The Breast 24 (2015) 62–67

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

# Adherence to adjuvant endocrine therapy: Is it a factor for ethnic differences in breast cancer outcomes in New Zealand?

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ARTICLE INFO

*Article history:*
Received 13 June 2014
Received in revised form
18 August 2014
Accepted 16 November 2014
Available online 5 December 2014

*Keywords:*
Breast cancer
Endocrine therapy
Medication adherence
Ethnicity
Inequity

ABSTRACT

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

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

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

*Conclusions:* Sub-optimal adherence to adjuvant endocrine therapy was a likely contributor for breast cancer mortality inequity between Māori and European women, and highlights the need for future research to identify effective ways to increase adherence in Māori women.



## Introduction

Breast cancer is the most common cancer and the second most common cause of cancer deaths for New Zealand women [1]. Māori, the Indigenous population in New Zealand are known to have one of the highest incidences of breast cancer among all populations in the world [2]. Age standardized rates of incidence and mortality from breast cancer are 28% and 60% higher for Māori compared to non-Māori women, who are predominantly of European origin [3]. Breast cancer mortality inequity between Māori and non-Māori women is greater than breast cancer mortality inequities between Indigenous and non-Indigenous populations in Australia, Canada and the USA [4]. While there has been an improvement in breast cancer survival both for Māori and non-Māori women over last two decades, a significant gap in survival persists [5]. An advanced cancer stage at diagnosis in Māori women has the greatest impact on breast cancer mortality inequity [3], while differences in treatment are also believed to make a substantial contribution [6].

Adjuvant endocrine therapy forms an integral part in breast cancer treatment and has shown to reduce mortality from hormone receptor positive breast cancer by about 30% [7,8]. Traditionally,

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http://dx.doi.org/10.1016/j.breast.2014.11.011
0960-9776/

endocrine therapy [tamoxifen or an aromatase inhibitor (AI) as single agent or in sequence] was prescribed for 5 years, although recent studies have shown additional improvement of breast cancer specific survival by continuing tamoxifen beyond 5 years [9]. Despite proven benefits, many women either do not take their medication daily as prescribed (i.e. low adherence) or do not complete the full duration of treatment (i.e. discontinuation) for the minimum of 5 years [10,11]. Based on previous studies, up to 22% of women discontinue endocrine therapy before the end of first year of therapy and only about 50% complete the full 5-years, while maintaining an optimum level of adherence [12–14]. These studies have also shown higher risks of breast cancer recurrence and mortality in women who are sub-optimally adherent or who discontinue their treatment [11,15].

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

## Patients and methods

### *Study population*

Eligible women for this study were identified from the Waikato Breast Cancer Registry (WBCR). The WBCR is a prospective database that records breast cancers of women who were residents of the Waikato District Health Board area at the time of diagnosis since 1999. The WBCR includes more than 98% of the cancers diagnosed over the study period and validity of its data has been reported previously [16]. The Waikato District Health Board covers a population of approximately 380,000 out of a total New Zealand population of 4.5 million [17]. All New Zealand citizens have access to free hospital care and, pharmaceutical and primary health care are heavily subsidized through a well-resourced public health service.

All women newly diagnosed with invasive breast cancer from 01/01/2005 to 31/12/2011 were identified from the WBCR ($n = 1558$). Of this, 1207 women with hormone receptor positive, non-metastatic (stage I to III), first primary breast cancer, who received adjuvant endocrine therapy were identified from the national pharmaceutical database. All women with at least one prescription for endocrine therapy after the date of primary surgery were deemed to have started endocrine therapy. Of this group, a further 57 women who were started on endocrine therapy not as adjuvant treatment, but as treatment following development of local or metastatic recurrence, or first endocrine therapy prescription issued later than a year after the date of diagnosis were excluded. The remaining 1149 women were analysed for treatment adherence and outcomes.

