Understanding risk factors in grade 3 breast cancer in NZ

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Abstract

Background: 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. This study analyzed data of patients selected out with the prognostic factor of Nottingham grade 3 tumors over a specified five- year period. These represent a heterogeneous group of cancers with variable survival rates.

Method: All women diagnosed with Nottingham grade 3 invasive breast cancer between 1st January 2011 to 31st December 2015, from four Breast Cancer Registries in New Zealand (Auckland, Waikato, Christchurch, and Wellington) were studied.

Results: Applying Fine-Gray analyses, the study of 2,493 women found that subjects in the older age group (>70 years) had a higher five-year mortality risk (SHR: 1.74 to 2.25, p: 0.053 to <0.001). Analysis of the hormonal receptors showed that tumors with hormonal profile ER-positive, PR negative, and ER-negative, PR negative subjects were at increased mortality risk (SHR: 3.56, p: <0.001) and (SHR: 2.67, p: <0.001) respectively. Molecular subtypes TNBC and Luminal B subjects were at increased risk of five-year mortality (SHR: 3.01 and 3.35 respectively, both p: <0.001). HER2 enriched subjects were at elevated risk (SHR: 1.66, p: 0.11). Women identifying as NZ European ethnicity were at elevated risk of mortality overall (SHR: 1.70, p: 0.11), and they also presented with the highest CIF across ethnicities. The NZ Europeans represented the largest proportion of HER2 enriched and TNBC subjects; however, Pacific Islanders experienced the highest HER2 CIF.

Conclusion: The survival rates for grade 3 breast cancer vary across the selected prognostic factors and ethnicity. Although grade 3 breast cancer is considered as high-grade heterogeneous cancer, this study has shown that not every patient has a poor outcome. NZ Europeans are worst affected followed by Pacific Islanders. Biology of cancer and ethnicity needs to be looked at as a possible factor associated with this disease for differences in survival. The results of this study make an initial contribution to the understanding of high-grade malignancy and other prognostic factors must be included to get a better understanding of the survival differences.

Keywords

Grade 3, Breast cancer, prognostic factors, survival

Background

Breast cancer is the most frequently diagnosed cancer for women worldwide and the disease has a considerable impact on our society[1]. New Zealand (NZ) is amongst the countries with the highest prevalence of breast cancer, with approximately 3,000 new registrations per year, affecting one in nine women and resulting in more than 600 deaths annually [2].

Of the top 20 countries in the world for the highest incidence of breast cancer, New Zealand/Australia (Australasian) was ranked as highest for incidence and mortality of overall breast cancer [3]. In developed countries, Northern America was ranked the highest, whilst in less developed countries, Eastern Africa was ranked the highest for the incidence and mortality of overall breast cancer [3].

Epithelial breast tumors are graded according to the Nottingham criteria (based on morphology and proliferation of the breast tumor cells). This is a three-tier classification. Within this group of grade 3 breast cancer are tumors with varied biology and size thereby resulting in a heterogeneous group of tumors [4].

This heterogeneity challenges the understanding of the pathology of these tumors. It is therefore of great value to understand the behavior of these often-aggressive cancers to establish an appropriate treatment and potentially improve the survival rate of women diagnosed with grade 3 breast cancer in New Zealand.

Data from the New Zealand Breast Cancer Register (NZBCR) for grade 3 breast cancer were analyzed with an attempt to stratify its impact in NZ.

The population of New Zealand is made up of very diverse ethnic groups. The presence of the largest population of Pacific Islanders (8.1%) outside of the Pacific Islands makes it a unique population. However, the largest ethnic group by far are Europeans followed by Maori [5]

Within this diverse ethnicity, breast cancer can be assessed for variable presentation, biology, and survival. This provides a comparison with global literature and a unique report on breast cancer mortality using the New Zealand Breast Cancer Register (NZBCR).

