006).

1.3.2.3 Progesterone receptor positive /negative breast cancer (Luminal subtype)

Progesterone is an endogenous steroid and, like Estrogen, is a sex hormone involved in the female reproductive system. Similar to ER, the expression of PR is a very powerful and an important prognostic indicator and a useful predictor of likely response to hormonal therapy (Ahmed et al. 2017; Badowska-Kozakiewicz et al. 2015; Carracedo et al. 2012).

Both ER and PR studies are carried out simultaneously using immunohistochemistry techniques for establishing the hormone receptor status. Different types of breast cancers will have a different hormone receptor status. This status influences breast cancer survival. The ER and PR profiling are also used as surrogates for gene profiling tumours into Luminal A and Luminal B, with the latter having a worse survival (5 and 10 years).

Luminal B subtype accounts for roughly 10-20% of all breast cancers and is distinguished by ER+ and/or PR-/HER2+ status. It has a more aggressive phenotype, grade 2 or 3, and a worse

prognosis (Creighton 2012; Ehinger et al. 2017). This subtype has a lower survival after relapse compared to luminal A breast cancers (Ellis et al. 2008). The main difference between luminal A and luminal B are the increased expression of proliferation and growth related receptor genes in luminal B (Reis-Filho et al. 2010). Approximately, 30% of HER2 positive cancers are classed as luminal B subtype (Loi et al. 2009). However, approximately 6% of luminal B subtype are negative for both ER and HER2 (Yersal and Barutca 2014). This explains the poorer outcome with hormonotherapy for this subtype when compared to luminal A (Paik et al. 2004; Rouzier et al. 2005)

1.3.2.4 HER2 positive/negative breast cancer

Human epidermal growth receptor 2 (HER2) gene and resulting protein control the growth of normal cells in all organs in the body. There are four subtypes (HER1, HER2, HER3, and HER4). HER2 is the common ligand partner for HER1 and HER4 to initiate the growth cycle and is therefore targeted in testing and therapy.

Several names have been given for this growth factor, for example; c-erb-2, cerbB-2, c-erbB-2, HER2, HER2/neu, ERBB2, erbB2, erbB2, neu/c-erbB2/oncogene neu, neu protein, and neu (Rubin and Yarden 2001). For this thesis, the term ‘HER2’ will be used.

In 15-20% of breast cancers, the HER2 gene is amplified resulting in protein overexpression. This overexpression allows the breast cells to grow in an uncontrolled manner (Goldhirsch et al. 2013; Tan et al. 2009). HER2 testing is performed into two modalities:

I. Immunohistochemistry – the protein on the membrane is stained with a HER2 antibody. The completeness of membrane staining and the intensity are used for scoring according to ASCO guidelines (Wolff et al. 2013). 0 or 1+ are regarded as “normal” and are HER2 negative, 2+ showing incomplete linear staining are equivocal and 3+ showing a complete linear staining in the >10% of tumour cells where the HER2 protein reside are HER2 positive as shown in Table 1.2 and Figure 1.4.
II. *In situ* hybridization (ISH) either with fluorescent (FISH) or silver (SISH) are performed on equivocal, 2+ IHC membrane staining. ISH measures the gene copy number and if amplified will mark a tumour as HER2 positive. Non-amplified tumours are HER2 negative.

Table 1.2. IHC HER2 scoring criteria

Method	Negative	Equivocal	Positive
IHC	No staining or faint, barely perceptible staining	Incomplete and/or weak to moderate membrane staining >10%, or uniform intense membrane staining ≤10%	Uniform intense membrane staining >10%

Source: (Carlson et al. 2006)

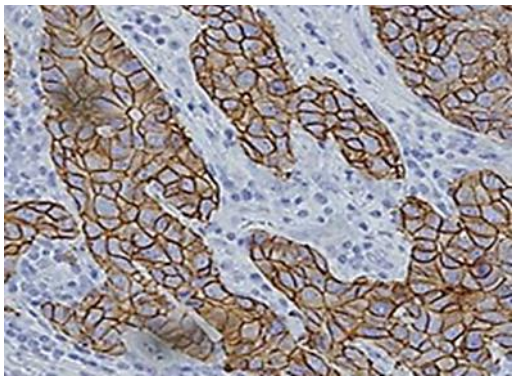


Figure 1.7. HER2 positive cells showing complete membrane staining in >10% of tumour cells

The tumours that are HER2 positive and are ER/PR negative are classified as HER2 enriched. Those that are ER/PR positive and HER positive are classified as luminal B tumours.

The results of the hormone receptor and the IHC HER2 test will help identify patients who will benefit from targeted therapy i.e. treatment with trastuzumab (Ulaner et al. 2016). Multiple treatment options are available for HER2 positive tumours.

1.3.2.5 Triple-negative breast cancer (TNBC)

Triple-negative breast cancer (TNBC) is a heterogeneous group. Some express basal markers (basal phenotype) and some express Claudin 1 (protein-coding gene). For the purpose of this study, all tumours that do not express ER/PR/HER2 will be termed ‘TNBC' and will not be further subclassified.

Since these cancers do not contain receptors for estrogen, progesterone, and HER2, they therefore cannot be treated with hormone or HER2 blocking therapies, therefore they lack effective target therapy. However, TNBC can be treated with chemotherapy, radiation and non-HER2 target therapy (Gluz et al.2009; Uscanga-Perales et al.2016).

1.3.3 Stage at diagnosis

The staging of breast cancer is important for its prognostic significance in determining the treatment plan. The tumour stage defines tumour aggressiveness and in combination with the other factors mentioned above, are associated with breast cancer survival (Narod, Iqbal, and Miller 2015).

The American Joint Committee on Cancer TNM classification scheme is used for staging breast cancers (Edge, Byrd, and Compton 2009). Staging defines the anatomic extent of disease and is based on three components: T- the size of a primary tumour, N- the absence or presence and extent of regional lymph node involvement and M- the absence or presence of distant metastasis.

Staging identifies whether breast cancer is an early stage or advanced disease. The early stage disease has a high 5-year survival rate when compared to an advanced stage, where the survival

sits low (72%) (www.cancer.org, n.d; www.gco.iarc.fr, n.d). The most advanced stage occurs when the disease has metastasized to multiple distant sites. This advanced stage occurs in less than 10% of breast cancer patients and is generally considered a heterogeneous group and have a poorer prognosis (Djordjevic, Karanikolic, and Pesic 2004; Bergman et al. 1991; Cluze et al. 2009). The heterogeneity of this advanced stage cancer is influenced by several prognostic factors, such as receptor status, HER2 status, and the location and the extent of the disease (Bergman et al. 1991). The Stage of the disease, together with the other prognostic factors e.g. (hormone receptor status), HER2 status, age at diagnosis, and grade; influence treatment modalities and outcome. The TNM classification is used as a measure of anatomical staging as shown in Table 1.3.

Table 1.3: Staging of Breast cancer

Stage	Tumour (T)	Node (N)	Metastases (M)
Early Breast cancer (Stage I or II)	T 1-2 Tumour up to 5 cm	N0- None N1- Up to 3 nodes are involved	No metastases
Locally Advanced (Stage III)	Any size	N2- 4 or more nodes, or fixed nodes N3- Nodes other than in axilla	No metastases
Metastatic (Stage IV)	Any size	Any Nodes	metastases

Source: (Singletary et al. 2002)

1.3.4 Age at diagnosis

Age, at the time of diagnosis, affects breast cancer survival. The risk of breast cancer increases with age (as shown in Figure 1.8, Figure 1.9, and Figure 1.10), with only 5% of all breast cancers occurring in women under 40 years of age (Han and Kang 2010). Younger women tend to develop a more advanced disease and poorer prognosis than older women. For younger women, the poor prognosis may be due to a presentation with higher-grade, tumours that tend to be more aggressive and less likely to be hormone receptor positive. This means that breast cancer may not respond well to treatment (Kocic et al. 2011; Korkola et al. 2003; Liukkonen et al. 2011).

The incidence of breast cancer is increasing particularly among women aged 50-64, due to breast screening compliance in this age group (McPherson, Steel, and Dixon 2000). Knowledge of breast cancer incidence and prevalence is essential to continue the management of this disease.

Age at diagnosis will be linked to intrinsic molecular subtype (histological type) and the stage to assess the survival of women with grade 3 breast cancer in New Zealand.

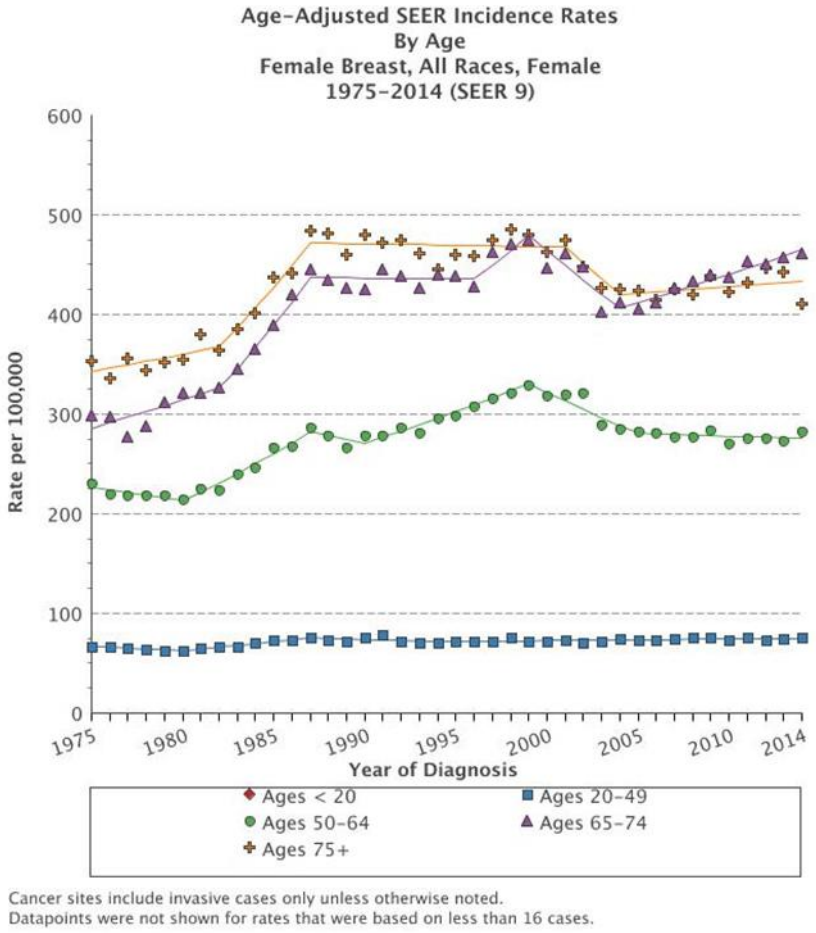


Figure 1.8. Age-adjusted incidence rate of female breast cancer of all races in the US, 1975-2014
Source: (NCI, 2018)

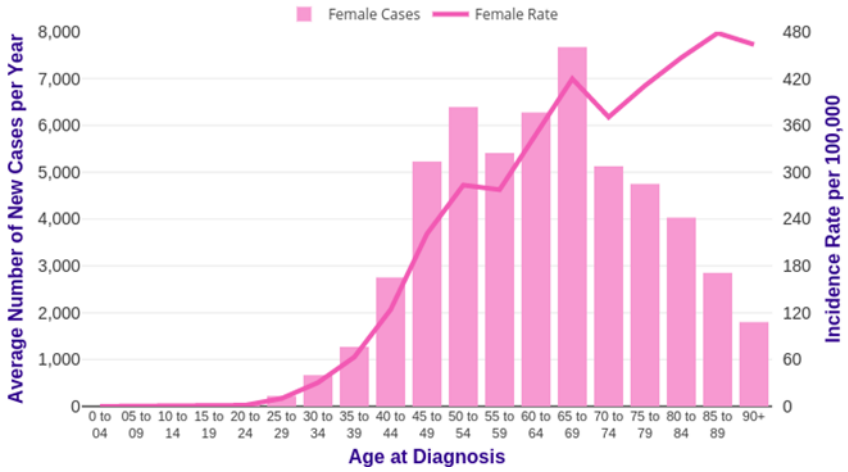


Figure 1.9. Age-adjusted incidence rate of female breast cancer of all races in the UK, 2013-2015
Source: (Cancer 2018)

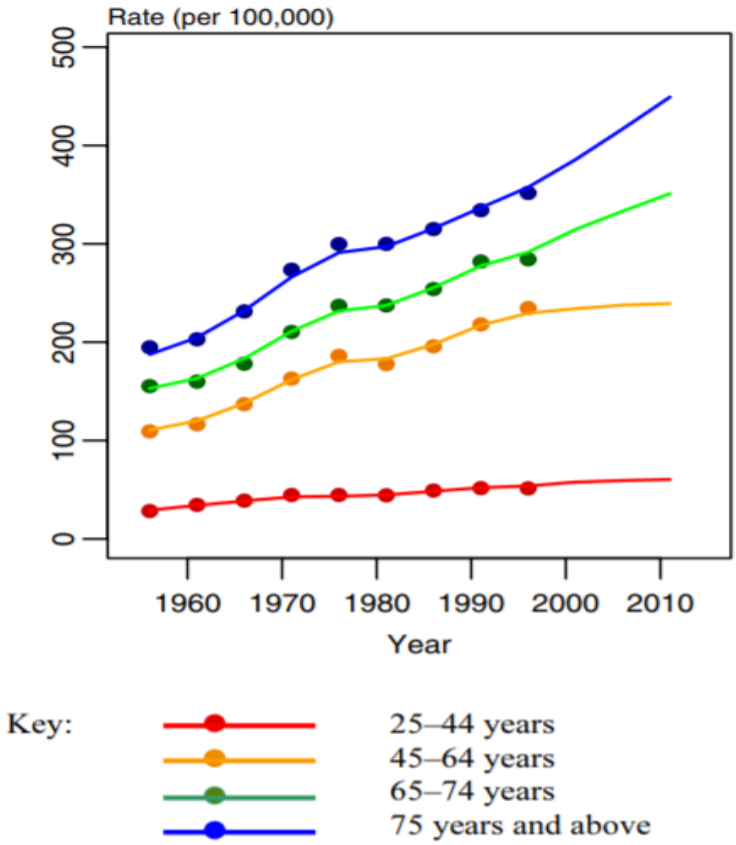


Figure 1.10. Age-adjusted incidence rate of female breast cancer of all races in NZ, 1960-2010
Source: (Tobias, Hodgen, and Cheung 2002)

1.3.5 Ethnicity

Ethnicity has been recognized to have a significant role in breast cancer survival. Several studies in different countries have shown that indigenous people in a given population have a poorer outcome when compared to their non-indigenous counterparts. The words ‘indigenous’ and ‘non-indigenous’ is more commonly used in Australasia (Australia and New Zealand) than any other parts of the world. In the UK, the ethnicity data used in the UK national statistics relies on individuals' self-definition.

In the US, African American (Black), Native American (white) and Latin American (people and descendants of Central America) referred to as Hispanics, are more frequently used to describe ethnicity. For example, in the US from 2008 to 2012, breast cancer incidence rates increased among Black women and Asian/Pacific Islander women and were stable among white, Hispanic, and American Indian/Alaska Native women. Historically, in the US, white women have had higher incidence rates than black women, however, in 2012, the rates converged.

