Differences in systemic treatments for breast cancer between patients with and without diabetes

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ABSTRACT

AIM: The objectives of this study are to investigate whether diabetes affects the systemic treatment of breast cancer.

METHODS: Patients diagnosed with invasive breast cancer between 2005 and 2020 were identified from the Te Rēhita Mate Ūtaetae – Breast Cancer Foundation National Register. Logistic regression modelling was used to estimate odds ratios (ORs) with 95% confidence intervals (95% CIs) for the outcomes of endocrine therapy for estrogen receptor+/progesterone receptor+ cancer, targeted therapy for human epidermal growth factor receptor 2+ (HER2) cancer and chemotherapy in patients with breast cancer, comparing those with and without diabetes.

RESULTS: Compared with patients without diabetes, patients with diabetes had lower probabilities of receiving endocrine therapy (64.2% vs 60.4%, p-value <0.001), HER2-targeted therapy (65.6% vs 54.8%, p-value <0.001) and chemotherapy (32.1% vs 20.4%, p-value <0.001). Most of the differences in receipt of endocrine therapy and HER2-targeted therapy between these two groups could be explained by adjustment for differences in age at diagnosis and comorbidity. The difference in usage of chemotherapy by diabetes status remained apparent after adjustment for other factors (OR 0.85, 95% CI 0.75–0.97), with a stronger difference in women with stage II breast cancer (OR 0.71, 95% CI 0.59–0.86) and in Pacific women (OR 0.70, 95% CI 0.51–0.94).

CONCLUSIONS: Women with diabetes are less likely to be treated with chemotherapy, and the difference is greatest in Pacific women and patients with stage II breast cancer. The lower usage of endocrine therapy and HER2-targeted therapy in patients with diabetes could be explained by the older age at diagnosis and more comorbidities.

Most patients with breast cancer are initially treated with surgery.[1] However, additional systemic treatment such as endocrine therapy, chemotherapy and targeted therapy can improve patient outcomes. The decision of whether to start these systemic treatments is based on patient and tumour factors. Patient factors include demographic factors such as age and access to care, comorbidities and patient choice. Tumour factors include stage of disease, grade and the presence of biomarkers. The common biomarkers for breast cancer are the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). The main systemic treatments for breast cancer include endocrine therapy, chemotherapy and HER2-targeted therapy. Invasive tumours that are ER and/or PR positive (+) are sensitive to endocrine therapy,[2–4] which can then be prescribed for 5–10 years depending on the risk of cancer recurrence. Patients who have HER2+ breast cancer would benefit from HER2-targeted therapy.[5,6] HER2-targeted therapy including trastuzumab (funded since 2002), pertuzumab (funded since January 2017), trastuzumab emtansine (funded since December 2019) and lapatinib (funded since 2012 as a first-line treatment only) are funded for patients with HER2+ breast cancer in Aotearoa New Zealand.[3,6–8]

Treatment toxicity is an important factor for decision making by patients and clinicians on initiating or ceasing a particular treatment, especially for patients who are frail and have multiple comorbidities.[9] Diabetes is a significant and common comorbidity,[10] and may itself cause complications including heart disease, chronic kidney disease, peripheral vascular disease and neuropathy, and other problems with oral health, vision, hearing and mental health. The prevalence of diabetes and its secondary complications may therefore influence the use of these systemic treatments. Several factors may explain these phenomena, including clinical concern for treatment toxicity and ability to complete the

treatment. A systematic review showed that chemotherapy toxicity was greater in patients with comorbidity and was associated with a greater likelihood of hospitalisation during treatment.[11]

Twelve percent of women with breast cancer in Aotearoa New Zealand also have diabetes at cancer diagnosis, and the prevalence of diabetes in Māori, Pacific and Asian women in the general population is greater than for European women.[12–13] Breast cancer characteristics, treatments and outcomes were also reported to be different between these ethnic groups.[6,14–16] How diabetes affects the systemic treatment of breast cancer may also differ by ethnic group, especially for Māori and Pacific peoples. The objectives of this study are to investigate whether diabetes affects the systemic treatment of breast cancer in Aotearoa New Zealand, and whether these effects vary by ethnicity.