Methods

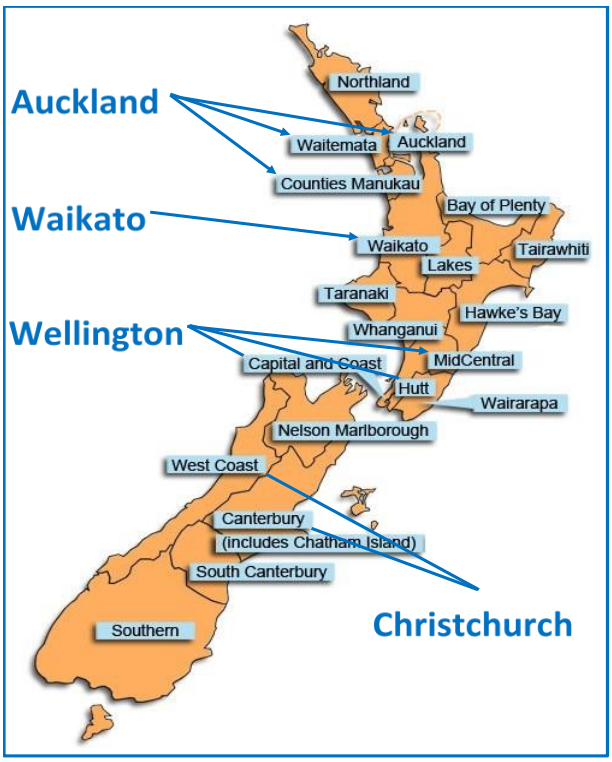
Study design

This is a retrospective cohort study of prospectively collected data, evaluating relevant prognostic factors and overall breast cancer survival of women diagnosed with grade 3 breast cancer in NZ from 1st January 2011 to 31st December 2015. The time frame selected allowed a consistent overlap of data from all four registers (figure 1) to provide a national five-year data set from the date of diagnosis for the multiple cohorts of women.

Data

The NZBCR is made up of data collected from across the country's four major regions. These include all patients treated for breast cancer in Auckland Region (Waitemata, Auckland, and Counties Manukau District Health Boards), Waikato, Wellington (Wairarapa, Capital & Coast, Hutt Valley District Health Boards), and Christchurch (Canterbury District Health Board), as shown in **Error! Reference source not found.**1. These include all patients treated in public and private settings. Approximately 67% of all national New Zealand breast cancer registrations are recorded in these registers [6]

Figure 1.



Sources of data for NZBCR data include pathology laboratories, oncology services, and the breast cancer registry [7]. The overall stage of diagnosis was calculated by using the staging classification of the American Joint Committee on Cancer (AJCC) 7th edition, collating data on tumor size, nodal status, and metastasis (TNM). The patients were stratified at diagnosis into stages 1-4 and X, where stage X was characterized as not assessable. The IHC HER2 status was assessed on the American Society of Clinical Oncology (ASCO) guidelines, into HER2 negative and HER2 positive. Untested status was not included, and missing data, coded as "Unknown," were also not included in the analysis. The histological type was divided into four categories: ductal, lobular, mixed, and others. Hormone receptor status was a combination of Estrogen Receptor (ER) and Progesterone Receptor (PR) positive and negative status. This was further categorized by combining the HER2 status into molecular subtype as luminal A, luminal B, Her2 enriched and Triple Negative Breast Cancer (TNBC.) Age at diagnosis was divided into seven 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.

Statistical Analysis

Descriptive analysis was carried out using standard approaches. The NZBCR characterized cause of death as breast cancer related or other causes, so univariate Fine-Gray competing risk models were carried out, instead of the traditional Cox proportional hazard regression, with subgroup hazard ratios (SHR) reported. The reference group selected for each dependent variable was the most favorable prognostic factor outcome in each group. Cumulative incidence factors (CIF) are reported, as competing risk models were run. Multivariate and interaction models were not able to be run due to small subgroup cell counts. All analyses were carried out using Statistical Data Analysis (STATA) version 16.0.

Results

Demographic factors

Over the five- year study period from 1st January 2011 to 31st December 2015, 2493 women were diagnosed with grade 3 breast cancer, the NZBCR recorded a breast cancer fatality rate of 42.9%. The cohort's overall demographics are summarised in **Error! Reference source not found.**, along with a descriptive summary by ethnicity. Table 2 summarises the univariate, Fine-Gray models. Briefly, women under the age of 50 were at a decreased risk of five-year mortality and this difference approached statistical significance (p=0.063). Women greater than 70 years were at elevated risk (p=0.053); women aged 81 or greater at significantly increased risk (p=0.008) of breast cancer-related causes. The NZ European population was at elevated risk (0.109). In contrast, the Māori and Pacific Islander populations were not at elevated risk of five-year mortality (p=0.363 and 0.440, respectively).