### *Study covariates*

Self-identified ethnicity collected as part of the WBCR consent process according to the Ministry of Health ethnicity data protocols [18] was identified from the WBCR, and was categorized in to Indigenous Māori, Pacific (including Samoan, Cook Island Māori, Tongan, Niuean, Tokelauan, Fijian and other Pacific Island), NZ European and Other. Comorbidity at the time of diagnosis was calculated using the Charlson Comorbidity Index (CCI) [19] and the CCI score was categorized to 0, 1–2 and 3+. Social deprivation was calculated using the New Zealand Deprivation Index 2006 (NZDep2006) [20]. The NZDep06 measures deprivation level based on place of residence at the time of cancer diagnosis. NZDep2006 uses nine socioeconomic variables measured during the population census in 2006 to allocate small areas of residence in a geographical map (mesh-blocks covering a population of approximately 100), a deprivation scale from 1 to 10; decile 1- least deprived, decile 10-most deprived. The residential status of each woman was classified as urban, semi-urban, or rural, based on the Statistics New Zealand urban/rural classification system [21]. Cancer stage at diagnosis was defined according to the Tumour, Node, and Metastasis (TNM) staging system [22].

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

### *Treatment adherence*

Prescription records for tamoxifen and AIs (i.e. anastrozole, letrozole and exemestane) for each eligible woman for the period from 01/01/2005 to 31/12/2013 were obtained from the National Pharmaceutical database. Prescription records were linked through the National Health Index number, which is a unique identifier that is used to identify individuals within the New Zealand health system. Dispensing date, drug type and number of days covered by each prescription were recorded. An adherence index/medication possession ratio (MPR) for each woman was calculated by dividing the number of days covered by prescriptions, by the total number of days for the follow up period, until death, or up to 5 years. Any gaps in treatment for more than 180 days were considered as discontinuation of therapy [15] and were censored at the last date covered by final prescription prior to discontinuation. An adherence index (MPR) of $\geq$80% was considered as a high/optimal level of adherence, which is a figure widely used in previous literature [14,15]. Adherence indices were calculated separately for each year of follow up and for the total follow up, to a maximum of 5 years.

### *Outcome variables*

Causes of death for all deceased women (censored on 31/12/2013) were identified from the WBCR and from the National Mortality Collection. The date of first cancer recurrence (local or metastatic) was identified from the WBCR records.

### *Statistical analysis*

Statistical analysis was performed in SPSS (Version 22). Categorical measures were summarized as numbers observed with percentages and mean/median with standard deviation/inter quartile range for continuous variables. Chi squared ($\chi^2$) tests for trend was used to test for univariate differences in distribution of treatment adherence and outcomes among groups of interest. Factors associated with adherence were explored in a multivariable logistic regression model. Multivariable Cox proportional hazard models were used to calculate hazard ratios with 95% confidence intervals to identify the association of adherence with breast cancer specific mortality, all-cause mortality and cancer recurrence. Kaplan–Meier survival curves were used to calculate 5-year crude breast cancer specific and disease free survival rates associated with high and sub-optimal adherence.

## Results

Median age of the cohort ($n = 1149$) was 60 years (range 24–99). Median ages of NZ European and Māori were 62 (range 24–99) and 57 (range 28–89) years, respectively. Median follow-up duration

was 51 months (inter-quartile range 32.1–73.0) months. There were a total of 131 (11.4%) cancer recurrences and 164 (14.3%) deaths, out of which 77 (47%) were due to breast cancer. Overall, 51% of women were followed up for at least 5 years or until death.

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

Overall, a high level of adherence (MPR ≥80%) was observed in 809 (70.4%) of women over the total duration of therapy. Highest adherence was seen during the first year of therapy where 76.8% maintained a high level of adherence. This figure gradually declined to 73.5%, 71.4%, 66.3% and 59.3% over the second to fifth years of treatment, respectively. Māori women were observed to have a significantly lower adherence compared with NZ European women, overall (62.1% vs. 72.5%, $p = 0.004$) and over each year of treatment (Fig. 1). Rates of sub-optimal adherence were significantly higher ($p < 0.05$) for Māori and Pacific women compared with NZ European women, in both univariate and multivariable models.