The incidence and mortality rates differ in various states in the US and the mortality disparity between the black and white women nationwide has continued to widen (DeSantis et al. 2016). This disparity in the US could potentially be due to African American women developing more aggressive, advanced stage breast cancer diagnosed at a younger age and dying from this

disease when compared to Asian American women, who have lower death rates. Factors such as socioeconomic status and access to health care interventions play a large part in this disparity.

The survival disparity amongst ethnicities is multifactorial and includes less access to mammography and quality medical care, as well as various lifestyle patterns.

Ethnic factors have also been linked to breast cancer biological type. Triple-negative breast cancers are more common among Black/African-American women than among women of other ethnicities in the US. A strong survival disparity among ethnicities exists in breast cancer cases especially in the ER-positive cancer cases (Hill et al. 2017; Ma et al. 2012; Pathy et al. 2011; Rauscher et al. 2008; Stark et al. 2008).

1.3.5.1 Ethnicity types in New Zealand

The population of New Zealand (NZ) is made up of very diverse ethnic groups. The 2016 statistics NZ estimated 74.6% Europeans, 14.9 % Māori, 11.8% Asian, 7.4% Pacific Islanders, and 1.2 % Latin America, Middle Eastern, and African (www.stats.govt.nz 2018). The presence of the largest population of Pacific Islanders (7.4%) outside of the Pacific Island makes it a unique population. This study will examine some of the ethnic variations in breast cancer in NZ.

1.4 Research aim

The research aims for this study are:

1. Describe the five selected factors in relation to grade 3 breast cancer (Chapter 1).
2. Review the international literature of these selected prognostic factors (Chapter 2).
3. Analyse the characteristics of grade 3 breast cancer (Chapter 4).
4. Compare and analyse NZ data with international data (Chapter 5).

1.5 Research questions

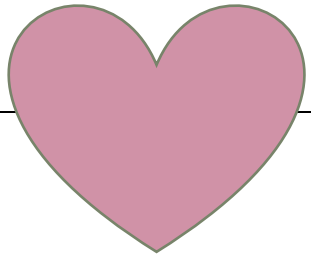
The research questions are:

1. Is there a survival difference in grade 3 breast cancer, when we consider the common prognostic factors?

2. Can we further characterize grade 3 breast cancer?

Chapter 2

Literature Review



This chapter presents a review of the national and international literature and other sources of relevant information, which discuss the survival of breast cancer patients. The review will cover the selected prognostic factors that include; molecular subtype, stage of disease, age at diagnosis and ethnicity in relation to overall survival including survival defined by grade 3 breast cancer.

2.1 Introduction

In 2012, New Zealand was ranked 4th among the top 20 countries with the highest incidence of breast cancer (www.wcrf.org).

The exact cause of breast cancer is not known, however, certain risk factors either modifiable (excess alcohol, diet, lack of exercise) or non-modifiable (age, ethnicity, family history, genetics, grade and stage of disease, molecular and histological type) have been linked to the increased likelihood of this disease. It is of great value to understand the behavior of these often-aggressive cancers to establish an appropriate treatment for this disease.

Whilst family history is high on the list of non-modifiable risk factors, genetics, and family history are beyond the scope of this research and therefore will not be discussed. Any reference to genetics in this review will only be mentioned as part of the incidence and outcome of breast cancer as affected by mutated genes (BRCA1 and BRCA2) in relation to survival with breast cancer.

In order to understand the outcome of breast cancer as a disease and prognostic characteristics in relation to the selected factors, a compilation of journal articles was utilized. Studies were collated via searches on scholarly databases particularly on breast cancer survival, specifically using PubMed, Medline, EBSCO health database, Google Scholar, Cochrane (via Ovid), Cochrane (via Wiley), Scopus and other relevant websites using relevant terms and combination of terms were used. The following keywords and combinations of these keywords were used: breast cancer, breast carcinoma, breast neoplasm, epidemiology, race/ethnicity, young women, mortality, survival, survival rate, outcome, molecular subtypes, prognostic factors, stage at diagnosis, age at diagnosis, hormone receptor status, grade, and high grade. In addition, New Zealand published journal articles followed by expert recommendations were examined and retrieved papers were cited in the reference list.

The literature review would include articles between a period of 2000-2018 with the majority of this published within the past eight years. Older references are only included to provide a historical context.

Analysis of the literature for the review entailed searching for themes that were (i) prominent and found to occur across the various continent, (ii) found across various ethnicities, (iii) specific to characteristics of the disease and (iv) overall survival of breast cancer.

This approach for literature search, therefore, is considered as being part systematic and part organic.

A total of 125 articles were identified by using the above search parameters with an emphasis on grade 3 breast cancer as shown in Figure 2.1. The selection criteria were further refined by specifics as required for each of the prognostic factors as defined by grade 3 breast cancer and will be reviewed under each subtype under its appropriate headings below.

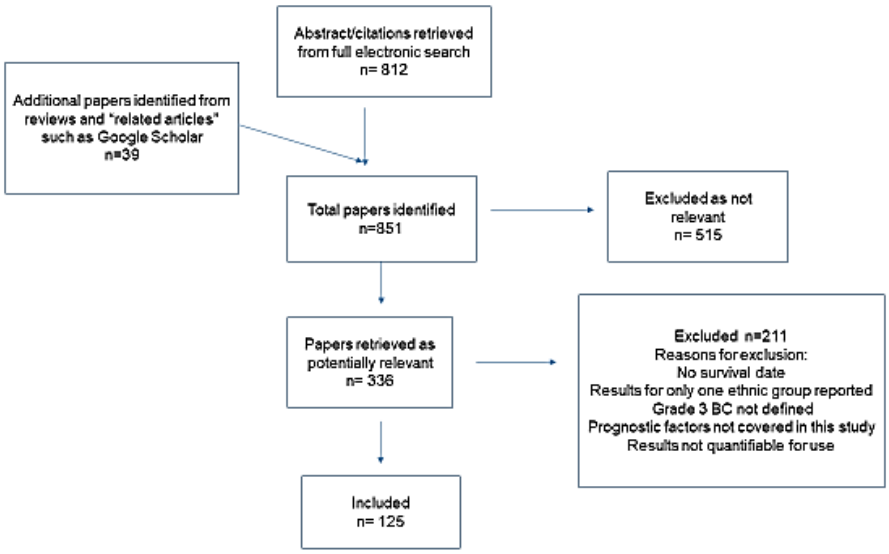


Figure 2.1. Flow diagram showing the selection of papers to be included in the literature review

2.1.1 Age at diagnosis

Studies have reported that age at diagnosis is a well-known prognostic factor for treatment decisions in breast cancer (Albain, Allred, and Clark 1994; Azim et al. 2012; Bonnier et al. 1995; Brandt et al. 2015).

Nineteen studies were included in the review. Two out of the nineteen studies defined grade 3 breast cancer and survival in association with age at diagnosis. The studies reviewed were from Europe, USA, Africa, Asia, and the Middle East and were from 1991 through to 2016. The association between age, other prognostic factors and the outcome of breast cancer has been somewhat controversial due to the presence of other confounding factors that may determine the outcome. Confounding factors are factors that can cause or prevent the outcome, but they are not intermediate variables of the factors under investigation. They tend to influence both the dependent variable and independent variable causing a spurious association. Hence they cannot be described in terms of correlations or associations.

Four studies reported that age was found to be an independent risk factor for younger women with HER2 positive breast cancer (Atiq-ur-Rehman et al. 2016; Bonnier et al. 1995; Kim et al. 2011; Kroenke et al. 2004). Five studies reported that young women with breast cancer were more likely to be ER negative and high grade (Kroman et al. 2000; Assi et al. 2013; Goksu et al. 2014; Ihemelandu et al. 2007; Kallel et al. 2015). Tumours in young women are prone to be more hormone receptor negative, which makes them less responsive to adjuvant endocrine therapy

such as tamoxifen; therefore, chemotherapy has been the choice of treatment (Brandt et al. 2015). Five studies reported that age alone as an independent prognostic factor for breast cancer survival was ambiguous, therefore other factors such as different molecular subtype associated with survival should also be taken into consideration (Azim et al. 2012; Desmedt et al. 2008; Jenkins et al. 2014; Paluch-Shimon et al. 2011; Yang et al. 2007). Three studies reported that the incidence and mortality of breast cancer co-morbidities increases with advancing age and the survival rate differs amongst different age groups (Arvold et al. 2011; Bergman et al. 1991; Cluze et al. 2009; Fleming and Fleming 1994; Jemal, Ward, and Thun 2007; Largillier et al. 2008; McPherson, Steel, and Dixon 2000).

Two studies reported that a high frequency of undifferentiated tumours (i.e. the cells do not look like cells in the tissue from which it arose from) was observed in younger women (under 35 years). These tumours were grade 3, suggesting a higher stromal activity (Bonnier et al. 1995; Nixon et al. 1994).

From the above reviews, it can be summarised that: (a) the occurrence of breast cancer increases with age, (b) age is one of the risk factors for breast cancer, (c) younger women under 40 years have a poorer prognosis, (d) age is a prognostic factor for treatment decisions in breast cancer, (e) younger women are more likely to be ER negative and therefore chemotherapy is the choice of treatment and, (f) incidence and mortality of breast cancer co-morbidities increase with advancing age.

2.1.2 Ethnicity

Disparities in breast cancer survival between indigenous and non-indigenous populations around the world are well documented (Maskarinec et al. 2011). There are several possible reasons such as differences in gene expression, that could account for survival disparity in different ethnicities with breast cancer (Bradley, Given, and Roberts 2002). Differences across ethnic groups have been reported in several studies with worse outcomes among ethnic groups of lower socioeconomic status (Lee et al. 2010; LeMarchand, Kolonel, and Nomura 1984; Newman et al. 2006; Ooi et al. 2012a; Reis-Filho and Tutt 2008; Sugarman, Dennis, and White 1994).

Nineteen studies were included in the review. The studies reviewed were from, the USA including Hawaii, Europe, Asia, and New Zealand and were from 1984 through to 2018. Only one out of the nineteen studies reviewed correlated grade 3 breast cancer with ethnicity.

Two studies reported that biological differences by ethnicity and molecular subtypes such as among luminal A and TNBC account for survival disparity between black and white women with breast cancer ((D'Arcy et al. 2015; Parada et al. 2017). Similarly, six studies reported that the worse predictors of outcome, such as low prevalence of luminal A and higher prevalence of TNBC, advanced stage of breast cancer and the negative ER/PR status were among women of African descent especially in the younger age (Albain et al. 2009; Carey et al. 2006; Chu et al. 2009; Komenaka et al. 2010; Maskarinec et al. 2011; Monzavi-Karbassi et al. 2016). Four studies

undertaken in New Zealand reported that ethnicity, especially between indigenous and non-indigenous groups contributed to the survival with the disease (Cunningham et al. 2010; Jeffreys et al.2009; Seneviratne et al. 2015; Tin et al. 2018). The studies from New Zealand also reported that, compared with New Zealand European women, Māori (indigenous people) and Pacific Island (immigrants or descended from the Pacific Islands) have a younger age distribution; and that there are major disparities in survival with Māori and Pacific Island women having lower survival than other ethnic groups. Similarly, Australian studies demonstrated that the Aborigines (indigenous people) had a worse survival rate than other Australians. Interestingly, the Māori in New Zealand has been well studied and display disparities in cancer outcomes similar to Indigenous Australians (Condon et al. 2014; Hortobagyi et al. 2005; Morris et al. 2007; Valery et al. 2006).

Two studies reported that there was a significant increase in mortality risk for patients with lower grade cancers for African American women compared with Caucasian women (Cunningham and Butler 2004; Henson, Chu, and Levine 2003). One study reported that in African American women, 43% of breast cancers were grade 3, compared with 27% or less in women of other ethnic/racial groups (Chlebowski et al. 2005).

From the above reviews, it can be summarised that: (a) differences in gene expression can account for survival disparity in breast cancer in different ethnicities, (b) higher prevalence of TNBC, advanced stage, negative ER/PR status and presence of younger age group was among women of African descent, (c) ethnicity disparity between indigenous and non-indigenous groups in a population contribute to survival disparity, (d) TNBC presents as the worse subtype among women of African descent, (e) in NZ, indigenous Māori women experience worse breast cancer outcomes compared with European women,(f) poor cancer survival rates and increasing cancer incidences have resulted in worsening cancer burden among Indigenous populations, (g) in the US, African American women experience higher rates of ER-negative and high-grade cancers than women of the other ethnic groups.

2.1.3 Molecular subtypes

The use of biomarkers helps to provide prognostic information that assists clinicians to facilitate treatment decisions as discussed in chapter one. This thesis will discuss biomarkers ER, PR and IHC HER2 index in relation to the overall survival of women with breast cancer.

Approximately 75% of luminal-like breast cancers are ER and or PR positive (Yersal and Barutca 2014). The ER-positive tumours express ER-responsive genes that encode proteins of luminal epithelial cells and are given the term luminal group. Luminal A and luminal B have been identified as the two main luminal-like subclasses (Habashy et al. 2012; Sotiriou et al. 2003). Each molecular subtype has shown specific features and different survival outcome (Li et al. 2018; Rouzier et al. 2005). Luminal breast cancers have been associated with the most favorable prognosis (Guarneri and Conte 2009; Kennecke et al. 2010).

2.1.4 Luminal A

Luminal A tumours are ER, PR positive and HER2 negative

Twenty-four studies were included in the review. Only one out of the twenty-four studies reviewed defines grade 3 breast cancer and survival. The studies reviewed were from Europe, USA, Canada, Asia, and Africa and were from 2006 through to 2017. Three studies reported that heterogeneity of luminal A subtype (the largest subgroup of breast cancer) may help guide therapy options (Aure et al. 2017; Lindström et al. 2017; Loi 2008). Six studies reported that survival (short- term) was dependent on the subtype of breast cancer. Luminal A subtype showed better survival when compared to the non-luminal especially the TNBC subtype (Carey, Cheang, and Perou 2014; Cheang et al. 2009; Dent et al. 2007; Engstrøm et al. 2013; Schrodi et al. 2016; Tobin et al. 2015). The differences in breast cancer survival occurred almost exclusively amongst the grade 2 tumours due to its heterogeneity and from 5 years after the time of diagnosis until the end of follow-up, there was no clear association with molecular subtype and grade with survival as reported by (Engstrøm et al. 2013). Nine studies reported that the usefulness of hormonal therapy was linked to overall survival for luminal A subtype (Badowska-Kozakiewicz et al. 2015; Berry et al. 2006; Borgquist et al. 2015; Bouchard-Fortier et al. 2017; Goldhirsch et al. 2011; Morgan, Refalo, and Cheung 2011b; Prat et al. 2013; Sundquist, Brudin, and Tejler 2017; Uscanga-Perales, Santuario-Facio, and Ortiz-López 2016). Three studies reported that breast cancer subtypes may be due to genetic ancestry, however, a current understanding of genetic aberrations may be contributing to the poor prognosis of the non-luminal subtypes (Banerji et al. 2012; Loi 2008; Rugo et al. 2017). One study reported that only a very small percentage (8.9%) of luminal A cancers were grade . The frequency of local therapy was unrelated to the grade of the disease and it was not related to the subtype i.e. luminal cancer. The study did, however, recommend that further research should be done and include patients who have undergone adjuvant chemotherapy for overall survival in order to get a better comparison (Niemiec et al. 2013).

