The impact of different tumour subtypes on management and survival of New Zealand women with stage I-III breast cancer

Abstract

Aims: This study aims to describe the prevalence and characteristics of the different ER/PR/HER2 subtypes in New Zealand women with breast cancer, and to explore their treatment and outcomes.

Methods: This study included women diagnosed with stage I-III breast cancer between January 2006 and May 2013, recorded in the combined Waikato and Auckland Breast Cancer Registers, and with complete data on their ER, PR and HER2 status. Five ER/PR/HER2 phenotypes were classified. Kaplan-Meier method and Cox proportional hazards model were used to examine the survival differences among these subtypes.

Results: Of the 6875 eligible women, 4274 (62.2%) were classified as Luminal A, 836 (12.2%) as Luminal B HER2-, 605 (8.8%) as Luminal B HER2+, 401 (5.8%) as HER2+ non-Luminal and 759 (11.0%) as Triple Negative. Māori and Pacific women were less likely to have Triple Negative disease, while Pacific women were more likely to be HER2+ non-Luminal. The 5-year breast cancer-specific survival was worst for HER2+ non-Luminal (80.1%) and Triple Negative (81.9%), followed by Luminal B HER2- (89.3%) and Luminal B HER2+ (91.6%), and was the best for Luminal A (96.8%). The adjusted breast cancer-specific mortality hazard ratio for Triple Negative and HER2+ non-Luminal compared to Luminal A was 4.91 (95% CI: 3.86-6.26) and 3.94 (95% CI: 2.94-5.30), respectively.

Conclusions: The pattern of phenotype in women with stage I-III breast cancer is similar to the overseas cohorts. Most New Zealand women with Luminal A breast cancer have a very good prognosis, but there are less common subtypes have relatively poor outcomes.

Key words: Breast cancer; Subtypes; Estrogen receptor; Progesterone receptor; Human epidermal growth factor receptor 2; Mortality

Introduction

Breast cancer outcomes have been shown to be strongly linked not only to patient characteristics, and the extent of disease at diagnosis but also to the presence or absence of hormonal biomarkers.[1-4] In the 1970s the discovery of an estrogen receptor (ER) led to the finding that only those tumours that were ER positive were sensitive to hormonal treatment.[5] This led to the routine measurement of ER status and targeting of treatment, and subsequently, the introduction of the measurement of a progesterone receptor (PR). ER and PR receptor status have implications for prognosis – women with breast cancers that are both ER and PR positive (+) have a better prognosis. ER status in particular, and to a lesser extent PR status currently have a major influence on the choice of systemic treatment.[6]

In New Zealand ER and PR status have been routinely measured for the last 25 years. The measurement of human epidermal growth factor receptor 2 (HER2) status became increasingly common from the first part of this century and has been routine since 2006. This is in line with many other countries.[7,8] In 2006, 12 months of adjuvant therapy was licensed by the FDA for the treatment of stage I-III HER2 positive breast cancer.[9] PHARMAC approved funding a 9-week course of trastuzumab for stage I-III breast cancer from July 2007,[10] and a 12-month course from July 2010.[11,12] Other biomarkers such as Ki67, or BRCA gene mutation status, are not routinely measured at this time but may become more relevant in the future.[13,14] It has become common practice to categorise cancer into conceptual molecular classes that have different prognostic features, and predict response to specific therapies. This has led to a more personalised approach to treatment based on a patient's molecular phenotype. While a number of studies have been published on the prevalence of individual biomarkers in different ethnic groups in New Zealand,[1,15-17] there has been little opportunity to look at different molecular categories and how they influence treatment or patient outcomes.

The aim of this study was to describe the prevalence and characteristics of the different breast cancer tumour types as indicated by these biomarkers in women with stage I-III breast cancer.

We then looked at the treatment of these women including the use of endocrine therapy, chemotherapy, and trastuzumab for breast cancers that were HER2+. Finally we wanted to examine the outcomes in these different groups of breast cancers.

Methods

The studied population have been identified from the combined Waikato and Auckland Breast Cancer Registers.[18] It has clinical details of 12372 women diagnosed with invasive breast cancer between June 2000 and May 2013. Only women who were diagnosed with stage I-III breast cancer between January 2006 and May 2013 and had complete data on their ER, PR and HER2 status were included in this study, as HER2 status testing has been routine since 2006.