A significant trend ($p < 0.001$) was observed between age and sub-optimal adherence with the lowest rate observed in women over the age of 80 years (OR = 0.37, 95% CI 0.17–0.83) and the highest rate in women younger than 40 years (OR = 2.22, 95% CI 1.16–4.27) (Table 1). There was a trend for higher rates of suboptimal adherence among women of higher deprivation categories, especially in the unadjusted model, which however was not statistically significant. Thirty-four (10%) and 43 (5.3%) breast cancer deaths were observed among women with sub-optimal ($n = 340$) and high adherence ($n = 809$), respectively. In both unadjusted and adjusted Cox regression models, sub-optimal adherence was associated with a significantly higher risk of breast cancer mortality (Hazard Ratio = 1.62 and 1.77 respectively) and breast cancer recurrence (HR = 1.90 and 2.14 respectively) (Tables 2–3). Adjusting only for adherence reduced the hazard ratio for breast cancer mortality for Maori from 1.44 (95% CI 0.82–2.55) to 1.36 (95% CI 0.77–2.42). Hazard ratios for overall mortality were also higher among sub-optimally adherent women (unadjusted HR = 1.02, 95% CI 0.74–1.41, $p = 0.968$, adjusted HR = 1.17, 95% CI 0.81–1.69, $p = 0.401$), although these were statistically non-significant.

Fig. 2 shows Kaplan–Meier survival curves demonstrating crude 5-year breast cancer specific survival rates of 93.3% and 89.5% for women with high and sub-optimal adherence, respectively ($p = 0.032$). Five year disease free survival rates were 86.8% for high and 77.2% for sub-optimally adherent women ($p = 0.001$).

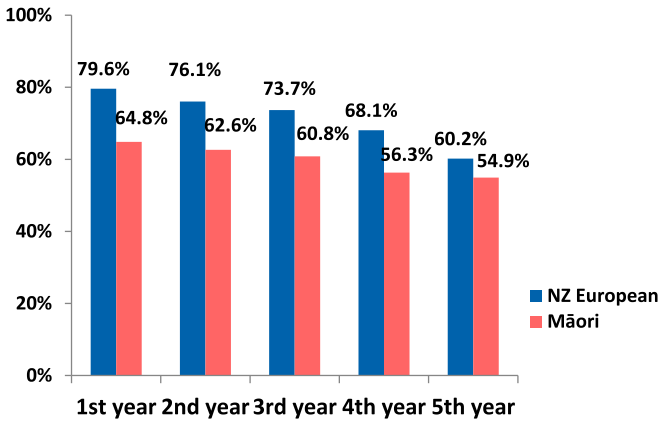


**Fig. 1.** Annual rates of high level of adherence (MPR≥80%) with adjuvant endocrine therapy for hormone receptor positive invasive breast cancer for NZ European and Maori women in Waikato, New Zealand 2005–2011.

## Discussion

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

Overall, the rate of optimum level of adherence to endocrine therapy seen in our study was comparable to other retrospective registry based studies [11,14,23], although much higher adherence rates are observed in endocrine therapy clinical trials [24]. The rate of sub-optimal adherence was significantly higher among Māori women and included more than one third of Māori women. Even after adjusting for covariates, the odds of sub-optimal adherence for Maori women was more than 50% higher compared to NZ European women. Failure of these adjustments to adequately explain the observed lower adherence among Māori is most likely due to the impact of confounders such as barriers to accessing healthcare and health literacy [25], which were unmeasured in the present study.