Prognostic factors

Ductal carcinoma represented the largest proportion of grade 3 cancers (Table 1). There was no statistically significant difference in the five–year mortality by histological type (Table 2). The histological subtype Luminal A was documented in the largest proportion of women with grade 3 breast cancer followed by TNBC (Table 1). HER2 enriched were at elevated risk of five-year mortality (p=0.105); TNBC was significant (p<0.001).

The ER/PR positive tumors were the most common hormone receptor status in women with grade 3 breast cancer (Table 1). Women with PR-negative combinations were at increased risk of five-year mortality (p<0.001). Of note, the Pacific Islander group represented more ER/PR positive tumors whereas the Māori group represented more ER/PR negative (Table 1).

A small percentage of women were excluded due to results not captured (Table 1). Early-stage disease: stage I and stage II predominated at diagnosis, 27.18%, 40.08% respectively (Table 1). A comparison between the two did not yield statistically significant differences in five-year mortality. Stage III cancers exhibited a statistically significant, increased risk; however, the error in these

findings is large. This is due to the inconsistent recording of the stage at diagnosis so our confidence in this particular result is preliminary.

Figures 2 and 3 summarize the cumulative incidence factors (CIF) by ethnicity alone and by molecular subtype and ethnicity respectively. Of note, Pacific Islanders had the lowest overall five-year CIF (Figure 2). In contrast, this same community experienced the highest five-year CIF for TNBC (Figure 3d). It should be noted from Table 1 that 48% of grade 3 cancers in the Pacific Islander group were luminal A subtype. This subtype has the lowest risk of five-year mortality cancer. The percentage of Pacific Islanders with TNBC is 15.8%. In contrast, for all other defined ethnic groups, there was a tendency for relatively lower proportions of luminal A (range: ~41%) and higher percentages of TNBC (range: 24-36%). Multivariate, Fine-Gray models were not able to be run due to low subgroup breast cancer mortality-ethnicity cell counts.

Table 1: Demographics and characteristics of women diagnosed with grade 3 breast cancer in NZ

Overall		
Ethnicity	**No.**	**%**
Asian	223	8.9
Maori	244	9.8
NZ European	1783	71.5
Pacific Islander	159	6.4
Other	84	3.4

			By Ethnicity									
			Asian		**Maori**		**NZ European**		**Pacific Islander**		**Other**	
Age			**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
<=40	269	10.8	30	13.5	34	13.9	166	9.3	26	16.4	13	15.5
41-50	627	25.2	74	33.2	76	31.1	413	23.2	47	29.6	17	20.2
51-60	654	26.2	72	32.3	81	33.2	438	24.6	47	29.6	16	19
61-70	511	20.5	32	14.3	42	17.2	387	21.7	28	17.6	22	26.2
71-80	267	10.7	10	4.5	9	3.7	228	12.8	11	6.9	9	10.7
>80	165	6.6	5	2.2	2	0.8	151	8.5	0	0	7	8.3
Cause of Death												
Breast Cancer	171	56.1	10	58.8	16	51.6	134	59.3	8	33.3	3	42.9
Other causes	134	43.9	7	41.2	15	48.4	92	40.7	16	66.7	4	57.1
Histological Type												
Ductal	2253	91.5	209	94.1	226	92.6	1590	90.6	149	94.3	79	94
Lobular	78	3.2	3	1.4	4	1.6	67	3.8	4	2.5	0	0
Mixed	18	0.7	2	0.9	3	1.2	13	0.7	0	0	0	0
Other	114	4.6	8	3.6	11	4.5	85	4.8	5	3.2	5	6
Stage												
0	5	0.2	1	0.4	0	0	3	0.2	1	0.6	0	0
I	709	28.4	58	26	65	26.6	537	30.1	21	13.2	28	33.3
II	1024	41.1	95	42.6	107	43.9	736	41.3	60	37.7	26	31
III	356	14.3	39	17.5	35	14.3	228	12.8	38	23.9	16	19
IV	363	14.6	29	13	34	13.9	251	14.1	36	22.6	13	15.5
X	36	1.4	1	0.4	3	1.2	28	1.6	3	1.9	1	1.2
Subtype												
Luminal A	749	41.9	63	41.7	78	42.9	526	41.3	58	48.3	24	38.1
Luminal B	153	8.6	16	10.6	26	14.3	99	7.8	8	6.7	4	6.3
Her Enriched	295	16.5	25	16.6	34	18.7	196	15.4	35	29.2	5	7.9
Triple Negative	592	33.1	47	31.1	44	24.2	452	35.5	19	15.8	30	47.6