The registers' data includes: 1) patient characteristics: age and ethnicity; 2) tumour information: diagnosis date, cancer stage and biomarkers, and 3) information on treatment: surgery, chemotherapy, trastuzumab, endocrine therapy and radiation therapy. Information on comorbidities has been obtained by reviewing linked data from the National Minimum dataset (NMDS) and characterising patients using the C3 comorbidity index: 1) less or equal to zero, 2) greater than zero but less or equal to one, and 3) greater than one.[19,20]

In this study, HER2+ was defined as FISH amplified or IHC 3+ according to the 2013 American Society of Clinical Oncology (ASCO) guideline.[21] Recommended in the 2001 St. Gallen Consensus, ER+ or PR+ was assessed as IHC positive (1+).[22] Based on whether the three biomarkers ER, PR and HER2 were either positive or negative, there were eight possible groups defined by ER, PR and HER2 status. We reduced these groups to five categories based on the St. Gallen Consensus recommendation[3,23,24] and clinical advice and practice in our region. The most common finding in women with breast cancer is a cancer that is both ER and PR positive but HER2 negative. These breast cancers were categorised as Luminal A.

Luminal B HER2- includes women whose breast cancer is ER+, but PR- and HER2–. This group is important as women with breast cancers that are PR negative have a poorer prognosis. There is also a small group (1%) of women with breast cancer that is ER- but PR+. We have included these cases in Luminal B HER2-. A further category is women with breast cancers that are HER2+. These women are usually offered adjuvant chemotherapy plus trastuzumab. These women can be divided into those who would benefit from endocrine therapy (i.e. breast cancers that are ER+ or ER- but PR+ (Luminal B HER2+) and a second group of breast cancers that are ER-, PR-, but HER2+ (HER2+ non-Luminal)). Finally there is a group that are Triple Negative (ER-, PR-, and HER2-).

Patient outcomes include breast cancer-specific survival and all-cause survival. These mortality data were derived from the New Zealand National Mortality Collection and linked by the National Health Index (NHI) number to the register data. The NHI number is a unique identifier for people who use health and disability services in New Zealand. For all-cause survival analyses, patients without mortality information were considered to be censored on the last updated date for Mortality Collection which was 31 December 2014. For cancer-specific analyses, deaths from other causes were censored on the date of death. Kaplan-Meier method was used to examine the breast cancer-specific survival in the five subtypes. We used Cox proportional hazards model to estimate the hazard ratio of breast cancer-specific mortality and all-cause mortality by subtype, ER status, PR status, HER2 status and lymph nodes after adjustment for age, ethnicity, stage, comorbidity and year of diagnosis. All data analyses were performed in IBM SPSS statistics 23 (New York, United States).

Results

Of the 12372 invasive breast cancer cases, 574 were metastatic at diagnosis and 11798 were stage I-III at diagnosis. Of the stage I-III breast cancer cases, 4475 cases were diagnosed in 2000-2005 and 7320 were diagnosed in 2006-2013. Of those 7320 cases diagnosed in 2006-

2013, 448 (6.1%) without complete ER, PR or HER2 results were excluded from this study. Those 6875 women who had complete information on their ER, PR and HER2 status were included.

Of the included cancer cases, 4274 (62.2%) cases were classified as Luminal A, 836 (12.2%) as Luminal B HER2-, 605 (8.8%) as Luminal B HER2+, 401 (5.8%) as HER2+ non-Luminal and 759 (11.0%) as Triple Negative (Table 1). The mean age varied by subgroup from 58.5 years in Luminal A, 61.1 years in Luminal B HER2-, 54.1 years in Luminal B HER2+, 53.5 years in HER2+ non-Luminal and 57.2 years in Triple Negative. Women with breast cancers that were HER2+ or Triple Negative breast cancer were younger than those classified as Luminal A or Luminal B HER2-. Māori and Pacific women were more likely to have HER2+ breast cancer but less likely to have Triple Negative disease than non-Māori/non-Pacific women. There were stark differences in stage and grade of cancer at diagnosis between the different subtypes: 32.4% of women in HER2+ non-Luminal had stage III cancer compared to 12.5% in Luminal A; 80.8% of women with Triple Negative cancer had grade 3 disease while only 12.0% in Luminal A had grade 3 cancer (Table 2).

As expected the treatment varied depending on the subtype identified. In total, 97.6% of women were treated with surgery, and women with Luminal A were more likely to be treated with breast conserving surgery. In contrast, 64.6% of women with ER-, PR- and HER2+ breast cancer (HER2+ non-Luminal) were treated with a mastectomy. Of Luminal A women, 71.7% received endocrine therapy compared to 87.6% of the women with Luminal B HER2+ cancer. Chemotherapy was more likely to be prescribed for breast cancers with the worst prognosis – i.e. cancers that were HER2+ or Triple Negative. Of the cancers that were HER2+, those who were ER- and PR- (HER2+ non-Luminal) were more likely to receive trastuzumab than those who were ER/PR positive (Luminal B HER2+).