Inferior quality of cancer care in Māori is known to be a significant contributor for poor survival from many cancers. For example for bowel cancer, Maori were less likely to be referred and to receive chemotherapy and were more likely to experience longer delays for chemotherapy compared to non-Māori patients [26]. Similarly, for non-metastatic lung cancer, Maori were four times less likely to receive curative treatment even after adjusting for sociodemographic and tumour related factors [27]. Furthermore, we have previously reported on the significantly longer delays experienced by Maori women for surgical treatment of breast cancer [6]. The present study adds to this growing knowledge base of inequities in cancer treatment experienced by Māori patients that is a significant contributor towards poorer survival rates.

Majority of women on endocrine therapy depend on general practitioners for follow up and regular endocrine therapy prescriptions, in between annual follow ups provided by specialist breast care clinics. Māori are known to experience more barriers and hence less access to primary health care providers compared with NZ European patients [25]. This is an important issue since barriers that interfere with primary care may prevent general practitioner visits, which impact on continuation of endocrine therapy. In addition, although endocrine medications are fully funded by the government, women are required to pay a consultation or prescription fee of NZ $15 to 50 which comes on top of travel costs, time off work and cost of care for dependents [28]. Although was not statistically significant, higher rates of suboptimal adherence were seen among women of higher deprivation groups, and this further supports the association between cost affordability and adherence. Māori are more likely to be socioeconomically deprived and live in rural areas with less access to transport compared with NZ Europeans [29]. As a result, Māori women are more likely to skip general practitioner visits which are a likely major contributor for sub-optimal adherence to endocrine therapy [30].

Good communication, regular advice and a good physician-patient relationship improve patient understanding and help maintain an optimum adherence with many medications including

**Table 1**
Factors associated with adherence to adjuvant endocrine therapy for hormone receptor positive invasive breast cancer unadjusted and adjusted multivariable models.