The overall survival for patients with luminal A breast cancer is considered to be good, however, in 2017, Mudduwa, studied the expression of Claudin 3 in the membrane of breast cancer cells using IHC studies (Mudduwa et al. 2017). Low Claudin 3 expressions have been associated with poorer survival and luminal A and B subtypes have been identified as the low expressing subtype. Claudin 3 expression is a plausible target for the type of therapy for patients and is an area still under investigation. Similarly, a study by (Kolokytha et al. 2014) has reported on the expression of Claudin 3 and Claudin 4 as being considered as a biomarker of favorable prognosis.

From the above reviews, it can be summarized that: (a) Luminal A patients have a better survival than non-luminal subtypes, (b) Luminal A tumours respond better to endocrine therapy than chemotherapy, (c) Luminal A tumours are less chemosensitive, (d) Luminal A tumours represent low proliferation, (e) Luminal A tumours have a higher rate of ER and PR +ve, and HER2 –ve,

(f) Luminal A tumours are mostly grades 1 and 2, (g) Luminal A, grade 3 tumours occur in younger women with a poorer outcome.

Whilst several studies documenting the incidence and outcome of luminal subtype breast cancer were available, there was very little evidence to define grade 3 breast cancer to luminal A subtype.

2.1.5 Luminal B

Luminal B tumours are ER, PR and HER2 positive.

Luminal B tumours' are distinguishable from luminal A tumours by the former having higher proliferation and poorer prognosis (Cheang et al. 2009; Loi et al. 2009; Reis-Filho et al. 2010).

Fourteen studies were included in the review. The studies reviewed were from Europe, USA, Canada, Asia, and Africa and were from 2003 through to 2017. Four studies reported that the aggressive phenotype of luminal B and higher grade were linked to a poorer prognosis (Creighton 2012; Dent et al. 2007; Ehinger et al. 2017; Niemiec et al. 2013). Five studies reported that 30% of luminal B tumours are HER2 positive, indicating that HER2 clinical marker alone is not sensitive enough to clearly identify luminal B breast cancers (Cheang et al. 2009; Loi et al. 2009; Paik et al. 2004; Rouzier et al. 2005; Yersal and Barutca 2014). One study reported that the survival with breast cancer was dependent according to proliferative indices and the histological grade. It concluded that histological grade was a strong determinant for the stratification of luminal class (Luminal A and B) regarding short-term survival (Sun et al. 2014). The study, however, did not define grade 3 as the determinant regarding survival. Four studies reported that luminal B breast cancers that express high levels of Ki67, (a nuclear marker of cell proliferation), are associated with worse outcomes (Domagala et al. 1996; Trihia et al. 2003). Due to the lack of clarity regarding how Ki67 measurements influence clinical decisions, it is not included for routine clinical decisions (De Azambuja et al. 2007; Ellis 2003). One study reported that certain alternative growth factor pathways, such as *fibroblast growth factor receptor 1 (FGFR1), HER1, phosphoinositide 3 kinase (PI3K) catalytic alpha polypeptide*, and *sarcoma proto-oncogene (Src)*, may contribute to higher proliferation and poorer prognosis of luminal-B breast cancer (Tran and Bedard 2011).

Whilst several studies documenting the incidence and outcome of luminal subtype breast cancer were available, one study clearly reported that molecular subtypes differ in geographic distribution, race, age, prognosis, and in the therapeutic targets they express. The study conducted in Eritrea, Africa, reported that breast cancers in that region have distinct biological behavior. The study reported that a large percentage (55%) of the cases for this region were luminal A, a small percentage (5%) were luminal B and 60% of the cases were grade 3 breast cancer with 68% patients under the age of 50 years, thus giving a very unique outlook of this subtype (Tesfamariam and Roy 2013).

From the above reviews, it can be summarised that: (a) Luminal B tumours that display an aggressive phenotype and are of higher grade is linked to worse prognosis; (b) Luminal B tumours are highly proliferative with a poor clinical outcome; (c) Luminal A and B breast cancers can be

distinguished by the expression of ER, PR, HER2, and Ki67 proteins;(d) Luminal B breast cancers are associated with poorer outcome in both the presence and absence of systemic adjuvant therapy; (e) Luminal B tumours have an increased expression of HER2 associated genes which have been associated with tamoxifen (hormone therapy drug used for breast cancer treatment) resistance; (f) Luminal B HER2 –ve tumours are treated with additional chemotherapy; (g) Luminal B, ER, PR +ve and HER2 –ve tumours indicate high proliferation and poor prognosis; (h) Luminal B, ER, PR +ve and HER2 +ve tumours can be treated with both endocrine and anti-HER2 therapy ;(i) Luminal B, grade 3 tumours occur in younger women.

2.1.6 HER2 enriched tumours

HER2 enriched tumours are ER, PR negative and HER2 positive

HER2 enriched “intrinsic” subtype along with the luminal subtype have been extensively studied by microarray and hierarchical clustering analysis (Fan et al. 2006; Hu et al. 2006; Perou et al. 2000; Sørlie et al. 2001). The overall conclusions from these studies reported that these subtypes add significant prognostic and predictive information for patient management. HER2 enriched tumours are ER, PR negative and HER2 positive and account for 15-20% of breast cancer subtype. These tumours are highly proliferative and 75% of HER2 +ve tumours have high grades (Yersal and Barutca 2014).

Fourteen studies were included in the review. The studies reviewed were from Europe, USA, Canada, Asia, and Egypt and were from 2001 through to 2016. In 2010, a study by Staaf identified three separate subtypes of HER2 positive tumours’, each with varying type of prognosis by using HER2 derived prognostic predictor (HDPP) gene analysis. The study reported that HER2 positive tumours defined a clinically challenging subgroup with variable prognosis and responses to therapy (Staaf et al. 2010).

Three studies reported that HER2 enriched cancers are characterized by high expression of the HER2 gene and about 15-20% breast cancers are classified as HER2-enriched. These HER2 enriched cancers express low levels of ER with an increased sensitivity to cytotoxic agents and are resistance to hormonal agents (Carey, Cheang, and Perou 2014; Foukakis and Bergh 2016; Voduc et al. 2010). Ten studies reported that HER2 positive subtype presents more aggressive biological and clinical behavior and are of a high grade with a poorer prognosis. The studies reviewed also reported that targeted therapies such as anti- HER2 drugs (Herceptin) showed improved survival (Ahmed 2016; Al-Khayat et al. 2016; Blows et al. 2010; Borgquist et al. 2015; Lee et al. 2014; Niemiec et al. 2013; Parise and Caggiano 2014; Slamon et al. 2001; Tsutsui et al. 2003; Yersal and Barutca 2014).

From the above reviews, it can be summarised that: (a) HER2 enriched tumours are highly proliferative, (b) 75% of HER2 enriched tumours are of high grade (grade >2), (c) HER2 enriched tumours present more aggressive biological and clinical behavior, (d) HER2 enriched tumours have poor prognosis in the absence of treatment, (e) targeted therapy (anti-HER2) drugs showed improved survival for HER2 enriched tumours, (f) HER2 enriched tumours express very low levels

of ER, (g) HER2 enriched tumours have increased sensitivity to cytotoxic agents and are relative resistance to hormonal agents.

2.1.7 Triple Negative Breast Cancers

Triple Negative Breast Cancer (TNBC) are ER, PR and HER2 negative and represent 10-20% of all breast cancers. This cancer subtype is of high histological grade, has more aggressive clinical behavior, has the worst disease-free survival and is more likely to be present in younger age, premenopausal women, women with BRCA1 gene mutation and women of African ancestry, when compared to the ER-positive luminal subtype breast cancers (Anders et al. 2009; Der et al. 2015; Heitz et al. 2009; Lee et al. 2010; Onitilo et al. 2009; Rakha and Ellis 2009; Reis-Filho and Tutt 2008; Schneider et al. 2008).

Twenty two studies were included in the review. The studies reviewed were from Europe, USA, Africa, Asia, and Turkey and were from 2013 through to 2017. Some of TNBC possess a basal phenotype and show varying degree of basal marker expressions, such as Epidermal Growth Factors Receptor (EGFR) and Cytokeratin 5/6 (CK5/6) (Cheang et al. 2008). It is important to clarify the terms TNBC and 'basal-like'. TNBC refers to the immunohistochemical classification of breast tumours' and include basal-like subtype which expresses basal keratins i.e. lacking ER, PR, and HER2 protein expression, whereas the basal-like subtype is defined via gene expression microarray analysis. The TNBC subtype is used in a clinical setting rather than the basal-like which is used more in a research setting (Kreike et al. 2007). Whilst TNBC and basal-like tumours show aggressive biological characteristics and a significantly poorer prognosis, these two groups of breast cancers are not synonymous (Kurebayashi et al. 2007; Reis-Filho et al. 2010).

Studies have reported that TNBC is associated with high grade and poorer outcome, however, this subtype can be treated with drugs, such as chemotherapy, radiation therapy and HER2 targeted therapy (Rakha and Ellis 2009). A high percentage (70-80%) TNBC are of grade 3 with the rest being grade 2 which accounts for its aggressive clinical behavior (Anders and Carey 2009; Der et al. 2015; Gluz et al. 2009; Ismail-Khan and Bui 2010; Krishnamurthy et al. 2012; Ma et al. 2012; Rouzier et al. 2005; Sotiriou et al. 2003). In 2009, Heitz reported that poor outcome was attributed to the aggressive clinical behavior of the majority of the tumours as being the infiltrating ductal type, and low expressions of Claudin (genes involved in tight junctions and cell-cell adhesions) 3, 4 and 7. Low Claudin has been reported as having a poor outcome in patients displaying TNBC phenotype, however, only a minority of TNBC are Claudin low (Dias et al. 2017; Heitz et al. 2009; Herschkowitz et al. 2007).

Four studies reported that the poorer outcome of this subtype was due to a lack of understanding of the molecular pathogenesis of TNBC. The studies reported that there was a need to better understand the nature of this subtype in order to allow for more individualized care as well as more effective therapies (Bulut and Altundag 2015; Rakha and Ellis 2009; Schneider et al. 2008; Uscanga-Perales, Santuario-Facio, and Ortiz-López 2016). Unfortunately, clinical trials to date examining survival improvement have not been very successful and an appropriate treatment

regime has not been established. TNBC tumours lack therapeutic target, therefore chemotherapy is the only effective systemic treatment for these patients. Three studies reported that the current and mainstay therapy regime for TNBC is the use of conventional cytotoxic therapies (Guarneri, Dieci, and Conte 2013; Schneider et al. 2008; Venkitaraman 2010).

From the above reviews, it can be summarised that: (a) TNBC comprise a range of tumours that include basal-like, (b) TNBC are BRCA1 enriched breast cancers, (c) the immunohistochemical markers ideal for TNBC are ER, PR, HER2, EGFR, and CK5/6, (d) TNBC present in younger women with an aggressive clinical course, (e) TNBC respond to neoadjuvant chemotherapy and the non-responders have a very poor outcome, (f) there is no viable target agent proven to improve the outcome of TNBC, (g) there are ongoing studies to identify molecular targets and unique agents to improve therapeutic efficacy for TNBC.

2.2 Stage of disease at diagnosis

Stage of disease at diagnosis is a key prognostic factor of breast cancer survival. Histologic grade, when combined with the stage of disease, can improve the prediction of outcome (Henson, Chu, and Levine 2003). The survival of women diagnosed with breast cancer varies by stage at diagnosis. A higher survival rate is seen in patients diagnosed with stages, 0, I, or II than patients diagnosed with stages III or IV (Fallahpour et al. 2017; Saadatmand et al. 2015). Advanced stage with the late diagnosis has been associated with the disparity in survival in minority ethnic groups (Seneviratne et al. 2016). Along with stage at diagnosis, the molecular subtype is an important clinical factor associated with breast cancer survival which reflects treatment responses (Anders et al. 2009; Hennigs et al. 2016; Ihemelandu et al. 2007; Parise and Caggiano 2014; Yersal and Barutca 2014; Zuo et al. 2017).

Thirteen studies were included in the review. The studies reviewed were from, USA, Europe, Asia, New Zealand, and Canada and were from 1991 through to 2017. Two out of the thirteen studies reviewed defined high-grade breast cancer with the stage at diagnosis (Henson, Chu, and Levine 2003; Li, Malone, and Daling 2003).

Four studies reported that higher grade and higher stage at diagnosis are associated with poorer survival when compared to lower grades and lower stage of disease in the younger age group (Carey et al. 2006; Parise and Caggiano 2014; Perou et al. 2000; Sørlie et al. 2001). Four studies reported that indigenous women are more likely to be diagnosed at a more advanced stage and high grade than Caucasian women (Henson, Chu, and Levine 2003; Li, Malone, and Daling 2003; Seneviratne et al. 2016; Ugnat et al. 2004).Two studies reported that treatment was dependent on stage and outcomes vary (Anders and Carey 2009; Nixon et al. 1994). For stage I and II the appropriate treatment would constitute either breast conservation surgery (BCS) combined with radiotherapy or a total mastectomy whilst advanced stages are treated with systemic therapy, which include a combination of two or more treatments, hormone therapy, chemotherapy, targeted therapy, mastectomy and radiation (Farrow, Hunt, and Samet 1992; Lazovich et al. 1991; Nattinger et al. 2000).

From the above reviews, it can be summarised that: (a) the extent of the stage of the disease determines survival, (b) differences in stage, treatment, and mortality are present in different ethnicities, (c) combination of socioeconomic and lifestyle factors, tumour characteristic are likely to contribute to a difference in stage at breast cancer diagnosis, (d) advanced stage and high grade are more likely to be reported in indigenous women, (e) a difference in treatment received due to the difference in stage may be the result of cultural factors, (f) younger women have a worse prognosis with high grade and advanced stage than older women.

2.3 Limitations of the review relating to the study

There are relatively few historical studies and a very small body of literature on the survival of women defined purely by grade 3-breast cancer.

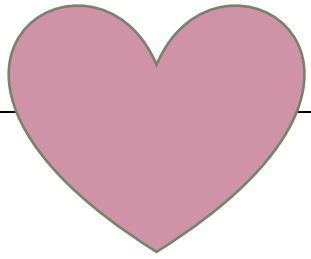
In New Zealand, although the overall survival of breast cancer has been studied by a number of authors (Campbell et al. 2015; Curtis, Wright, and Wall 2005a; Jeffreys et al. 2005; Lawrenson, Lao, et al. 2016; McKenzie, Ellison-Loschmann, and Jeffreys 2010; Ooi et al. 2012a; Saadatmand et al. 2015; Seneviratne et al. 2014; Seneviratne et al. 2017; Tin Tin et al. 2018) it is timely to provide a review of the literature that over-arches this with a focus on the heterogeneity of high grade (grade 3) breast cancer and its survival. This is currently lacking in the reviews. The goal is to understand the behavior (clinical and biological) of grade 3 breast cancer, which is described as aggressive cancer with poor prognosis. The survival of breast cancer defined by grade 3 is poorly described in the literature; it is, therefore, the aim to provide some valuable information to the breast cancer treating clinicians.