Table 1. Demographics of patients by cancer subtype

Subgroups	Luminal A		Luminal B HER2-		Luminal B HER2+		HER2+ non-Luminal		Triple Negative		P-value for Chi-square test	Total
Region											<0.001	
Auckland	3421	63.4%	563	10.4%	424	7.9%	342	6.3%	647	12.0%		5397
Waikato	853	57.7%	273	18.5%	181	12.2%	59	4.0%	112	7.6%		1478
Year of diagnosis											<0.001	
2006-2007	963	58.0%	221	13.3%	142	8.6%	117	7.1%	216	13.0%		1659
2008-2009	1167	62.4%	209	11.2%	156	8.3%	106	5.7%	232	12.4%		1870
2010-2011	1202	63.9%	226	12.0%	161	8.6%	97	5.2%	194	10.3%		1880
2012-2013	942	64.3%	180	12.3%	146	10.0%	81	5.5%	117	8.0%		1466
Age (years)											<0.001	
<40	179	43.3%	39	9.4%	67	16.2%	45	10.9%	83	20.1%		413
40-49	1044	65.0%	125	7.8%	169	10.5%	107	6.7%	161	10.0%		1606
50-59	1135	61.5%	209	11.3%	179	9.7%	130	7.0%	192	10.4%		1845
60-69	1102	63.8%	252	14.6%	125	7.2%	80	4.6%	167	9.7%		1726
70-79	510	62.9%	124	15.3%	44	5.4%	29	3.6%	104	12.8%		811
80+	304	64.1%	87	18.4%	21	4.4%	10	2.1%	52	11.0%		474
Ethnicity											<0.001	
Others	3539	61.8%	730	12.7%	479	8.4%	306	5.3%	672	11.7%		5726
Māori	454	64.2%	83	11.7%	75	10.6%	40	5.7%	55	7.8%		707
Pacific	281	63.6%	23	5.2%	51	11.5%	55	12.4%	32	7.2%		442
Total	**4274**	**62.2%**	**836**	**12.2%**	**605**	**8.8%**	**401**	**5.8%**	**759**	**11.0%**		**6875**

Table 2. Tumour characteristics and treatment by cancer subtype

Subgroups	Luminal A		Luminal B HER2-		Luminal B HER2+		HER2+ non-Luminal		Triple Negative		P-value for Chi-square test	Total	
Tumour size (mm)											<0.001		
0~10	720	17.1%	133	16.5%	70	11.9%	71	18.3%	84	11.2%		1078	16.0%
10~20	1661	39.5%	251	31.1%	187	31.7%	93	24.0%	220	29.3%		2412	35.8%
20~30	931	22.2%	208	25.7%	158	26.8%	82	21.2%	217	28.9%		1596	23.7%
30~50	603	14.4%	154	19.1%	115	19.5%	86	22.2%	178	23.7%		1136	16.9%
50+	286	6.8%	62	7.7%	60	10.2%	55	14.2%	53	7.0%		516	7.7%
Unknown	73		28		15		14		7			137	
Stage											<0.001		
I	2223	52.0%	358	42.8%	214	35.4%	121	30.2%	268	35.3%		3184	46.3%
II	1515	35.4%	346	41.4%	245	40.5%	150	37.4%	358	47.2%		2614	38.0%
III	536	12.5%	132	15.8%	146	24.1%	130	32.4%	133	17.5%		1077	15.7%
Grade											<0.001		
1	1545	36.7%	190	23.3%	30	5.1%	5	1.3%	17	2.3%		1787	26.5%
2	2164	51.4%	374	45.9%	282	47.5%	74	19.1%	126	16.9%		3020	44.7%
3	504	12.0%	250	30.7%	282	47.5%	309	79.6%	603	80.8%		1948	28.8%
Unknown	61		22		11		13		13			120	
Lymph nodes											<0.001		
No positive lymph nodes	2601	63.8%	479	60.6%	296	50.7%	175	45.3%	462	62.4%		4013	61.0%
Positive lymph nodes	1479	36.3%	312	39.4%	288	49.3%	211	54.7%	278	37.6%		2568	39.0%
Unknown	194		45		21		15		19			294	