| | Adherence ≥80% | Adherence <80% | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|---|
| | *N* = 809 | *N* = 340 | Or | 95% C.I. | *p* | Or | 95% C.I. | *p* |
| | *n* (%) | *n* (%) | | | | | | |
| **Ethnicity** | | | | | | | | |
| NZ European | 665 (82.2) | 252 (74.1) | 1.00 | | | 1.00 | | |
| Māori | 113 (14.0) | 69 (20.3) | 1.61 | 1.16–2.25 | 0.005 | 1.51 | 1.04–2.17 | 0.028 |
| Other | 21 (2.6) | 5 (1.5) | 0.63 | 0.23–1.68 | 0.356 | 0.55 | 0.20–1.54 | 0.256 |
| Pacific | 10 (1.2) | 14 (4.1) | 3.69 | 1.62–8.42 | 0.002 | 3.16 | 1.29–7.75 | 0.012 |
| **Age group (years)** | | | | | | | | |
| <40 | 23 (2.8) | 30 (8.8) | 2.17 | 1.18–4.01 | | 2.22 | 1.16–4.27 | |
| 40–49 | 130 (16.1) | 78 (22.9) | 1.00 | | <0.001 | 1.00 | | 0.015 |
| 50–59 | 203 (25.1 | 95 (27.9) | 0.78 | 0.54–1.13 | | 0.85 | 0.51–1.40 | |
| 60–69 | 232 (28.7) | 79 (23.2) | 0.57 | 0.39–0.83 | | 0.62 | 0.33–1.15 | |
| 70–79 | 121 (15.0) | 34 (10.0) | 0.47 | 0.29–0.75 | | 0.52 | 0.26–1.06 | |
| 80+ | 100 (12.4) | 24 (7.1) | 0.40 | 0.24–0.68 | | 0.37 | 0.17–0.83 | |
| **Deprivation** | | | | | | | | |
| 1–2 | 99 (12.2) | 34 (10.0) | 1.00 | | 0.422 | 1.00 | | 0.814 |
| 3–4 | 81 (10.0) | 31 (9.1) | 1.11 | 0.63–1.97 | | 0.88 | 0.48–1.62 | |
| 5–6 | 191 (23.6) | 84 (24.7) | 1.28 | 0.80–2.04 | | 1.13 | 0.69–1.85 | |
| 7–8 | 249 (30.8) | 96 (28.2) | 1.12 | 0.71–1.77 | | 1.02 | 0.62–1.67 | |
| 9–10 | 189 (23.4) | 95 (27.9) | 1.46 | 0.92–2.32 | | 1.18 | 0.71–1.94 | |
| **Residence profile** | | | | | | | | |
| Urban | 425 (52.5) | 167 (49.1) | 1.00 | | 0.559 | 1.00 | | 0.655 |
| Semi-urban | 318 (39.3) | 142 (41.8) | 1.14 | 0.87–1.48 | | 1.15 | 0.86–1.54 | |
| Rural | 66 (8.2) | 31 (9.1) | 1.20 | 0.75–1.90 | | 1.05 | 0.63–1.73 | |
| **Charlson score** | | | | | | | | |
| 0 | 682 (84.3) | 294 (86.5) | 1.00 | | 0.107 | 1.00 | | 0.171 |
| 1–2 | 116 (14.3) | 37 (10.9) | 0.74 | 0.50–1.10 | | 0.90 | 0.58–1.39 | |
| 3+ | 11 (1.4) | 9 (2.6) | 1.90 | 0.78–4.63 | | 2.49 | 0.90–6.87 | |
| **Tumour stage** | | | | | | | | |
| T1 | 444 (54.9) | 187 (55.0) | 1.00 | | 0.342 | 1.00 | | 0.198 |
| T2 | 303 (37.5) | 116 (34.1) | 0.91 | 0.69–1.20 | | 1.02 | 0.73–1.42 | |
| T3 | 31 (3.8) | 18 (5.3) | 1.38 | 0.75–2.53 | | 1.76 | 0.90–3.43 | |
| T4 | 28 (3.5) | 19 (5.6) | 1.61 | 0.88–2.96 | | 2.02 | 0.98–4.15 | |
| Unknown | 3 (0.4) | 0 | | | | | | |
| **Lymph node stage** | | | | | | | | |
| N0 | 478 (59.1) | 203 (59.7) | 1.00 | | 0.597 | 1.00 | | 0.685 |
| N1 | 227 (28.1) | 85 (25.0) | 0.88 | 0.65–1.19 | | 0.85 | 0.60–1.19 | |
| N2 | 100 (12.4) | 50 (14.7) | 1.18 | 0.81–1.72 | | 1.00 | 0.62–1.61 | |
| Unknown | 4 (0.5) | 2 (0.6) | | | | | | |
| **Grade** | | | | | | | | |
| I | 205 (25.3) | 110 (32.4) | 1.00 | | 0.082 | 1.00 | | 0.038 |
| II | 441 (54.5) | 175 (51.5) | 0.74 | 0.55–0.99 | | 0.71 | 0.52–0.98 | |
| III | 134 (16.6) | 46 (13.5) | 0.64 | 0.43–0.96 | | 0.55 | 0.34–0.89 | |
| Unknown | 29 (3.6) | 9 (2.6) | | | | | | |
| **Therapeutic Surgery** | | | | | | | | |
| No | 36 (4.4) | 14 (4.1) | 1.00 | | 0.801 | 1.00 | | 0.516 |
| Yes | 773 (95.6) | 326 (95.9) | 1.08 | 0.58–2.04 | | 0.73 | 0.28–1.91 | |
| **Chemotherapy** | | | | | | | | |
| No | 569 (70.3) | 228 (67.1) | 1.00 | | 0.272 | 1.00 | | 0.317 |
| Yes | 240 (29.7) | 112 (32.9) | 1.16 | 0.89–1.53 | | 0.81 | 0.53–1.23 | |
| **Radiotherapy** | | | | | | | | |
| No | 246 (30.4) | 95 (27.9) | 1.00 | | 0.404 | 1.00 | | 0.873 |
| Yes | 563 (69.6) | 245 (72.1) | 1.13 | 0.85–1.49 | | 0.97 | 0.70–1.35 | |

**Table 2**
Adherence to adjuvant endocrine therapy and breast cancer mortality unadjusted and adjusted for age, comorbidity, deprivation, tumour factors (size, lymph node status, grade) and other treatment modalities (surgery, radiotherapy and chemotherapy).