2.4 Literature Review Findings

Grade 3 breast cancer is a heterogeneous group that can include HER2 enriched and luminal-type tumours and this group is linked to poorer prognosis. This review has found that there are common themes in the literature regarding the overall survival of breast cancer in association with the established prognostic factors, and an attempt to define grade 3 breast cancer relating to the selected prognostic factors was made. The importance of these findings and relating it to how New Zealand sits internationally with this disease will be discussed in chapter five (Final Discussion). This information, however is lacking in the literature review. However, the studies presented thus far provide a good basis for understanding that the established prognostic factors play a vital role in the overall survival of women diagnosed with breast cancer and further studies are needed to better understand the molecular pathway of this disease.

Chapter 3

Methodology



3.1 Introduction

This chapter presents the methodology and its rationale used in this thesis. It aims to create an archetype to describe quantitative impacts of women diagnosed with grade 3 breast cancer in New Zealand and the overall survival in this group of women.

3.2 Study design

This is a retrospective cohort study of the selected prognostic factors using data that was prospectively collected and examined the association between selected prognostic factors and overall breast cancer survival of women diagnosed with grade 3 breast cancer in NZ during 1st January 2011 to 31st December 2015. No other grade of breast cancer is part of this design and analysis.

3.3 Data

The Auckland Breast Cancer Study Group (ABCSG) was formed in 1976 by multidisciplinary clinicians interested in breast cancer treatment in the face of recognizing the need for a database to assist with the ongoing management, research, and audit of breast cancer. On 1st June 2000, the Auckland Breast Cancer Register (ABCR) was established. Together with the three other regional breast cancer registers (Waikato, Wellington, and Christchurch), approximately 64% of all New Zealand breast cancer registrations (around 1600 cases per annum) are collected. The New Zealand Breast Cancer Register (NZBCR) was therefore established in a background of important advances made in all areas of breast cancer. Information collected by the register about current practice is vital as it plays a key role in supporting the multidisciplinary teams that are necessary for high-quality patient care. The information collected on the database is used by study groups to feed back into the community for improved future management of breast cancer.

The NZBCR includes 4 regions. These include Auckland (which covers Waitemata, Auckland, and Counties Manukau District Health Boards), Waikato, Wellington (which covers Wairarapa, Capital & Coast, Hutt Valley District Health Boards), and Christchurch (Canterbury District Health Board), as shown in Figure 3.1.

Data collection for each of the four regions began as follows (Breast cancer foundation, NZ):

- Auckland- 1 June 2000
- Wellington- 1 January 2010
- Christchurch- 15 June 2009
- Waikato- 1 January 2005

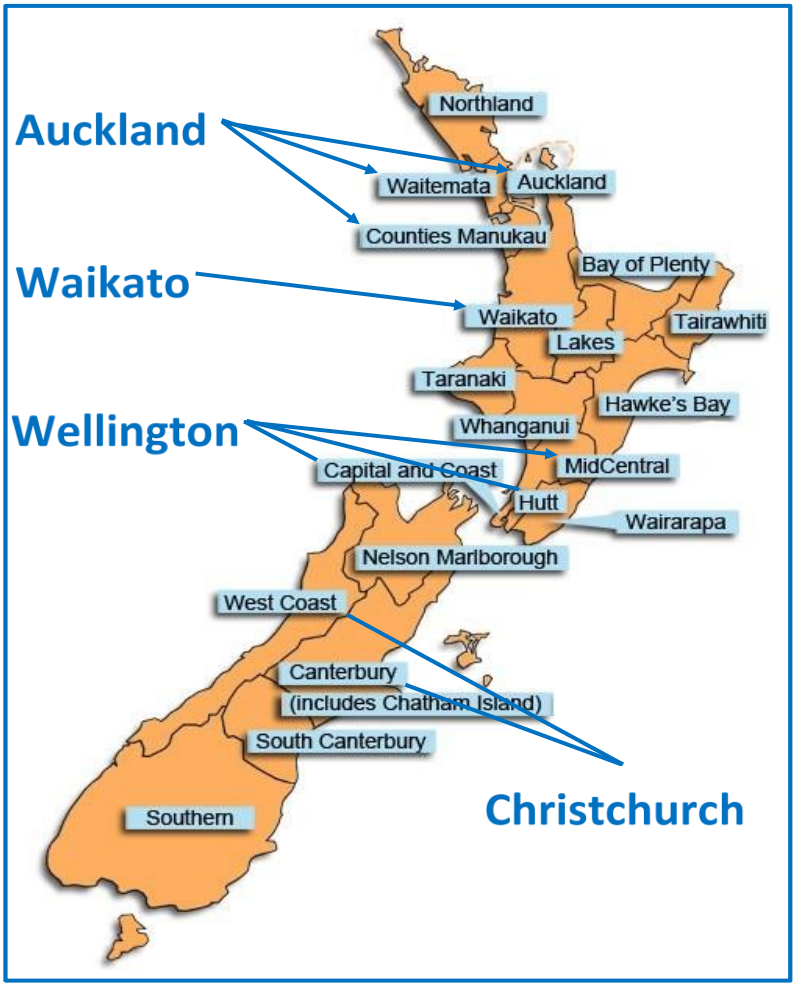


Figure 3.1. Four breast cancer register regions covered by the DHB. Courtesy of Val Davey of NZBCR, May 2018

All pathology laboratories are required since 1994 to register any new cases of breast cancer in NZ with the National Cancer Register. Hence pathology laboratories are the primary source of information for the NZBCR (Ward et al. 2004). Therefore, the utility of breast cancer register is dependent upon the accuracy and completion of the regional data.

For this thesis, all women with grade 3 breast cancer registered on the NZBCR from 1st January 2011 to 31st December 2015 (study group) were identified. The de-identified clinical data that was used for this study were abstracted from the overall NZBCR dataset by the trained administrative staff at NZBCR.

Prognostic variables (ER, PR, HER2 status, histological type, stage at diagnosis, age at diagnosis and ethnicity) were extracted from the data. It is important to inform the reader that the overall stage of diagnosis was established manually by using the breast cancer staging classification of the American Joint Committee on Cancer (AJCC) from the Tumour, Node, and Metastasis (TNM) information that was recorded by the NZBCR.

Information on Receptors (ER, PR) and IHC HER2 status have been available on the NZBCR since 2002 from the Ministry of Health, NZ. The classification of these receptors is discussed in

chapter 2. Missing data and any data coded as “Unknown” were not included in the analysis, leaving the only receptor positive and negative data for analysis. The IHC HER2 status was grouped into 5 categories: 0+, 1+, 2+, 3+ and not tested. This was further categorized to include HER2 negative which included 0+ and 1+ and HER2 positive which included 2+ and 3+ to get an overall status of this cohort. Untested status was not included.

Histological type was divided into 4 categories: ductal, lobular, mixed and other. Any data identified as other than ‘ductal’, ‘lobular’ or ‘other’ was identified as “mixed”. The ‘mixed’ group was very small in numbers and therefore combined with the group called “other”.

Age at diagnosis was divided into 7 groups: 20-40 years (due to the low numbers this was grouped as group 1), 41-50 years (group 2), 51-60 years (group 3), 61-70 years (group 4), 71-80 years (group 5), and >80 (group 6.

Ethnicity data were grouped into 5 categories: Māori, Pacific Islander, NZ European, Asian and Other. For the purpose of this research anyone who identified themselves as Māori were categorized as Māori, people of any Pacific nation were identified as Pacific Islander, people who identified themselves as European were identified as NZ European, people of any Asian countries were identified as Asian, people outside of any of these nations/countries were identified as ‘Other’.

The stage at diagnosis was divided into 9 categories: Stage 1A, 1B, 2A, 2B, 3A, 3B, 3C, 4 and X as discussed in chapter 2. Data that was indicated as “X” (not assessable) was identified as “X” for analysis. The stage at diagnosis was further combined to include stage 1 which included 1A and 1B, stage 2 which included 2A and 2B, stage 3 which included 3A, 3B, and 3C, stage 4 and X to get an overall status of this cohort.

Data covering a 5-year period from 1st January 2011 to 31st December 2015 has been retrieved from the New Zealand Breast Cancer Register (NZBCR). These cut-off dates were particularly selected in order to give all four regions a common start date, due to all four regions starting their data collection at different dates. The selected time frame allows a consistent overlap of data from all four registers in order to provide a national 5-year data set from the date of diagnosis for the multiple cohorts of women. A 5-year survival analysis will not be possible for patients who were diagnosed in 2014 and 2015. Therefore, an overall survival will be discussed, and international 5-year survival will be used as a tool for comparison.

3.4 Analysis

Descriptive analysis was initially conducted to explore the variables and summarise the data. Chi-square statistics were used to test for any relationship between categorical variables. The chi-square test is an approximation. The test was used to determine whether there is a significant association between the two variables. It performs a hypothesis test and constructs confidence intervals for the standard deviation of a normally distributed variable.

The chi-square distribution is identified by the degrees of freedom. The chi-square test uses the *p*-value approach, where $p < 0.05$, then the null hypothesis *(Ho)* shows that there is no association between the variables tested and is therefore rejected and it is stated that the test result is statistically significant.

The universal Cox regression was used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI) of overall risk of breast cancer by the selected prognostic variables in the study group. It, therefore, explored the relationship between the 'survival' of a subject and the categorical variable. Hence, Cox-regression survival analysis looks at the association between predictor variables and survival i.e. it is used to predict the rate of occurrence or for investigating the effect of several variables upon the time a specified event takes to happen, in the case of this study, the outcome is the event i.e. death. The outcome variable (death) is binary which means it can take on only two possible outcomes: which are alive and dead at the time of analysis.

The hazard ratio (HR) and 95% confidence interval (CI) were calculated to estimate the association between the predictor variable having the worse prognostic factors. The hazard ratio is an important concept in survival analysis. It is the probability that an individual will experience an event at the time (*t*) i.e. the hazard rate is the unobserved rate at which events occur. An important feature of the hazard rate is that whilst it is an unobserved variable, it controls both the occurrence and the timing of the events. It is the fundamental dependent variable in survival analysis. Hazard rate is particularly of interest for this survival study because it will describe the relationship of a factor of interest to the time to an event, in the presence of several covariates, such as age at diagnosis, ethnicity, the histological type, stage of disease and receptor status.

The reference group selected for each dependent variable was the most favorable prognostic factor outcome in each group.

Survival analysis was used to analyse data in which the time until death was noted i.e. how long until death occurred. Survival analysis is used when one or more predictor variables may be associated with the time until an event occurs i.e. how long people will live, and what influences that. Here censoring is permitted and that is the key reason that a survival analysis was performed. Censoring means that the information about survival time is incomplete.

Because the survival probabilities are only point estimates for a population for an event, it is important to compare a 95% confidence interval for the population. It is important to distinguish the individual contributions of predictor variables and their association.

Survival rate was estimated by Kaplan-Meier graph. Kaplan-Meier survival curves can be compared statistically and graphically as a function of time. These are shown in the next chapter.

All analysis was carried out using Statistical Data Analysis (STATA) version 15.0.

3.5 Ethics

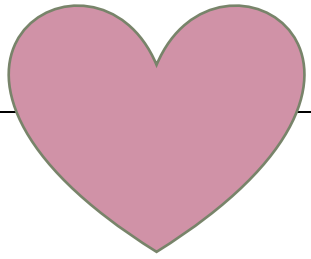
Auckland University of Technology Ethics subcommittee (AUTEC) has approved this research as shown in Appendix A.

Cancer Advisory Group Committee (CAG) has given full approval for the use of the de-identified information (data) from the four Breast Cancer Registries for this research as shown in Appendix B.

This research does not require submission to the Health and Disability Ethics committee (HDEC) as shown in Appendix C. This research is an observational, cross-sectional study that aims to investigate by the audit, factors affecting the survival of women with grade 3 breast cancer in NZ.

Chapter 4

Results



4.1 Introduction

The cohort's overall demographics are summarised in Table 4.1, with a descriptive summary of the breast cancer characteristics summarised in Table 4.2 and Table 4.3, by ethnicity and age at diagnosis respectively.

The tables are presented in the next two pages in this chapter.

The five- year study period of women diagnosed with grade 3 breast cancer in New Zealand recorded fatality of (9.73%).These fatalities comprised of breast cancer (9.59%) and of other causes (8.36%).

The results presented in this chapter solely present breast cancer cause fatality.

Table 4.1. Overall Demographics (%) of Ethnicity and Age at diagnosis of women with breast cancer in NZ (2011 -2015)

	Variable	N (%)					
	Total number of subjects	2667					
	Ethnicity						
Age at diagnosis (years)	NZ European	Māori	Pacific Islander	Asian	Other	Overall	Fatalities from BC only
<40	6.64	1.38	1.12	1.19	6.63	10.84	1.19
41-50	16.31	3.07	1.83	2.85	16.31	24.71	1.99
51-60	17.28	3.22	1.83	2.77	17.28	25.72	2.21
61-70	15.18	1.61	1.12	1.19	15.1	19.95	1.31
71-80	9.74	0.33	0.44	0.41	9.74	11.32	1.84
>80	6.71	0.11	0.03	0.29	6.71	7.46	1.19

Table 4.2. Overall Breast Cancer characteristics by Ethnicity (%) in NZ women (2011-2015)

Ethnicity	Molecular Subtype				Histology Type				HR Status				Stage					
	LA	LB	HER2 enriched	TNBC	Ductal	Lobular	Mixed	Other	ER +ve PR +ve	ER +ve PR -ve	ER –ve PR +ve	ER -ve PR -ve	I	II	III	IV	X	Fatalities from BC only
Overall	29.73	12.73	11.77	23.86	90.08	3.29	4.38	0.75	44.05	17.24	1.24	36.48	27.18	40.08	14.21	16.95	1.39	
NZ European	20.80	8.53	7.82	18.19	63.97	2.81	0.52	3.29	30.96	12.5	30.96	26.88	20.54	28.98	9.11	12.03	1.08	7.76
Māori	3.20	1.23	1.34	1.68	9.04	0.19	0.11	0.41	0.14	1.83	0.14	3.07	2.51	4.16	1.46	1.49	0.11	0.86
Pac Is	2.35	1.19	1.31	0.78	5.99	0.19	0	0.19	3.63	0.56	0.03	2.13	0.82	2.28	1.49	1.64	0	0.33
Asian	2.40	0.97	1.08	1.83	8.21	0.11	0.07	0.29	3.52	1.87	0.15	2.99	2.24	3.67	1.49	1.23	0.03	0.52
Other	0.93	0.41	0.18	1.16	2.99	0	0.04	0.19	1.34	1.34	0	1.34	1.04	0.97	0.63	0.52	0.03	0.11

Table 4.3. Overall Breast Cancer characteristics by Age at diagnosis (%) in NZ women (2011-2015)

Age at Diagnosis (years)	Molecular Subtype				Histology Type				HR Status				Stage				
	Luminal A	Luminal B	HER2 enriched	TNBC	Ductal	Lobular	Mixed	Other	ER+ve PR+ve	ER+ve PR-ve	ER-ve PR+ve	ER-ve PR-ve	I	II	III	IV	X
Overall	29.73	12.73	11.77	23.86	90.21	3.29	0.75	5.14	44.05	17.24	1.24	36.48	27.18	40.08	14.21	16.95	1.39
<40	2.39	1.83	1.46	2.65	10.01	0.04	0.18	0.52	4.24	1.88	0.26	4.42	1.99	4.95	1.84	1.91	0.11
41-50	8.08	3.85	2.99	5.42	22.76	0.56	0.18	1.05	12.41	3.22	0.29	8.47	7.12	9.82	4.35	3.29	0.11
51-60	7.18	2.92	3.96	6.17	23.81	0.63	0.26	0.89	25.72	14.89	0.33	10.16	7.76	10.24	3.52	3.82	0.26
61-70	6.14	1.98	1.98	5.24	17.55	1.05	0.07	1.05	8.39	3.82	0.15	7.35	6.75	7.57	2.69	2.66	0.29
71-80	3.33	1.16	0.97	2.54	9.89	0.67	0	0.56	5.32	2.06	0.15	3.75	2.39	4.95	1.31	2.55	0.11
>80	2.02	0.22	0.37	1.34	6.19	0.34	0.04	0.29	3.49	1.54	0.03	2.32	1.16	2.36	0.56	2.69	0.49

4.2 Age at diagnosis

The mean age of NZ women at diagnosis with breast cancer was 57.23 years when ranging from 20 to 98 years.