Table 2: Univariate Fine-Gray models of women diagnosed with grade 3 breast cancer in NZ

Age	SHR	Robust SE	Z	p	CI	
41-50	0.578	0.170	-1.86	0.063	0.324	1.030
51-60	0.944	0.253	-0.22	0.830	0.558	1.597
61-70	0.728	0.213	-1.08	0.278	0.411	1.291
71-80	1.738	0.495	1.94	0.053	0.994	3.038
>80	2.253	0.689	2.66	0.008	1.237	4.104
Ethnicity						
Maori	1.445	0.584	0.91	0.363	0.654	3.191
NZ European	1.695	0.558	1.60	0.109	0.889	3.232
Other	1.287	0.833	0.39	0.697	0.362	4.574
Pacific Islander	1.440	0.681	0.77	0.440	0.570	3.639
Histotype						
Ductal	1.347	0.684	0.59	0.557	0.498	3.645
Mixed	0.779	0.525	-0.37	0.711	0.208	2.917
HR Status						
ER-/PR+	1.200	1.181	0.19	0.853	0.175	8.257
ER+/PR-	3.555	0.774	5.82	0.000	2.320	5.447
ER-/PR-	2.672	0.534	4.92	0.000	1.807	3.952
Stage						
II	1.829	1.081	1.02	0.307	0.574	5.828
III	1.994	1.409	0.98	0.329	0.499	7.964
IV	79.415	40.194	8.64	0.000	29.450	214.148
X	6.189	6.949	1.62	0.104	0.685	55.886
Subtype						
Luminal B	3.354	1.094	3.71	0.000	1.770	6.358
Her2 Enriched	1.659	0.519	1.62	0.105	0.899	3.062
Triple Negative	3.013	0.715	4.65	0.000	1.892	4.799