Table 2. Continue

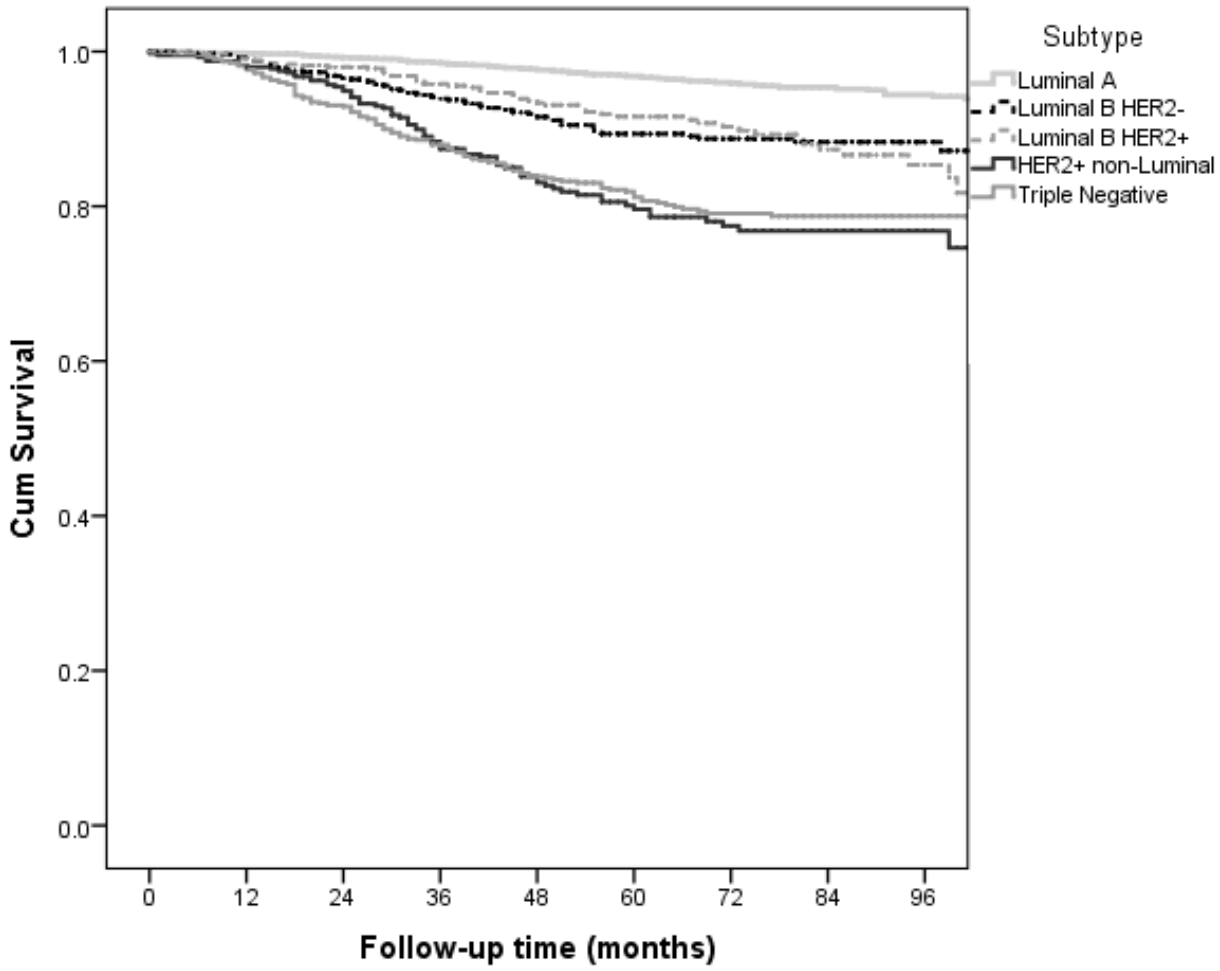
Subgroups	Luminal A		Luminal B HER2-		Luminal B HER2+		HER2+ non-Luminal		Triple Negative		P-value for Chi-square test	Total	
Surgery											<0.001		
Breast conserving surgery	2520	59.0%	424	50.7%	267	44.1%	132	32.9%	361	47.6%		3704	53.9%
Mastectomy	1650	38.6%	384	45.9%	324	53.6%	259	64.6%	390	51.4%		3007	43.7%
No primary surgery	104	2.4%	28	3.3%	14	2.3%	10	2.5%	8	1.1%		164	2.4%
Endocrine therapy											<0.001		
No Endocrine therapy	1210	28.3%	213	25.5%	75	12.4%	381	95.0%	723	95.3%		2602	37.8%
Endocrine therapy	3064	71.7%	623	74.5%	530	87.6%	20	5.0%	36	4.7%		4273	62.2%
Chemotherapy											<0.001		
No Chemotherapy	3302	77.3%	575	68.8%	173	28.6%	92	22.9%	252	33.2%		4394	63.9%
Chemotherapy	972	22.7%	261	31.2%	432	71.4%	309	77.1%	507	66.8%		2481	36.1%
Trastuzumab											<0.001		
No Trastuzumab	4264	99.8%	832	99.5%	204	33.7%	106	26.4%	750	98.8%		6156	89.5%
Trastuzumab	10	0.2%	4	0.5%	401	66.3%	295	73.6%	9	1.2%		719	10.5%
Total	**4274**		**836**		**605**		**401**		**759**			**6875**	