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

**Table 3**
Adherence to adjuvant endocrine therapy and breast cancer recurrence unadjusted and adjusted for age, comorbidity, deprivation, tumour factors (size, lymph node status, grade) and other treatment modalities (surgery, radiotherapy and chemotherapy).

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

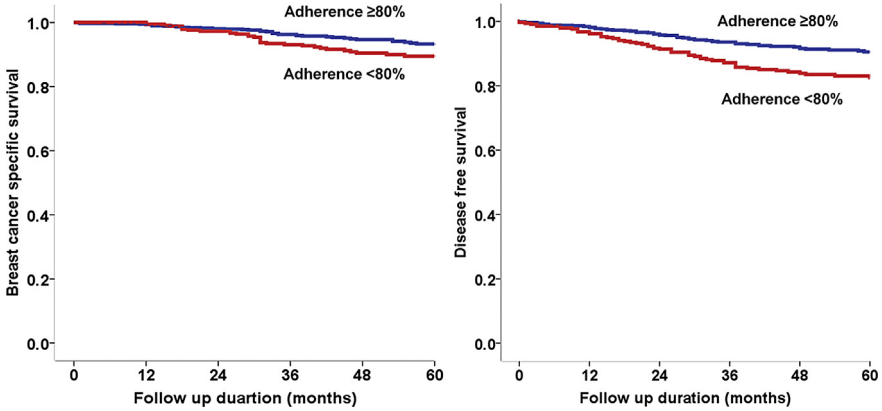


**Fig. 2.** Kaplan–Meier survival curves for 5-year breast cancer specific and disease free survival by adherence to adjuvant endocrine therapy in Waikato, New Zealand 2005–2011.

endocrine therapy [31]. A good health literacy enables a patient to process and understand health information and promote better health decision making [32]. Three out of four Maori females have poor health literacy skills, which is approximately 50% higher than NZ European women [33]. Improving health literacy among women with breast cancer has the potential to improve adherence to endocrine therapy as well as to increase uptake and adherence with other adjuvant therapies, including chemotherapy and radiotherapy [34]. Whilst low health literacy is a greater issue for Maori women and hence Maori are more likely to benefit from any initiative aimed at improving health literacy, substantial proportions of women of other ethnicities may also benefit due to the widespread nature of both low adherence and low health literacy.

The main strengths of this study are that it encompassed a highly complete, population-based, regional cohort of women and was analysed using a prospectively collected comprehensive database. Therefore, our results are likely to be relevant and applicable nationally. A limitation of our study design was the assumption that all prescribed medications were actually consumed by the patient. Despite that, this design has been shown to provide better estimates of adherence compared to other designs such as patient surveys or direct patient observation and has been validated by several previous studies [11,14,23]. Although we managed to identify several associated factors for lower adherence, we were unable to identify specific underlying causes for lower adherence, as reasons for sub-optimal adherence were not available from our database. Moreover, the relatively short follow up of our study may have underestimated the actual survival benefit of good adherence, as the benefits of endocrine therapy are known to extend well beyond 10 years [8].

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

Ethical approval for this study was obtained from the New Zealand Northern 'A' Ethics Committee (Ref. No. 12/NTA/42).

## Conflict of interest statement

The authors have declared that they have no financial conflicts of interest.

## Acknowledgements

We acknowledge funding support received from the Waikato Breast Cancer Trust, the Cancer Society of New Zealand, the New Zealand Breast Cancer Foundation, the Lion Foundation, the Grassroots Trust and the WEL Energy Trust towards the WBCR and for additional data collection included for this study.

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