Figure. 2

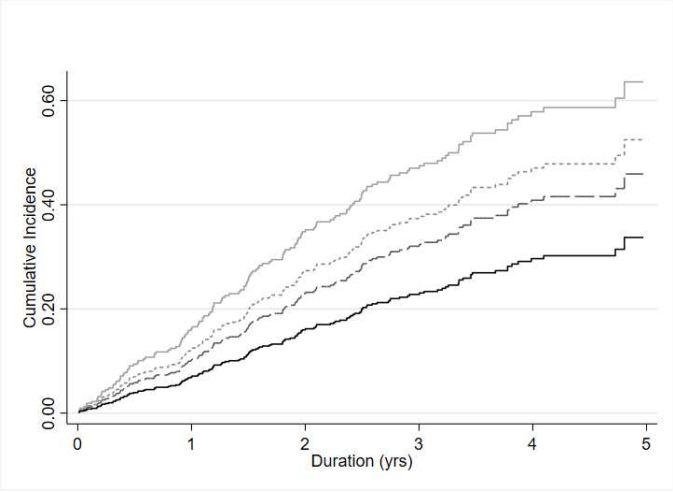


Figure. 3a

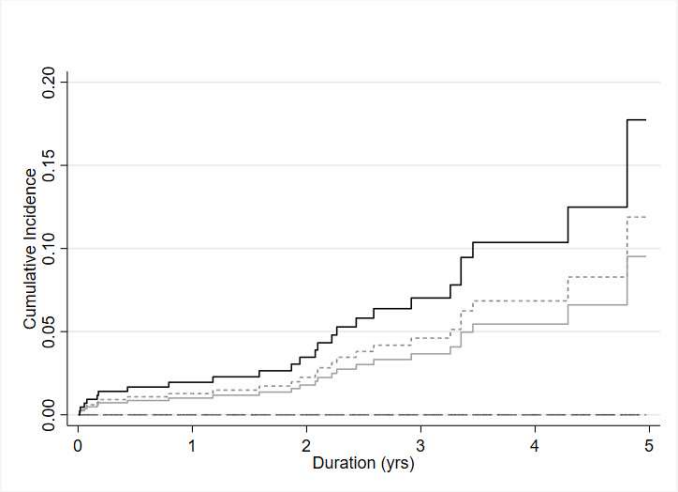


Figure. 3b

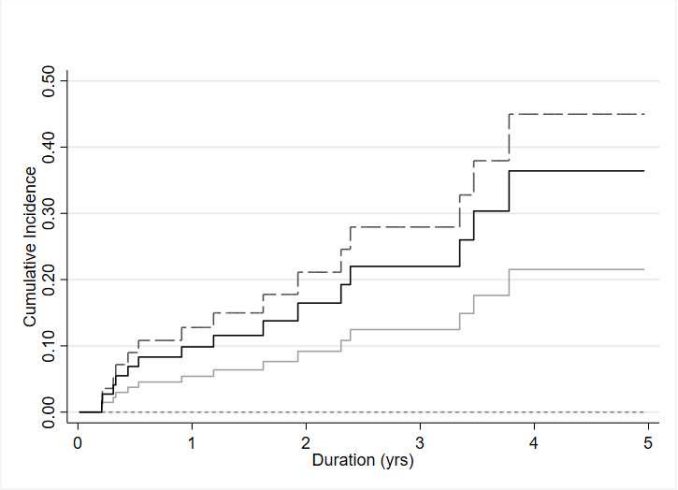


Figure. 3c

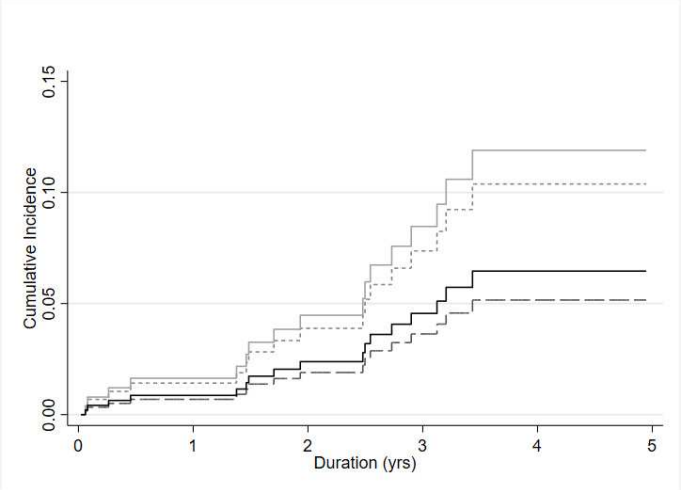
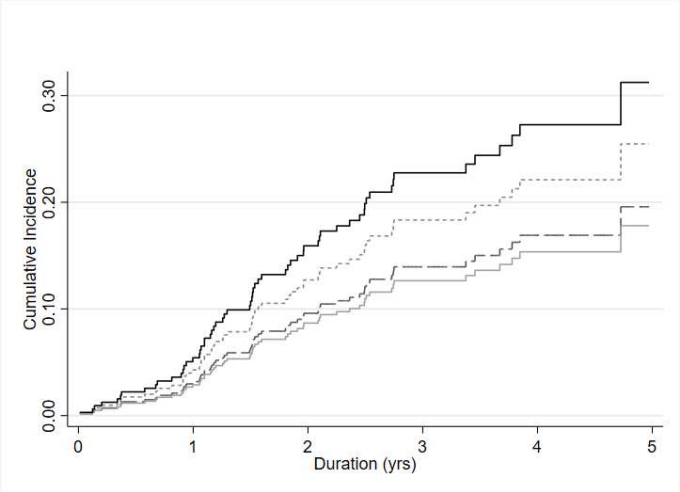


Figure.3d



Discussion

A limited range of common prognostic factors deemed relevant for this study was selected, to provide a preliminary understanding of the characteristics of grade 3 breast cancer in New Zealand women.