This study found that age groups 41-50 years and 51-60 years represented the largest proportion of women with grade 3 breast cancer, (25.72%) and (24.71%) respectively (Table 4.1).

The Univariate Cox proportional hazards model was additionally carried out, where the age group <40 years served as the reference group. Subjects aged 41-50 years were at decreased risk of five-year mortality and this difference was statistically significant. In contrast, subjects aged 71 years and older were at increased risk of five-year mortality. Subjects aged 61-70 years were at elevated, but not a statistically significant increased risk of five-year mortality rate (Table 4.4, Figure 4.1).

Table 4.4. Hazard ratios and 95% confidence intervals for breast cancer-related death by age at diagnosis

Age at diagnosis (yrs)	Hazard Ratio	Std. Err	P	95% Conf. IntervalCI
<40	-	-	-	-
41-50	0.61	0.12	0.009	0.42-0.88
51-60	0.92	0.16	0.635	0.65-1.29
61-70	0.69	0.13	0.054	0.47-1.01
71-80	1.63	0.29	0.008	1.13-2.34
>80	4.34	0.76	0.000	3.07-6.13

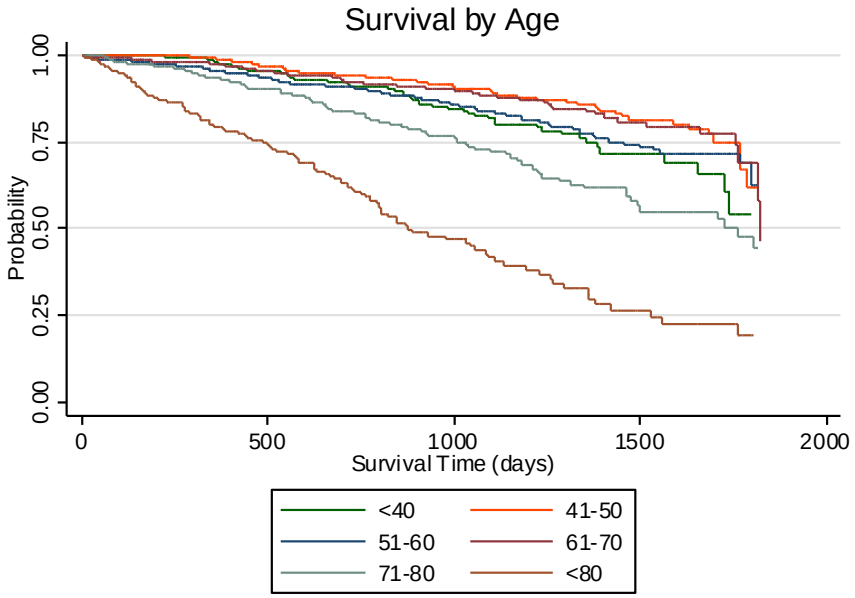


Figure 4.1. Kaplan-Meier survival estimates for age at diagnosis

4.3 Ethnicity

The overall demographic summary for ethnicity groups for this study is shown in Table 4.1.

Univariate Cox proportional hazards model was also carried out, where Asian group served as the reference group. The Pacific Islander group were at increased risk of five- year mortality and this difference was statistically significant.

In contrast, the Māori group were at decreased risk of five-year mortality approaching significance (Table 4.5, Figure 4.2).

Table 4.5. Hazard ratios and 95% confidence intervals for breast cancer risk by ethnicity

Ethnicity	Hazard Ratio	Std. Err	P	95% Conf. Interval CI
Asian	-	-	-	-
Māori	0.61	0.16	0.057	0.37-1.01
NZ European	1.12	0.18	0.478	0.82-1.53
Other	1.13	0.42	0.728	0.55-2.32
Pacific Islander	1.71	0.39	0.020	1.09-2.67

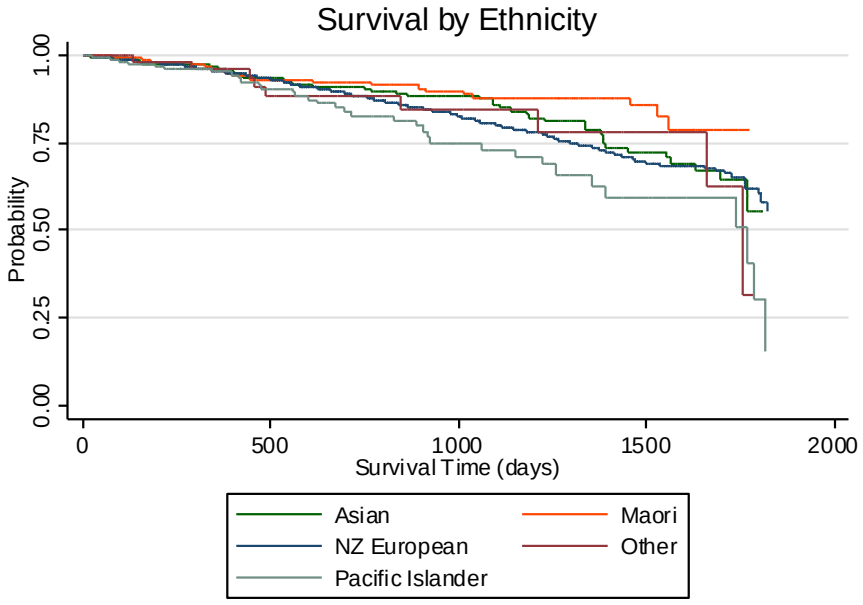


Figure 4.2. Kaplan-Meier survival estimates for ethnicity

4.4 Histological type

The overall demographics summary of histological type is shown in Table 4.1 and Table 4.3 for ethnicity and age at diagnosis respectively.

This study found that ductal carcinoma represented the largest proportion of histology type in NZ women with grade 3 breast cancer (Table 4.3, Table 4.3).

The Univariate Cox proportional hazards model was additionally carried out, where lobular carcinoma served as the reference group.

The study showed that there was no statistically significant difference in the five –year mortality for the histological type (Table 4.6, Figure 4.3).

Table 4.6. Hazard ratios and 95% confidence intervals for breast cancer risk by Histological type

Histological Type	Hazard Ratio	Std. Err	P	95% Conf. Interval CI
Lobular	-	-	-	-
Ductal	0.96	0.25	0.881	0.58-1.59
Mixed	0.99	0.75	1.000	0.23-4.35
Other	0.69	0.25	0.315	0.34-1.41

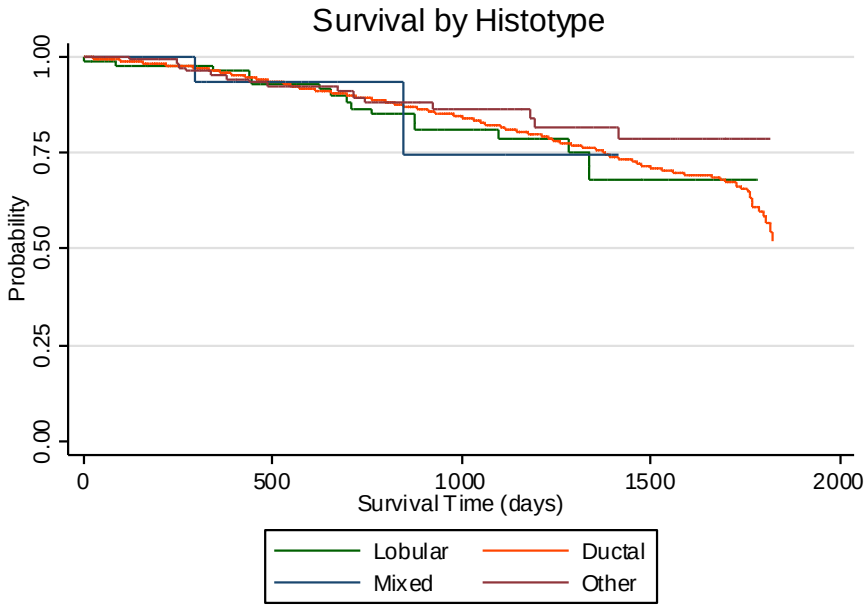


Figure 4.3. Kaplan-Meier survival estimates for the Histological type.

4.5 Molecular Subtype: Luminal A, Luminal B, HER2 enriched and TNBC

The overall demographic summary for the molecular subtype is shown in Table 4.12 and Table 4.3.

This study found that Luminal A represented the largest proportion of women with grade 3 breast cancer in the age groups 41-50, 51- 60 and 61-70 years followed by TNBC (Table 4.3).

Additionally, molecular subtype by ethnicity found that Luminal A and TNBC were common across all the ethnicity groups (Table 4.3).

The Univariate Cox proportional hazards model was also carried out, where Luminal A served as the reference group. The study found that HER2 enriched and TNBC were at increased risk of five-year mortality and this difference was statistically significant (Table 4.7, Figure 4.4).

The overall occurrence of TNBC is shown in Table 4.2. Of note, NZ Europeans have the largest proportion of this molecular subtype, yet, the Pacific Islander groups are at increased risk of mortality by grade 3 breast cancer (Table 4.5).

Table 4.7. Hazard ratios and 95% confidence intervals for breast cancer risk by Molecular Subtype

Molecular subtype	Hazard Ratio	Std. Err	P	95% Conf. Interval
Luminal A	-	-	-	-
Luminal B	0.84	0.17	0.402	0.56-1.26
HER2 enriched	1.44	0.22	0.016	1.07-1.95
TNBC	1.73	0.23	0.000	1.32-2.25

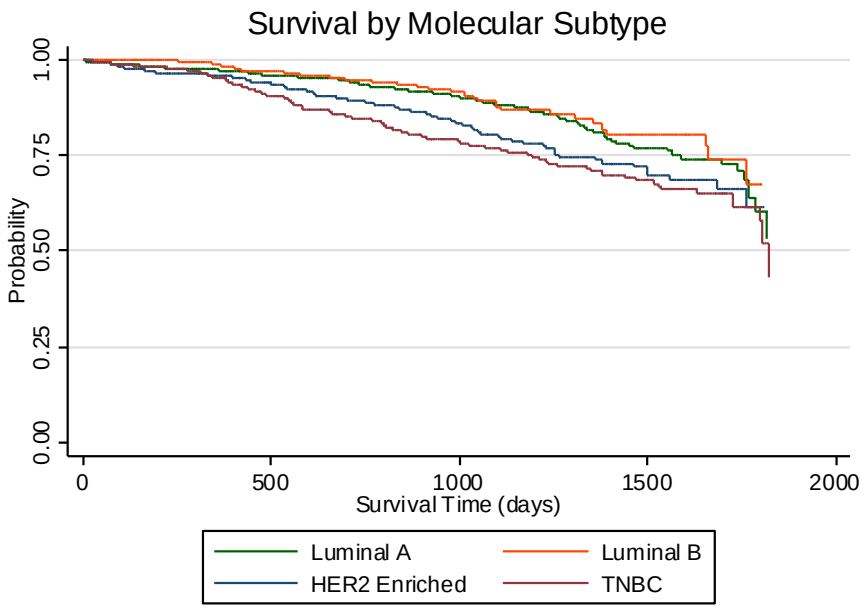


Figure 4.4. Kaplan-Meier survival estimates for the Molecular subtype

4.6 Hormone Receptor status

The overall demographics summary of hormone receptor status in regards to ethnicity and age at diagnosis are shown in Table 4.1 and Table 4.3 respectively.

This study found that ER/PR positive and ER/PR negative tumours represented the largest proportion for hormone receptor status in women with grade 3 breast cancer 44.05%, 36.48%, respectively (Table 4.3).

Subjects aged in the 51-60 year age group represented a large proportion in the ER/PR positive group (25.72%), and similarly, subjects aged in the same age group, 51-60 years represented a large proportion in the ER/PR negative group (10.16%), (Table 4.3).

Additionally, hormone receptor status by ethnicity found that ER/PR positive and ER/PR negative tumours were represented in larger proportion across all ethnicities. Of note, the Pacific Islander group represented more ER/PR positive tumours whereas the Māori group represented more ER/PR negative (Table 4.2).

The Univariate Cox proportional hazards model was additionally carried out, where ER/PR negative tumours served as the reference group. The model showed that ER-negative PR positive groups were at increased risk of five-year mortality and this difference was statistically significant (Table 4.8).

In contrast, the ER/PR positive group were at decreased risk of five-year mortality and this difference was statistically significant (Table 4.8, Figure 4.5).

Table 4.8. Hazard ratios and 95% confidence intervals for breast cancer risk by Hormonal Status

HR status	Hazard. Ratio	Std. Err	P	95% Conf. Interval
ER-ve PR-ve	-	-	-	-
ER+ve PR+ve	0.66	0.07	0.000	0.54-0.83
ER-ve PR+ve	1.29	0.16	0.031	1.02-1.64
ER+ve PR-ve	0.99	0.45	0.995	0.41-1.42

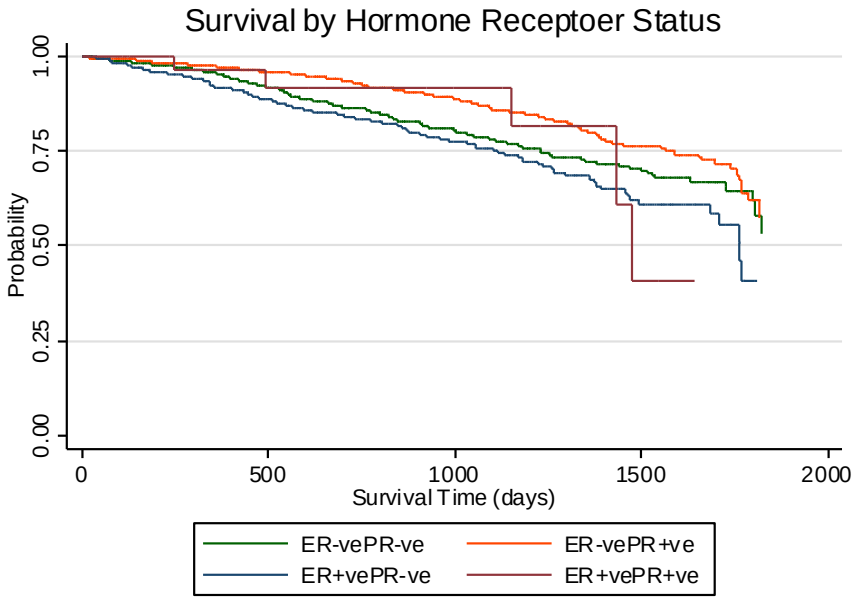


Figure 4.5. Kaplan-Meier survival estimates for HR status

4.7 Stage at diagnosis

The overall demographics summary of the stage at diagnosis of grade 3 breast cancer is shown in Table 4.1 and Table 4.3.