Overall Luminal A women had a very good prognosis while women with cancers that were HER2+, ER- or were Triple Negative had a relatively poor prognosis (Fig 1). The 5-year breast cancer-specific survival (Table 3) was worst for HER2+ non-Luminal (80.1%) and Triple Negative (81.9%), followed by Luminal B HER2- (89.3%) and Luminal B HER2+ (91.6%), and was the best for Luminal A (96.8%, Log-rank test p-value <0.001).

Table 3. 5-year breast cancer-specific survival and all-cause survival by subtype

Subtype	Breast cancer-specific survival		All-cause survival	
	5-year survival	(95% CI)	5-year survival	(95% CI)
Luminal A	96.8%	(96.2%-97.4%)	91.9%	(90.9%-92.8%)
Luminal B HER2-	89.3%	(86.9%-91.8%)	81.6%	(78.6%-84.7%)
Luminal B HER2+	91.6%	(89.0%-94.2%)	87.5%	(84.4%-90.6%)
HER2+ non-Luminal	80.1%	(75.6%-84.6%)	78.1%	(73.5%-82.7%)
Triple Negative	81.9%	(78.9%-84.9%)	76.7%	(73.4%-79.9%)

CI: confidence interval



Follow-up time (months)		0	12	24	36	48	60	72	84	96
Number of women at risk	Luminal A	4274	4241	3916	3209	2578	1987	1413	866	452
	Luminal B HER2-	836	814	733	582	460	349	261	170	88
	Luminal B HER2+	605	596	549	436	355	267	192	125	62
	HER2+ non-Luminal	401	394	350	277	217	169	125	85	40
	Triple Negative	759	738	651	544	420	342	260	157	80

Fig 1. Breast cancer-specific survival by subtype using the Kaplan Meier method

After adjustment for age, ethnicity, stage, comorbidity and year of diagnosis, women with Triple Negative breast cancer had the worst prognosis (Table 4): hazard ratio of 4.91 (95% CI: 3.86-6.26, p-value<0.001) for breast cancer-specific mortality and 2.74 (95% CI: 2.29-3.28, p-value<0.001) for all-cause mortality compared to Luminal A. The second worst prognosis was HER2+ non-Luminal with a hazard ratio of 3.94 (95% CI:2.94-5.30, p-value<0.001) for breast cancer-specific mortality and 2.46 (95% CI:1.92-3.15, p-value<0.001) for all-cause mortality compared to Luminal A. Breast cancer-specific mortality hazard ratios were 3.19 (95% CI: 2.65-3.85, p-value<0.001) for ER-, 3.29 (95% CI:2.72-3.98, p-value<0.001) for PR-,

1.58 (95% CI:1.28-1.96, p-value<0.001) for HER2+ and 1.18 (95% CI:0.89-1.55, p-value=0.248) for lymph node positive, respectively.