The mortality is related to breast cancer only. NZ subjects in the older age group of >70 years were at increased risk of five-year mortality. This is consistent with the literature finding [8-12]

Amongst all ethnicities, the NZ European population was at elevated risk overall; however, the CIF across ethnicity varied by molecular subtype (figure 3). The analysis also reported that the NZ European group presented the largest group in proportion to the population for HER2 enriched and TNBC and the subjects from these two molecular subtypes were at increased risk of five-year mortality. Whilst the morphology type showed there was no statistically significant difference observed, the molecular subtypes (HER2 enriched and TNBC) subjects were at increased risk of five-year mortality. The latter is consistent with literature finding [13-20]. The study could not do full SHR's for the ER and PR for the various ethnicity groups due to small cell counts, so our outcome is preliminary here.

Luminal B subtype has a poorer prognosis and women with PR-negative combinations (luminal B subtype) were at increased risk of five-year mortality and this is consistent with literature finding [21]. It must be noted that in this study the luminal B subtype was relatively more frequent in the Maori

group. In contrast, the Luminal A subtype is associated with better five-year survival. However, despite, showing a lower and better biological profile of tumor risk marker, overall, the Pacific Islander group showed poorer survival in comparison with the other ethnic groups in this study.

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 [22], which appears to be re-confirmed in this study. Therefore, this study reflects a strength in that it provides additional information on the Pacific Islander group with grade 3 breast cancer.

The study included an analysis of data from four breast cancer registries. The registry represents 67% of all breast cancer diagnosed in New Zealand [6]. Data analysis was used to assess the impact of the disease in New Zealand with an emphasis on grade 3 breast cancer. The data is linked to census data to allow researchers to investigate the outcome of breast cancer across different regions. The study also 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 reflective of the population of New Zealand.

The inconsistent recording of disease stage at diagnosis and treatment data may pose significant limitations for researching the causes of inequities [23, 24]. Whilst stage III breast cancers exhibited a statistically significant increased risk of five-year mortality, due to the inconsistent recording, the error in these findings is large, therefore our confidence in the results for this particular prognostic factor (stage at diagnosis) is tentative.

The histologic type of breast cancer in this group was assigned by multiple pathologists in multiple institutions. Although standardized guidelines from the Nottingham grading system are used, there is subjective variation, therefore the diagnostic criteria may vary somewhat by both individual pathologists and establishment, resulting in a certain degree of misclassification error.

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 [25-27].

Studies describing equity-focussed improvements in health care may have improved the survival disparity between Māori and NZ European women [28]. The studies highlight that when there is an improvement in service access, quality, and timeliness of care, patient risk profiles, and understanding of biological factors, there is an opportunity for earlier intervention and therefore improved survival [23, 29-33]. However, whilst studies have reported on ethnic inequities in breast cancer outcomes in New Zealand, there is insufficient data to fully understand its underlying contribution to these differences [24, 34-37]

From the analysis, we found that survival rates for breast cancer varied across the selected prognostic factors and confirms that it is dependent on multiple factors. Some of these include patient factors, tumor biology, and ethnicity, as well as access to health interventions and treatment, socioeconomic status, availability of drugs, and the treatment type available [38-40].

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.

Based on the literature and results, to help understand survival disparities within the ethnic groups, in particular Maori and Pacific Islander, the following recommendations/suggestions should be considered: understanding tumor biology and genetic susceptibility of grade 3 breast cancer, understanding of patient risk profile, understanding how better access to service impacts on the outcome, quality and timeliness of care for patients, understanding mortality with family history, benefits of personalized care.

Further analysis of the prognostic factors that were not included in this study such as 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.

These factors may each independently and/or collaboratively influence survival and could help to further categorize grade 3 breast cancer in NZ women.