This study found that a very small group were stage 0, and stage X (unknown). Stage 0 will not form part of the analysis, however, stage X will be further discussed in the next chapter.

Stage I and stage II represented the largest proportion for the stage at diagnosis in women with grade 3 breast cancer, 27.18%, 40.08% respectively (Table 4.2).

Similarly, stages I and II represented large proportions across all ethnicity groups. Additionally, Asian, Māori, NZ European, and Pacific Islander groups represented a higher proportion of stage III tumours when compared to the ethnicity group called “Other” (1.49%, 1.46%, 9.11% and 1.49%) respectively (Table 4.2).

The Univariate Cox proportional hazards model was also carried out, where stage I served as the reference group. Stages II, IV and X were at increased risk of five-year mortality and this difference was statistically significant and stage III is approaching significance (Table 4.9, Figure 4.6).

Table 4.9. Hazard ratios and 95% confidence intervals for breast cancer risk by stage at diagnosis

Stage at diagnosis	Hazard Ratio	Std. Err	P	95% Conf. IntervalCI
I	-	-	-	-
II	1.76	0.46	0.029	1.06-2.94
III	1.71	0.48	0.058	0.98-2.98
IV	2.63	0.63	0.000	1.65-4.20
X	3.99	1.70	0.001	1.74-9.20

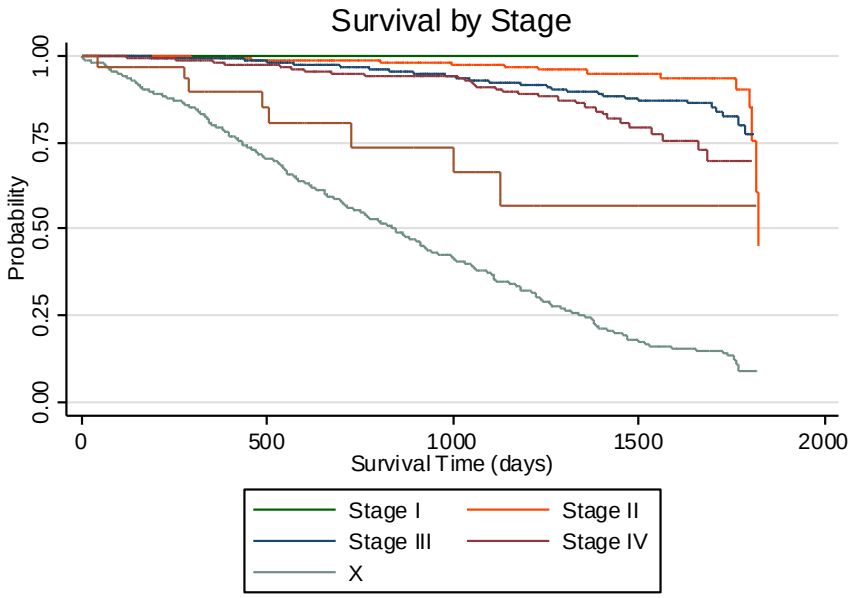
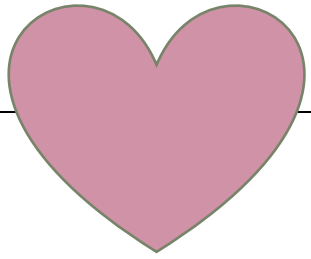


Figure 4.6. Kaplan-Meier survival estimates for the stage at diagnosis

Chapter 5

Final Discussion



5.1 Introduction

This study set out to characterise Grade 3 breast cancer, a heterogeneous group of tumours and found that NZ subjects in the older age group of >70 years were at increased risk of five-year mortality.

Of the ethnicity groups, the Pacific Islander group were at increased risk, whereas the Māori group were at decreased risk of five-year mortality.

The Histology type showed there was no statistically significant difference observed, whereas with the molecular subtypes HER2 enriched and TNBC subjects were at increased risk. The study also reported that NZ European group presented the largest proportion of HER2 enriched and TNBC within the subjects and the subjects from these two molecular subtypes were at increased risk of five-year mortality.

The hormonal receptor analysis reported that ER-negative PR positive group were at increased risk and in contrast, the ER/PR positive group were at decreased risk.

Subjects from stages II, IV and X were at increased risk, however, subjects from stage III were approaching significance.

From the analysis, it can be reported that the survival rates for breast cancer vary across the selected prognostic factors and therefore it can be deduced that the survival of this disease is dependent on multiple factors. These factors can include patient factors, tumour biology and resource-related such as access to health interventions. Therefore, the causes of the observed survival differences are likely to be multifactorial and include factors such as socioeconomic status and treatment as well as biological differences among the cancers themselves (Ademuyiwa and Olopade 2003; Eley et al. 1994; Joslyn 2002)

Additionally, from the analysis of this study, it is proposed that it: (a) will provide a basis for continuation of studying the additional data for grade 3 breast cancer in New Zealand women enrolled in the NZBCR, (b) will highlight treatment modalities, and (c) will help to identify factors affecting survival for improved patient management of grade 3 breast cancer in New Zealand.

5.2 Comparison of study findings to existing literature

There were common themes present in the literature that was reviewed regarding the survival of breast cancer relating to the selected prognostic factors. Whilst several international studies have linked these factors to the overall survival of breast cancer, there was little or no evidence that isolated grade 3 breast cancer as an independent factor to the behavior and outcome. Therefore, this study is unique in exploring this grade as a stand-alone factor, adding to the information on breast cancer.

Age at diagnosis has a significant effect on survival and is a well-known prognostic factor for treatment decisions (Albain, Allred, and Clark 1994; Azim et al. 2012; Bonnier et al. 1995; Brandt

et al. 2015). However, the association with age and other prognostic factors including the outcome of breast cancer have been somewhat controversial due to the presence of other confounding factors. Confounding factors influence the dependent as well as the independent variable causing a spurious association and as such cannot be described in terms of correlations or associations. These factors can cause contrived association in terms of correlation and association and therefore it is important to note that the age structures of various populations worldwide for the disease are quite different (Wang et al. 2013).

For example, in Europe (EU), the population has a much higher proportion of older women and 43% of breast cancer occurs in women over the age of 65 years (Ferlay et al. 2015). In contrast, amongst the Asian countries, the median age of breast cancer at diagnosis is around 50 years. This is nearly 10 years younger than the Western countries such as the United States and EU. This is because there is no population-based breast cancer screening program and hence the majority of patients present with advanced disease (Kwong et al. 2008; Song et al. 2014; Yip 2009).

The variation in the median age at diagnosis for different ethnic groups is observed nationally and internationally. For instance, in the US, the median age at diagnosis of patients with breast cancer was 62 years among White females and 58 years among Black females (Howlader et al. 2012). In comparison, in New Zealand, approximately 75% of all breast cancers occur in women over the age of 50 years and 6% occurs under the age of 40 years (Ministry of Health 2015). The median age at diagnosis for this study was 57 years which is closer to the median age in the US (62 years) as opposed to the median age in the EU (65 years). Furthermore, in this study, the median age at diagnosis for NZ European, Māori, Asian, Pacific Islander, and Other groups were 58, 51, 52, 52, 57 years respectively. Māori and Pacific Island women have a higher proportion of younger women diagnosed with breast cancer when compared to the non-Māori and non-Pacific Island women and this group has been known to have poorer outcomes (Campbell et al. 2015; McCredie et al. 1999).

The youngest subject in this study cohort was a 20 year old Asian. These results are comparable to the international data where indigenous woman are diagnosed younger when compared with the non- indigenous women (Gabriel and Domchek 2010). Similarly, the finding in the Asian group is also consistent with international Asian studies where the age at diagnosis is nearly 10 years earlier than the United States and EU (Kwong et al. 2008; Song et al. 2014; Yip 2009). In the United Kingdom, where the age-standardized incidence and mortality in breast cancer is high, the incidence among women aged less than 50 years approaches two per 1000 women per year, and the disease is the single commonest cause of death among women aged 40-50 years (McPherson, Steel, and Dixon 2000).

Breast cancer in young women is uncommon. They tend to be diagnosed at a later stage and are prone to be more hormone receptor negative (Joslyn 2002). These cancers are more aggressive, hence have a higher mortality rate (Assi et al. 2013; Goksu et al. 2014; Ihemelandu et al. 2007; Kallel et al. 2015; Kroman et al. 2000). Late detection could be due to the unavailability of an

effective breast cancer screening tool for women under 40. Younger women have breast tissue that prevents routine mammograms from being used as a useful screening tool (Elwood, Cox, and Richardson 1993).

The hazard risk of survival with breast cancer in the 5-year study period for this cohort is higher in older women than in younger women and this result is comparable to the 5-year survival rate from the USA (SEER Cancer Statistics Review) and Japan where a higher risk of survival rates was reported in the 65 years or older age group (Howlader et al. 2012). Similar findings were seen in from Norway and UK in overall breast cancer survival.

The results of this study are consistent with the literature review findings that show the mortality of breast cancer increases with advancing age and is higher in the older age group. The results also show that the survival rate varies with different age groups (Arvold et al. 2011; Bergman et al. 1991; Cluze et al. 2009; Fleming and Fleming 1994; Jemal, Ward, and Thun 2007; Largillier et al. 2008; McPherson, Steel, and Dixon 2000). However, our results should be interpreted with caution due to small numbers in sample size in some categories, especially in the Pacific Island group. The 'Other' is a heterogeneous group, therefore, it is not discussed in detail in this chapter.

The variation in survival with breast cancer in different ethnic groups was observed nationally and internationally.

Ethnicity or race is complex in its make-up as well as in its definition. Its meaning varies from country to country. These are poorly defined terms that serve as flawed surrogates for the multiple environmental and genetic factors in disease causation which includes geographic origins, socioeconomic status, education and access to health care (Collins 2004; Lee et al. 2010; LeMarchand, Kolonel, and Nomura 1984; Newman et al. 2006; Ooi et al. 2012b; Reis-Filho and Tutt 2008; Sugarman, Dennis, and White 1994). For example, the difference between Far Eastern and Western countries is depreciating and studies involving migrants from Japan and Hawaii show that the rates of breast cancer in migrants assume the rate in the host country within one or two generations, indicating therefore that the environmental factors are of greater importance than genetic factors (McPherson, Steel, and Dixon 2000)

The variation may also explain disparities in overall breast cancer survival and particularly in different indigenous and non-indigenous populations around the world (Henson, Chu, and Levine 2003; Li, Malone, and Daling 2003; Maskarinec et al. 2011; Seneviratne et al. 2016; Ugnat et al. 2004). Quite often, the disparities are referred to in terms of ethnicity or socioeconomic status which are viewed as independent of each other (Advani et al. 2014; Bennett 2007; Blakely et al. 2007; Clegg et al. 2009; Cunningham et al. 2010). It can be argued that breast cancer survival disparity in different ethnicities may be due to biological differences among breast cancers which reflect genetic influences, differences in lifestyle, or nutritional or environmental exposures (D'Arcy et al. 2015; Parada et al. 2017). In addition, studies that include ethnicity as a characteristic must take into account that there is significant disagreement as to how ethnicity is measured and interpreted in medical research.

The accuracy of recording ethnicity on registers is likely to be different for different ethnic groups. This information is usually abstracted from patient medical records and is particularly reliant on being self-assigned or at times on the assumption of a health professional. However, these disparities are well documented (Ademuyiwa and Olopade 2003; Advani et al. 2014; Albain et al. 2009; Blakely et al. 2007; Chlebowski et al. 2005; Crowe et al. 2005; Cunningham and Butler 2004; Curtis et al. 2008; Daly and Olopade 2015).

Many US studies rely on the SEER data, which are not representative of the minority population in terms of ethnicity. There has been misclassification reported for Hispanics, Asians, and Pacific Islander ethnicities in the US (Kish et al. 2014). For example, for breast cancer, the proportion of women diagnosed with the distant-stage disease is higher among African Americans, Hispanics and American Indians/Alaskan Natives than among Whites, Asians, and Pacific Islanders. Although Whites have the highest incidence rates of breast cancer for all stages combined, African American women have higher rates of distant-stage disease (Foy et al. 2018). The breast cancer mortality rate is about 40% higher in African American women than in White women, despite a 10-20% lower breast cancer incidence (Cunningham and Butler 2004; Henson, Chu, and Levine 2003). These findings demonstrate the difference in breast cancer occurrence in different ethnicities.

Additionally, the poorer survival in the US also appears to result in more from disparities in access to care and quality of cancer treatment than from biological differences in tumour characteristics, and treatment outcomes between African Americans and Whites (Maskarinec et al. 2011). These disparities have seen poorer outcomes among ethnic groups of lower socioeconomic status (Lee et al. 2010; LeMarchand, Kolonel, and Nomura 1984; Newman et al. 2006; Ooi et al. 2012b; Reis-Filho et al. 2010; Sugarman, Dennis, and White 1994). Generally, breast cancer disparities in the US are mostly reported between White Americans and African American women, and less frequently including Hispanic and Asian women. (Furberg et al. 2001; Ihemelandu et al. 2007; Morris et al. 2007). Similarly, limited data are available on breast cancer disparities between settler White American women and indigenous populations in the US which include American Indians and Alaskan Natives.

Māori women in New Zealand show a similar outcome for breast cancer to the African women in the US (Advani et al. 2014; Bramley et al. 2004; Chlebowski et al. 2005; Cunningham and Butler 2004; Cunningham et al. 2010; Curtis et al. 2008; McKenzie, Ellison-Loschmann, and Jeffreys 2011; McKenzie, Jeffreys, and Pearce 2008; Seneviratne, Campbell, et al. 2015b).

Suggestions are frequently made that the poorer survival with ethnicities is due to genetics (Bradley, Given, and Roberts 2002). For example, Jewish women that come from multi-generational Jewish families are at increased risk. This increased risk is of genetic origin. While there is a lack of major systemic genetic differences between ethnic groups, there are extensive differences in lifestyle suggesting therefore that the survival disparities are most likely driven by environmental factors (McPherson, Steel, and Dixon 2000).

Previous studies done in New Zealand indicate that Māori and Pacific Island women are more likely to have higher grade breast cancers at the time of diagnosis than non-Māori /non-Pacific Island women (Campbell et al. 2012; Meredith et al. 2012). Similarly, African-American, Hispanic, and Hawaiian women are diagnosed more frequently with higher grade and or advanced stage than white women and in contrast, Japanese women are diagnosed less frequently with larger, advanced tumours (Furberg et al. 2001; Miller, Hankey, and Thomas 2002). However, the results of this study reported that whilst the Māori women reported an increase in numbers with grade 3 breast cancer, the Pacific Islander women were at most risk of five-year mortality.