Table 4. Hazard ratios in breast cancer-specific mortality and all-cause mortality after adjustment for age, ethnicity, stage, comorbidity and year of diagnosis

Subgroups	Breast cancer-specific mortality			All-cause mortality		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Subtype						
Luminal A	Ref			Ref		
Luminal B HER2-	2.64	1.98-3.51	<0.001	1.85	1.52-2.25	<0.001
Luminal B HER2+	2.04	1.47-2.82	<0.001	1.46	1.14-1.88	0.003
HER2+ non-Luminal	3.94	2.94-5.30	<0.001	2.46	1.92-3.15	<0.001
Triple Negative	4.91	3.86-6.26	<0.001	2.74	2.29-3.28	<0.001
ER status						
ER+	Ref			Ref		
ER-	3.19	2.65-3.85	<0.001	2.21	1.91-2.56	<0.001
PR status						
PR+	Ref			Ref		
PR-	3.29	2.72-3.98	<0.001	2.12	1.85-2.43	<0.001
HER2 status						
HER2-	Ref			Ref		
HER2+	1.58	1.28-1.96	<0.001	1.36	1.14-1.62	<0.001
Lymph nodes						
No positive lymph nodes	Ref			Ref		
Positive lymph nodes	1.18	0.89-1.55	0.248	1.08	0.88-1.32	0.480

Discussion

The proportion of women in each subgroup was similar to that found in other large studies with 62% women having Luminal A tumours and 11% having Triple Negative type tumours.[25] The differences in characteristics by subtype in our study are also consistent with other international cohorts.[2,26] As age increased, the proportion of women with Luminal A breast cancer increased. HER2+ non-Luminal and Triple Negative breast cancers were more likely to be grade 3 (80%), and Luminal A cancers were the least likely to be grade 3 (12%). HER2+ cancers were more likely to have positive lymph nodes and worse cancer stage than other subtype cancers.[2,26]

The findings from two large cancer centres in New Zealand show that treatment for stage I-III breast cancer is tailored to the subtype with variation in the use of endocrine therapy, chemotherapy and trastuzumab. Women with rarer subtypes such as HER2+ and Triple Negative were more likely to receive chemotherapy and when identified either endocrine therapy or trastuzumab. On the other hand, women with Luminal A disease who have a good prognosis were less likely to receive chemotherapy. Surgical treatment also varied by subtype. Women with Luminal A cancer were more likely to be treated with breast conserving surgery. However, women with phenotypes with poor prognosis were less likely to receive breast conserving surgery. No doubt this is affected by the prognosis of the subtype, but other factors such as the size of the tumour, lymph node involvement, stage and grade also affect surgical treatment.[27]

As well as noting the different characteristics and treatment of women at the time of diagnosis in the five subgroups there were also differences in outcomes. The survival curves show that in the majority of women, i.e. those in Luminal A, the 5-year survival was 97%, while for those with ER and PR negative, HER2+ disease only 80% survive 5 years. Having a cancer that was either ER or PR negative was also an important prognostic indicator, with a hazard ratio for ER negative of 3.19 and for PR negative of 3.29. Women with HER2+ or Triple Negative disease and are more likely to be younger and have grade 3 disease. On the other hand women with Luminal A disease are likely to be older and do better. This is consistent with the literature.[2,28] We also know that in New Zealand outcomes for Māori and Pacific women are poor.[1,29-31] While they may be slightly more likely to have HER2 positive disease, they are less likely to have the subtype with the worst prognosis i.e. Triple Negative disease. It has been shown that for Māori the differences in biology only make a small contribution to the differences in outcomes.[1]

The strength of this study is that it comprises a relatively large population based database with comprehensive data on patient characteristics, patient treatment as well as outcomes. One weakness is that we did not take into account other important biomarkers such as Ki67. We

also have not included grade of disease in our classification. Some classification systems would classify ER+, PR+ and HER2- breast cancers as luminal B rather than luminal A if they are high grade or have a high Ki67,[32-34] but these were all classified into Luminal A in our study. Doing the classification this way would slightly bias luminal A cases towards worse outcomes in our study. Our classification may differ from a classification based on gene expression profiling. On the other hand, our grouping of cancers into 5 subtypes is also a strength of this study as breast cancer treatment decisions are generally based on the presence or absence of these three biomarkers. Gene expression profiling is not routinely available in clinical practice and only infrequently used to assist treatment decisions in New Zealand at present.

Conclusions

The pattern of phenotype in women with stage I-III breast cancer is similar to the international cohorts. Most New Zealand women with Luminal A breast cancer have a very good prognosis, but there are less common subtypes have relatively poor outcomes. We have demonstrated differences in tumour grade, stage, patient age and ethnicity according to breast cancer subtype in a New Zealand population. The treatment of women with stage I-III breast cancer varies by molecular phenotype. Treatment is becoming personalised to their individual molecular phenotype. Despite this there was a major variation in the prognosis of women with stage I-III breast cancer with differing molecular phenotype.

Ethics

Ethical approval for the study was granted through the Northern A Health and Disability Ethics Committee, reference: 12/NTA/42/AM01.

Conflicts of Interest

Nil.

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