Conclusion

Grade 3 breast cancer is referred to as heterogeneous and high-grade cancer. Despite being high-grade cancer, it does not have a poor outcome for every patient. This study has shown that there are survival differences in the various ethnic groups studied. The New Zealand Europeans and the Pacific Islanders are at increased risk of early death. The trajectory towards poor overall survival for Pacific Islanders needs further examination, therefore more research is needed to identify the causes of these survival disparities. A multitude of factors may each independently and/or collaboratively influence survival; elucidation of these could help to further categorize grade 3 breast cancer in NZ women. This, in turn, will contribute to a greater understanding of the risk factors of grade 3 breast cancer in NZ, and possibly enable better outcomes for all.

Abbreviations

AUTEC- Auckland University of Technology Ethics Committee

CIF- Cumulative Incidence factor

ER-Estrogen Receptor

HER2- Human Epidermal Growth Factor Receptor 2

IHC- Immunohistochemistry

NZ- New Zealand

NZBCR- New Zealand Breast Cancer Register

PR- Progesterone Receptor

SHR- Subgroup Hazard Ratio

STATA- Statistical Data Analysis

TNBC- Triple-Negative Breast Cancer

TNM- Tumour, Node, Metastasis

Declarations

Ethics approval and consent to participate

This study (Reference 17/81) was approved by the Auckland University of Technology Ethics subcommittee (AUTEC). No other ethics approval was required due to the retrospective nature of the study. The patient information used for data analysis for this study is anonymous. The analysis and publication of the study will not infringe on enrolled patients' health, safety, and privacy.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from New Zealand Breast Cancer Register but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of New Zealand Breast Cancer Register.

Competing interests

No competing interests

Funding

Not Applicable

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Authors' contributions

RB contributed to the study design, data analysis, and interpretation. RR contributed to clinical interpretation and study design. FM contributed to study design. The authors read and approved the final manuscript.

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List of Figures

Figures

Figure 1

Coverage of the New Zealand Breast Cancer. Curteosy of Breast Cancer Foundation.

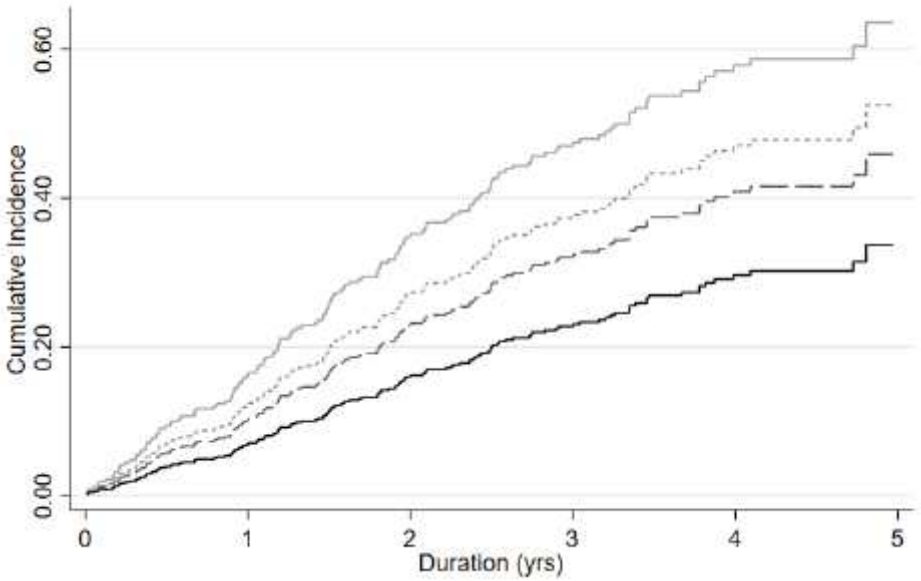

Figure 2

Cumulative Incidence of five-year mortality of Grade 3 breast cancer by ethnicity