In New Zealand, the Ministry of Health reports show that Māori women are 1.4 times more likely to be diagnosed with breast cancer, 1.5 times more likely to die from breast cancer than non-Māori and less likely to be diagnosed early (Ministry of Health 2015; Robson, Cormack, and Purdie 2016). Studies have also demonstrated survival disparities in indigenous and non-indigenous Australians (Condon et al. 2014; Hortobagyi et al. 2005; Morrell, You, and Baker 2012; Valery et al. 2006).

In this study, ethnicity disparity for survival was confirmed. For example, the Pacific Islander group were at increased risk, whereas the Māori group were at decreased risk of the five-year mortality from breast cancer. This demonstrates that the targeted breast screening programme for the Māori women in New Zealand is proving to be a useful tool for a decreased risk in the five-year mortality rate and is making a difference (Curtis, Wright, and Wall 2005b).

The results of this study are consistent with the literature review findings where indigenous disparities exist in populations around the world for breast cancer survival (Cunningham et al. 2010; Jeffreys et al. 2009; Monzavi-Karbassi et al. 2016; Seneviratne, Campbell, Scott, Coles, et al. 2015; Tin Tin et al. 2018).

The ‘mixed’ group which consist of ethnicity that did not fit into the four main ethnicity groups for this study was very small in numbers and therefore will not be discussed.

The interpretation of survival disparity in different ethnicities is complex in view of numerous known putative risk determinants such as the modifiable and non-modifiable risk factors.

There are several unanswered questions regarding survival disparities in different ethnicities. For example, whether the minority ethnic group seek medical advice at a later stage when compared to their majority ethnic group and what is the reason for this delay? Secondly, whether cancer biology plays a role in the survival disparity between the indigenous (Māori) and the non-indigenous (NZ European) population? Thirdly, whether the selected prognostic factors contribute to the overall survival of this disease? 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 selected prognostic factors toward breast cancer disparities between Māori, Pacific Islander, Asian and NZ European women

will inform future research and guide strategies for a tailored approach for the treatment of grade 3 breast cancer in New Zealand.

The variation in survival in this study was also demonstrated by analysing breast cancer characteristics. Histological typing can provide useful prognostic information and is important in determining treatment (Weigelt, Geyer, and Reis-Filho 2010). The favorable prognosis of certain histological types of breast cancer is well recognized. For example, Lobular carcinoma has a better prognosis when compared to the ductal type (Ellis et al. 1992). The two most common histologic types of invasive breast cancer are ductal and lobular carcinomas, accounting for approximately 75% and 15% of all cases respectively (Li, Malone, and Daling 2003). This is consistent with this study finding where a higher percentage (90%) were ductal and a small percentage (3%) were lobular carcinoma. Due to the small sample size present in this thesis, and histological typing showed no statistical significance. This was not helpful and therefore not further analysed.

Lobular and ductal carcinomas are less likely to be ER/PR negative (Gruvberger et al. 2001; Joslyn 2002). The molecular markers which include ER, PR, and IHC HER2 index and how they relate these to the outcome with breast cancer are discussed below.

The utility of molecular markers provides useful prognostic information to the treating clinicians (Aure et al. 2017; Lindström et al. 2017; Loi et al. 2008). Studies suggest that lobular carcinomas are more likely than ductal carcinomas to be hormone receptor positive (Arpino et al. 2004). In this study, the lobular carcinoma was more likely to be pleomorphic in type, and were ER/PR negative. In this study, being predominantly ductal, it was reported that the cohort as being ER and PR positive which showed a decreased risk of five-year mortality. This categorizes the group to be luminal-like breast cancer and luminal types have been associated with the most favorable prognosis (Guarneri and Conte 2009; Kennecke et al. 2010).

Hormone receptor status has been identified as an independent indicator of breast cancer (Dunnwald, Rossing, and Li 2007; Engstrøm et al. 2013; Gapstur et al. 1996). Estrogen and Progesterone receptors are often overexpressed in malignant breast tissue and together with HER2, they establish distinct tumour subtypes with potential varying risk factors and outcome (Dai et al. 2015). Hormone receptor-positive tumours have a better prognosis than the hormone receptor-negative tumours. The latter is usually associated with aggressive tumours (Dunnwald, Rossing, and Li 2007).

There is increasing evidence that women of different ethnicities experience the disproportionate risk of various breast cancer subtypes. For example, in the US, Black or Hispanic women are more likely to have ER and PR negative breast cancer compared with non-Hispanic or White women. Black women are also more likely than White women to have TNBC (Carey, Cheang, and Perou 2014; Cheang et al. 2009; Dent et al. 2007; Engstrøm et al. 2013; Furberg et al. 2001; Gapstur et al. 1996; Li, Malone, and Daling 2003; Schrodi et al. 2016; Tobin et al. 2015). Similarly, Asian and Indian women in the US had more ER and PR negative tumours with invasive ductal

carcinomas subtypes and had a poorer prognosis than when compared to White women (Kakarala et al. 2010), whilst in Asia, there is a higher proportion of hormone receptor negative women presenting with higher grade (Yip 2009). A study of women in the UK reported that a higher proportion of TNBC and poorer survival was present in Black and in the South Asian women than in White women (Jack et al. 2013). These results were similar to the study done by in 2011 by Telli (Telli et al. 2011).

Receptor negative tumours are not amenable to hormonal therapy (Legha, Davis, and Muggia 1978; Joslyn 2002). The differences in these various groups of women could explain some of the inequalities in survival. The presence of differential subtypes of the disease could be due to different risk factors and this should also be accounted for.

Differences with age at diagnosis and histological type were observed between the various ethnicities in this study. All these factors appeared to be contributing at varying degrees towards the final survival differences. Luminal A should confirm increased survival, however, in some ethnic groups such as the Pacific Islander in this study, reported worse survival which suggests that it may not be related to the marker but rather to do with screening and access to health care.

There were differences in the status of IHC HER2 in the various groups in this study. In particular, the Pacific Islander group of women showed a higher occurrence of HER2 enriched subtype than any of the other groups, suggesting that there are some biological differences in this group. These differences may be genetically determined and a likely explanation for the observed differences in the overall survival. HER2 negative tumours have a better survival than HER2 positive tumours, therefore a targeted therapy approach would be necessary to improve survival (Ahmed 2016; Carlson et al. 2006; Kaptain, Tan, and Chen 2001).

HER2 positive cancers tend to be more aggressive than HER2 negative cancers and are associated with poorer survival (Ahmed 2016; Carlson et al. 2006; Kaptain, Tan, and Chen 2001). These tumours are highly proliferative and have higher grades. HER2 positive tumours have been defined as a clinically challenging subgroup with variable prognosis and survival (Staaf et al. 2010; Yersal and Barutca 2014). This study reports a higher percentage of a HER2 negative than HER2 positive putting these groups into the HER2 enriched subtype which may explain the survival disparity, especially in the Pacific Islander group.

In New Zealand, Māori and Pacific Island women are more likely to have HER2 positive breast cancer than non-Māori and non-Pacific Island women and Māori women are less likely to have a negative ER and PR status (Curtis, Wright, and Wall 2005a; Meredith et al. 2012; Tin et al. 2018). The patterns of Māori and Pacific Island women's hormone receptor status may be linked to the survival rate of these group of women. The results of this study suggest that Māori women may have a better prognosis for hormonal treatments than another ethnic group such as the Pacific Island women.

This study also reports that LA and TNBC are the most common molecular subtypes across all the age groups. The younger age group (41-60 years) demonstrated HER2 enriched and TNBC

subtypes. Similarly, the study demonstrated that Pacific Islander women had a higher occurrence of HER2 enriched subtype than the Māori women whereas the Māori women showed a higher occurrence of TNBC. The Pacific Islander women also showed TNBC as did the NZ European women. These results demonstrate that the survival differences in these groups may be influenced by tumour biology. The ER/PR positive tumours made up the large majority of the study group.

ER/PR positive tumours were most common in NZ European than in other ethnic groups. These results are consistent with the literature reviewed whereby ER and PR positive tumours are more common in White American women (indigenous) compared to African American women (non-indigenous) (Gapstur et al. 1996; Dunnwald, Rossing, and Li 2007; Joslyn 2002).

In this study, variability in outcome was also demonstrated by stage at diagnosis. Stage at diagnosis is a key prognostic factor for breast cancer survival and, together with grade, predict the outcome of this disease (Henson, Chu, and Levine 2003). For female breast cancer, 62.1% are diagnosed at the local stage and the 5-year survival for localized female breast cancer is 98.7% (Farrow, Hunt, and Samet 1992; Lazovich et al. 1991; Nattinger et al. 2000).

Studies have reported differences across all age groups in stage at diagnosis and argue that stage disparity was more likely attributed to biology than to the screening factors (Farley and Flannery 1989). Even though biological factors, without doubt, play a role in this divergence in stage at diagnosis, there remain variations by ethnicity that contribute to this survival disparity (Daly and Olopade 2015; Iqbal et al. 2015). In contrast, in the US, African Americans have lower stage-specific survival than Whites for many cancers (Lantz et al. 2006). The poorer survival appears to result in more from inequality in access to care and quality of cancer treatment than from biological differences in tumour characteristics treatment outcomes between the two groups (Jemal, Siegel, and Ward 2008; Jemal, Ward, and Thun 2007; Morris et al. 2007).

In New Zealand, advanced cancer stage at diagnosis in Māori women has been shown to be a possible contributor for a higher breast cancer mortality in this group when compared with NZ European women (Seneviratne et al. 2016). In this study, advanced stages were present in the >70 years age group. Similarly, in the ethnicity groups, stage III and IV were more common in the Pacific Islander women when compared to Māori or Asian women. The results from this study demonstrated an increased risk of five- year mortality for stages II and IV and approaching significance for stage III. These results demonstrate that stage at diagnosis has a contributing role in the survival of women with grade 3 breast cancer in New Zealand.

The incidence and mortality rates of breast cancer in New Zealand are high in comparison to the rest of the developed world. On a global scale, approximately 1.67 million women were diagnosed with breast cancer with an estimated 522,000 related deaths in the vast majority of the countries worldwide (Globocan 2012). One measure of the quality of breast cancer treatment could be the use of five-year survival for patients with the same stage at diagnosis. Studies of treatment outcome in settings where all patients have equal access to treatment and supportive care have

documented that similar treatments yield similar outcomes (McCollum et al. 2002; Ward et al. 2004).

Whilst more advanced cancer stage at diagnosis has an impact on the survival, the differences in biological characteristics appear to be a contributor for inequities in breast cancer mortality between indigenous (Māori) and non-indigenous (NZ European) women (Lawrenson, Seneviratne, et al. 2016). Underlying causes for these differences in biological characteristics are unclear at present and are an area for future research.

5.3 Limitations of the literature reviews

Several hypotheses have been proposed to explain the heterogeneity nature of breast cancer (Polyak 2011). One such hypothesis is that the heterogeneity is reflected by the established prognostic factors and this heterogeneity is a basis of tailoring targeted treatment (Turashvili and Brogi 2017). Turashvili and Brogi also stated that understanding the molecular mechanisms of cancer heterogeneity are relevant for treatment development and advancement in this area (Turashvili and Brogi 2017). In 2015, Der reported that due to its complexity and heterogeneity, unique subtypes such as TNBC will not fit in a predetermined treatment regime (Der et al. 2015). Similar studies also echoed this (Austin et al. 2002; Badowska-Kozakiewicz et al. 2015; Botha et al. 2003; Ghoncheh, Pournamdar, and Salehiniya 2016; Morgan, Refalo, and Cheung 2011b; Onitilo et al. 2009; Shen et al. 2015; Uscanga-Perales, Santuario-Facio, and Ortiz-López 2016).

Ethnicity alone does not affect the outcome but may highlight population groups that are at higher risk, therefore, increase screening and increase socioeconomic status would be important.

Studies seldom report explicitly on the extent of a single prognostic factor affecting the overall survival of breast cancer, and so some caution should be exercised when applying this. However, one study reporting on ethnicity alone as a prognostic indicator for survival does break down this cautionary measure. The study suggested that African American ethnicity was a poor prognostic indicator for breast cancer survival and the outcome was independent of other established prognostic factors (Wieder, Shafiq, and Adam 2016). Ethnicity with regards to causality versus confounding factors is important in order to understand the variation, for e.g. homogenous Jewish populations have a higher mortality rate owing to cultural traditions around marriage. For example with Orthodox Jews this has resulted in a double recessive gene leading to a higher BRCA base risk (Roa et al. 1996). In contrast, in NZ, historically there has been poorer survival outcomes based on whether a person is of Māori or Pacific Island ethnicity. The poorer outcome could, in fact, be related to socioeconomic status and the availability of healthcare services. Some recent studies indicate that the surveillance programmes targeting areas of deprivation identifying patients sooner and therefore improve survival rates (Seneviratne, Campbell, Scott, Coles, et al. 2015; Seneviratne, Campbell, et al. 2015a; Shavers and Brown 2002; Tin Tin et al. 2018).The data of studies showing this trend should be available in the next 4-5 years.

However, there are the confounding and inconsistent use of ethnicity in the literature with the definition of the word ‘ethnicity’ varying from country to country. The variations may be due to history, cultural affiliations, language, religion, and even biology, for e.g. in the US, the coding for ethnicity is extracted from authoritative sources such as Census whilst in Europe, the European Union uses ethnicity in the legal and social context (Aspinall 2011; SEER Cancer Statistics Review). In contrast, the classification of ethnicity in NZ is rigorously done by stating the ethnic group people identify with or feel they belong to including cultural affiliation (Stats NZ, 2013).

Several studies noted ethnicity with the disparity in survival in patients with ER-positive cancers (Hill et al. 2017; Ma et al. 2012; Pathy et al. 2011; Rauscher et al. 2017; Stark et al. 2008). However, these studies did not consider cancer behavior in different ethnicities and proposed that understanding the cancer phenotypes in different ethnicities is important.

Incidence and mortality variations have been reported in studies widely (Bray, McCarron, and Parkin 2004; Ferlay et al. 2015; Miller et al. 2000). However, in terms of research, they may experience problems with data censoring, limited data availability and selective observation. For example, in the study examining the outcome of breast cancer in the indigenous and non-indigenous populations in Australia, New Zealand, Canada and USA, there was a clear difference in cancer profile between the two groups of the population (Moore et al. 2015). Moore also stated that evidence prior to the study was limited and was lacking on whether the incidence of indigenous women within each country had been previously reported across jurisdiction (Moore et al. 2015). For researchers the "draw of the interpretation", risks presenting a biased impression that these two groups of population present a clear difference in cancer profile with data that were somewhat limited. For example the mortality patterns and incidence trends over time were not investigated due to limited or incomplete data availability, difference in health-care systems in countries, differences in treatments in countries, and also the assumption and interpretation of being ‘indigenous’ by an individual (Advani et al. 2014; Bernstein et al. 2003; Condon et al. 2014; Seneviratne et al. 2015; Sugarman et al. 2014; Ward et al. 2004). In 2015, Moore suggested that collaboration between government and the indigenous communities were needed to improve cancer surveillance to relieve the burden of cancer (Moore et al. 2015). Certainly, in many of the articles cited in this study, there is a reference to breast cancer survival being associated with established prognostic factors.

Cancer staging and grading are generally used together to predict clinical behavior and establish an appropriate treatment strategy for breast cancer. Studies have shown that the outcome of advanced stage breast cancer is in relation to factors such as age at diagnosis (younger age), ethnicity (indigenous) and socioeconomic status (low), (Chang et al. 2003; Cluze et al. 2009; Carey et al. 2006). Stage at diagnosis is an independent prognostic factor in all types of breast cancer (Elnashar, Ali, and Gaber 2012; Kamil et al. 2010; Rakha and Ellis 2009; Telloni 2017), hence the use of different treatment strategies (Engstrøm et al. 2015). Factors such as, tumour size, grade of disease and ethnicity, all have a significant effect on survival while the stage and age at diagnosis have a significant effect that varies over time (Rosenberg, Chia, and Plevritis 2005).

Several articles for literature review were excluded because their results were not reported in a manner whereby the effect could be quantified for use.

It is common for papers to adjust for the prognostic factors for e.g.: age-adjusted or stage adjusted, which may at times hinder an investigation to which specific factors could be important determinants of survival disparity.

Another concern is that the reviews from the literature reported a lack of information regarding certain potential confounders, including hormonal, reproductive and lifestyle factors that may be associated with both different histologic types of breast cancer as well as with different clinical and pathologic tumour characteristics that were analysed.

5.4 Study Strengths

This study analysed data from all four breast cancer registries representing 64% of all breast cancer diagnosed in New Zealand in order to demonstrate a view of the impact of the disease in New Zealand and in particular examining grade 3 disease-specific as cancer.

The data is linked to census data to allow researchers to investigate the outcome of breast cancer across the different regions.

There is limited literature on breast cancer for Pacific Island women. Studies thus far have reported that Pacific Island women have lower breast cancer incidence but higher mortality risk than Māori and European women in New Zealand (Meredith et al. 2012). Within the confines of Grade 3 tumours, this incidence rate is re-confirmed. Therefore, this study reflects a strength in that it provides a relatively complete analysis of Pacific Islander group for this disease.

A further strength of this study is that it lies within the population-based nature of the breast cancer registry and the outcome (death) is linked via the patient record. Furthermore, the various ethnic groups present in the four regions are included and represent the population of New Zealand.

Limitations of research pertaining to this study

There is dependence on the data administrators to enter all data accurately and consistently in a timely manner. The data standardization for all four registries in NZ took effect from 2017 making future research using the breast cancer registry more efficient (HRC 2016).

However, there are some data that are missing in the breast cancer registry. It is important that missing data is accounted for. Due to a significant degree of missing or unknown data for some variable, it is important that for future use, the missing data must be taken into consideration in order to improve the overall picture.

Furthermore, this study did not include data on health insurance status or lifestyle factors (e.g., body mass index, weight, physical activity, diet, etc.,) breast density or genetic testing, all of which

can influence breast cancer outcome since these were not available from the registries (Amaral et al. 2010; Kampman et al. 2012; Liu et al. 2017).

Whilst studies have reported on ethnic inequities in breast cancer outcomes in New Zealand, there is insufficient data to fully understand its underlying causes of these differences (Cunningham et al. 2010; McKenzie, Ellison-Loschmann, and Jeffreys 2011, 2010).

The inconsistent recording of disease stage at diagnosis and treatment data may pose significant limitations for researching the causes of inequities (Bennett 2007; Cunningham et al. 2010).

It is also important to acknowledge the limitations before interpreting the results of this study. The histologic categorizations used that was based on diagnoses made by multiple pathologists in multiple institutions. The diagnostic criteria may vary somewhat by both individual pathologists and establishment, resulting in a certain degree of misclassification error.

5.5 Recommendations

Several studies have described the need to understand the molecular mechanism of breast cancer in order to improve overall survival. These studies reported that with better knowledge of molecular mechanisms, a better insight to the disease was provided which would lead for opportunities for therapeutic intervention (Bulut and Altundag 2015; Ellis 2003; Rakha and Ellis 2009; Uscanga-Perales, Santuario-Facio, and Ortiz-López 2016). Additionally, given that there is no evidence in the analysis of the genetic basis for the survival disparity (it is commonly believed that the genetic make-up of a person is different), it may be important to learn from comparisons of survival between majority and minority ethnic groups (Pearce et al. 2004).

Similarly, in New Zealand, studies describing equity-focussed improvements in health care may have improved the survival disparity between Māori and NZ European women (Jeffreys et al. 2005). The studies highlight that when there is improvement in service access, quality, and timeliness of care, patient risk profiles, and understanding of biological factors, there is opportunity for earlier intervention and therefore improved survival (Bennett 2007; Campbell et al. 2015; Seneviratne et al. 2015; Seneviratne et al. 2015).

It is beyond the scope of this study to be able to address the ethnic and socioeconomic status and its impact on the overall survival of women with grade 3 breast cancer, therefore it is recommended that this should be explored.

In summary, based on the literature and results, in order to achieve a tailored approach for the treatment of women diagnosed with grade 3 breast cancer in NZ, the following recommendations/suggestions should be considered: (a) understanding of molecular mechanisms of breast cancer, in particular, grade 3 breast cancer, (b) understanding of patient risk profile, (c) understanding how better access to service impacts on the outcome, (d) quality and timeliness of care for patients, (e) understanding tumour features and mortality with family history.

5.6 Future Directions

This study only covered a small percentage of topics and hence there are limitations to this study. However, listed below are a few areas that could be investigated.

A further analysis of the prognostic factors that were not included in this study such as other variables, for example; lymph-vascular invasion (LVI), height, weight, biomarker(FISH) studies, number of nodes removed, type of surgery, type of treatment and loco-regional recurrence status should be included in future investigation. These additional variables will assist in understanding the prognostic factors that further define grade 3 breast cancer in New Zealand women.

There is also a need to further analyse the interaction of the various ethnicities with each of these variables. Similarly, the effect of treatment and survival time should also be examined. These further analysis could potentially help to further categorise grade 3 breast cancer in NZ women.

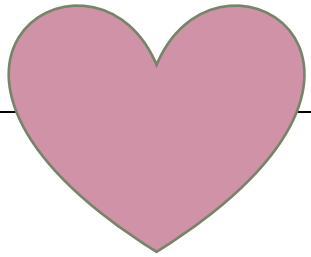
Additionally, a survival analysis investigation should be considered to establish the effect of socioeconomic status (SES). SES can influence a patient's nutritional choice, access to transportation, access to health care intervention service, employment status, medical insurance status, and physical activity. These factors may each independently and/or collaboratively influence the stage at diagnosis, treatment, post-treatment and ultimately survival.

Individualized treatment regimens are gaining popularity worldwide. In order for women to benefit from such personalized care, further research is required with Indigenous participants echoing the efforts made to engage American Indian cancer patients in clinical trials in order to better understand potentially different treatment responses (Guadagnolo et al. 2009).

Finally, the study of tumour biology and genetic susceptibility to help to identify factors that determine the survival disparity in the various groups of women diagnosed with grade 3 breast cancer in NZ should be explored.

Chapter 6

Conclusion



Grade 3 breast cancer is referred to as a heterogeneous high grade group. The disease can be categorized in several ways, including based on its clinical features, its expression of tumour markers, and its histologic type. Breast cancer differs greatly among different patients and even within an individual tumour.

Whilst the ultimate goal is to eliminate breast cancer as a major health problem, it is important to first understand the heterogeneity nature of breast cancer.

This study established that the overall survival during a five year study period of women diagnosed with grade 3 breast cancer in New Zealand is different for the various ethnic groups.

This study also confirmed that despite being high grade, it is not a poor outcome for every patient. Most of the tumours were luminal subtype and a large percentage of the women studied had luminal A subtype which has a better survival. However, despite being a luminal subtype, a smaller percentage were of TNBC subtype which has a poorer survival rate. Therefore, survival is linked to other factors which are of greater importance.

The study also confirmed that Grade 3 tumours are more likely to be a pleomorphic subtype and ER/PR negative.

The results of this study make an initial contribution to the understanding of this high-grade malignancy. The selected prognostic factors were used primarily as a preliminary study into the overall survival of this disease. The inclusion of other factors would add scope for further studies into this aggressive cancer; and such studies should be supported in order to obtain a better understanding and establishment of measures for the prediction and survival with grade 3 breast cancer in New Zealand women.

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Glossary

Adjuvant therapy	Treatment is given in addition to surgery to improve outcome. This may be radiotherapy, chemotherapy, hormonal therapy or treatment with new biological agents such as Herceptin.
BRCA1	Breast cancer gene 1. A gene that is defective in about 2% of women with breast cancer.
BRCA2	Breast cancer gene 2.
Cancer	The growth of abnormal cells that can spread around the body.
Carcinoma	Cancer arising from an epithelial surface – see cancer.
Carcinoma in situ	Cancer cells confined to the inside of the breast duct. Cells have not spread through the basement membrane or lining of the duct. Pre-invasive cancer.
Chemotherapy	The use of various drugs that kill cancer cells.
DCIS	Ductal carcinoma in situ. Cancer cells are confined within the lining of the duct and have not spread.
Duct	A small tube. In the breast, small milk ducts connect the milk sacs to the nipple.
Ductal cancer	Cancer arising in one of the breast ducts.
Grade	There are 3 grades describing how aggressive the cancer cells look. Grade 1 is the “best behaved” cells and Grade 3 the most “troublesome” looking cells.
Heterogeneous	Diverse in character or content.
Hormone	A chemical messenger.
Hormonal therapy	That use of drugs that block the stimulation of cancer cells by estrogen. These drugs are effective in treating cancers that are hormone receptor positive.
Herceptin	A monoclonal antibody that can block the HER2 receptor.
HER2	Human epidermal growth factor receptor 2.
IDC	Invasive ductal carcinoma (IDC), also known as infiltrating ductal carcinoma, is cancer that began growing in a milk duct and has invaded the fibrous or fatty tissue of the breast outside of the duct.
Immunohistochemistry	(IHC) involves the process of selectively imaging antigens (proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues.
Incidence	The occurrence of a disease.
Indigenous	naturally existing in a place or country rather than arriving from another place
Invasive cancer	cancer in which malignant cells have spread from their normal location into the surrounding tissue.
LCIS	Lobular carcinoma in situ. Cancer cells are confined within the lining of the lobule and have not spread.
Lobular cancer	Cancer arising from one of the breast lobules.
Malignant	A tumour that has the ability to spread around the body.

Mammogram	A mammogram is an x-ray of the breast tissue. The breast is carefully positioned and gently compressed between 2 plates to spread out the tissue evenly. An x-ray beam passes through the tissue and creates an image that is stored on a photographic plate.
Metastasis	Cancer that has spread from original cancer and grown at a distance site in the body.
Milk sacs	The structures within the breast that produce milk.
Oestrogen receptor	See hormone receptor.
Prevalence	The proportion of a population that has the condition.
Progesterone receptor	See hormone receptor.
Receptor	A site on the surface of the interior of a cell that can bind a particular molecule such as estrogen, progesterone or HER2. Binding activates the receptor and signals the cell to perform an activity.
Staging	The process of determining the extent and spread of cancer.
Survival rate	An overall survival rate shows the percentage of people who are alive after a certain period of time after the diagnosis of a disease.
Tumour	“A swelling” – a term usually refers to an abnormal growth of cells. Benign Tumours increase in size but do not spread. Malignant Tumours can spread around the body.

Appendices

Appendix A: Approval letter from Auckland University of Technology (AUTEC)

30 March 2017

Fabrice Merien
Faculty of Health and Environmental Sciences

Dear Fabrice

Re Ethics Application: **17/81 Audit of grade 3 breast cancer in New Zealand women**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Subcommittee (AUTEC).

Your ethics application has been approved for three years until 30 March 2020.

As part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 30 March 2020;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 30 March 2020 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Sharita Meharry

Appendix B: Approval letter from the Cancer Advisory Group (CAG)

Reply following CAG review - Full & final approval

THE NEW ZEALAND BREAST CANCER FOUNDATION

Researcher: Sharita Meharry
Project: Audit of Grade 3 Breast Cancer in New Zealand women
Evidence of ethics approval: Out of Scope letter (copy on file)

Dear Sharita,

Thank you for your request to obtain data from the New Zealand Breast Cancer Register (NZBCR). Your request was reviewed by the Clinical Advisory Group (CAG) on 4 May 2017.

Full & final approval

The CAG has given full approval for your project.

The cost incurred – Nil

Data extraction is scheduled in the next two weeks using the finalized list of data fields you submitted with your application.

Currently, the dataset is recorded on four separate registers and will be forwarded to you as four datasets. You will have to merge this yourself. Please let me know if this is an issue.

Standard conditions for use of data:-

- The New Zealand Breast Cancer Register be acknowledged in any media publication or presentation;
- NZBCR CAG reviews all draft publications in a timely manner
- A signed Memorandum of Understanding is returned to the data manager

Please do not hesitate to contact the data manager undersigned if you have any further queries.

Yours sincerely,

Val

Val Davey

Data Coordinator
Christchurch Breast Cancer Patient Register
Christchurch Hospital
Tel: 03-364 0640, Ext 86389
Direct dial: 03-378 6389; Fax: 03-364 0352
Mobile: 021 687 467

Appendix C: Approval letter from Health and Disability Ethics Committees (HDEC)

Health and Disability Ethics Committees
20 Aitken Street
Freyberg Building
PO Box 5013
Wellington

0800 4 ETHICS
hdecs@moh.govt.nz

Thursday, 16 March 2017

Mrs. Sharita Meharry
Auckland University of Technology

Dear Mrs. Meharry,

Study title:	Audit of Grade 3 Breast Cancer in New Zealand women.

Thank you for emailing HDEC a completed scope of review form on 27 February 2017. The Secretariat has assessed the information provided in your form and supporting documents against the Standard Operating Procedures.

Your study will not require submission to HDEC, as on the basis of the information you have submitted, it does not appear to be within the scope of HDEC review. This scope is described in section three of the Standard Operating Procedures for Health and Disability Ethics Committees.

Your study meets the student-led research exemption criteria described below. Your study is an observational, cross-sectional study that aims to investigate by an audit the significant factors in determining survival in women with Grade 3 breast cancers in New Zealand".

For the avoidance of doubt, a study conducted wholly or principally for the purposes of an educational qualification requires HDEC review only if it:

- is an intervention study, or
- is not conducted at or below a Master's level.

If you consider that our advice on your project being out of scope is in incorrect please contact us as soon as possible giving reasons for this.

This letter does not constitute ethical approval or endorsement for the activity described in your application but may be used as evidence that HDEC review is not required for it.

Please note, your locality may have additional ethical review policies, please check with your locality. If your study involves a DHB, you must contact the DHB's research office before you begin. If your study involves a university or polytechnic, you must contact its institutional ethics committee before you begin.

Please don't hesitate to contact us for further information.

Yours sincerely,

Tom Kent

Advisor

Health and Disability Ethics Committees

hdecs@moh.govt.nz