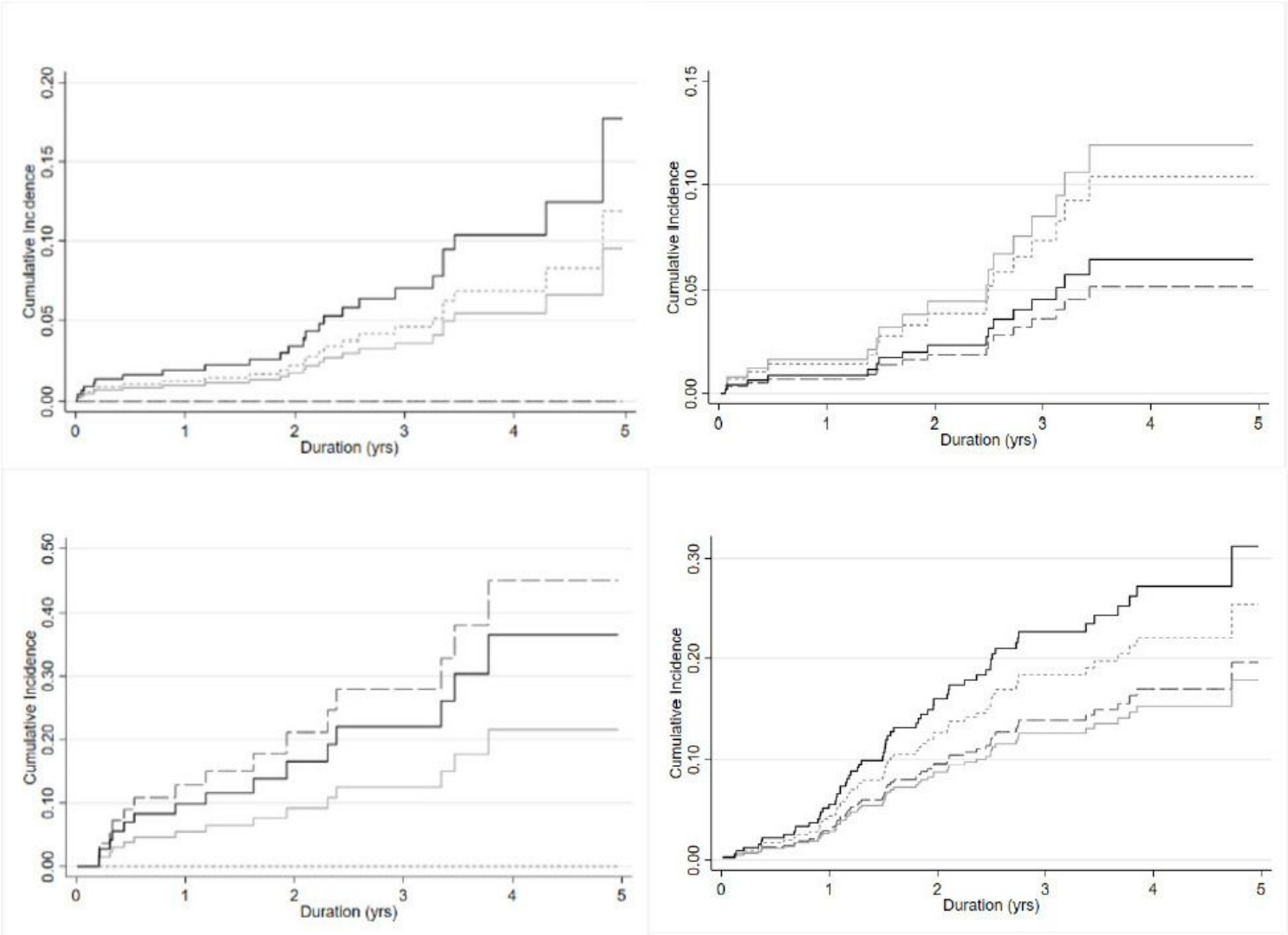

Figure 3

(Top left) a. Cumulative Incidence of five-year mortality of molecular subtype Luminal A by Ethnicity
(Bottom left)b. Cumulative Incidence of five-year mortality of molecular subtype Luminal B by ethnicity
(Top right) c. Cumulative Incidence of five-year mortality of molecular subtype Her2 enriched by Ethnicity
(Bottom right)d. Cumulative Incidence of five-year mortality of molecular subtype TNBC by Ethnicity