Methods

Women diagnosed with invasive breast cancer between 2005 and 2020 were identified from the Te Rēhita Mate Ūtaetae – Breast Cancer Foundation National Register (NBCR). Men were not included. The NBCR combines the Auckland, Waikato, Wellington and Christchurch registers, which includes 98% of prevalent breast cancer patients in these regions.[17] This study used data on age at diagnosis, menopausal status, ethnicity, diagnosis date, mode of detection (screen detected or symptomatic), tumour, node and metastasis (TNM) cancer stage (I, II, III and IV, 8th edition of American Joint Committee on Cancer [AJCC] Cancer Staging),[18] grade (1, 2 and 3), biomarkers (ER, PR and HER2) and systemic treatments. These NBCR data were linked by National Health Index (NHI) number to national-level health data to determine diabetes status (from the Virtual Diabetes Register [VDR]) at the time of cancer diagnosis, comorbidities (from the National Minimum Dataset [NMDS]) and systemic treatments (from Pharmaceutical Collection [PHARMS]). The NHI number is a unique identifier for people receiving healthcare services in Aotearoa New Zealand. The VDR is used to determine official diagnosed diabetes prevalence, but does not differentiate between type 1 and type 2 diabetes.[19] The PHARMS contains claim and payment information from pharmacists for subsidised dispensings. The VDR and PHARMS cover the whole population in Aotearoa New Zealand.

Patients were classified into Māori, Pacific, Asian and European/Other ethnic groups. Ethnicity is self-identified in Aotearoa New Zealand and recorded in the NBCR. Socio-economic deprivation was defined using the New Zealand Index of Deprivation 2018 (NZDep2018) and was analysed by quintile, from 1 (least deprived) to 5 (most deprived).[20] The study period was separated into three groups: 2005–2009, 2010–2014 and 2015–2020. Breast cancer subtypes were categorised into five groups according to biomarker status:[4,6,15,21] 1) luminal A: ER+, PR+ and HER2-; 2) luminal B HER2-: ER or PR+ (but not both +), HER2-; 3) luminal B HER2+: ER+ and/or PR+, HER2+; 4) HER2 non-Luminal: ER-, PR-, HER2+; and 5) triple negative: ER-, PR-, HER2-. Patients ever recorded as having diabetes before cancer diagnosis based on the VDR were considered to have diabetes at the time of cancer diagnosis. Comorbid conditions recorded on the NMDS for hospitalisations in the 5 years up to the index hospitalisation date were identified to calculate a C3 Index score for each patient.[22] The C3 Index is a cancer-specific index of comorbidity, with scores categorised into "0" ($\leqslant$0), "1" ($\leqslant$1.00), "2" ($\leqslant$2.00) and "3" (>2.00).[22] Diabetes was excluded as a comorbidity from the C3 Index score calculation.

We compared the proportion of patients with ER+/PR+ cancer who received endocrine therapy, the proportion of patients with HER2+ cancer who had targeted therapy and the proportion of women who had chemotherapy between the diabetes group and the non-diabetes group. Logistic regression modelling was used to estimate odds ratios (ORs) with 95% confidence intervals (95% CIs) for the outcomes of endocrine therapy for ER+/PR+ cancer, targeted therapy for HER2+ cancer, and chemotherapy in patients with breast cancer comparing those with and without diabetes. Analyses are reported stratified by cancer stage, after adjustment for period of diagnosis, age, menopausal status, ethnicity, deprivation quintile, mode of detection, comorbidities (C3 Index score), grade and biomarker subtype. The ORs were estimated from an overall model that included all patients, and then in separate analyses stratified by cancer stage and ethnic group.

All data analyses were performed in R 4.0 (R Institute, Vienna, Austria). Ethics approval for the study was granted through the University of Waikato Human Research Ethics Committee (reference: HREC(Health)2021#89).

Results

During the study period, 26,968 women were diagnosed with breast cancer, of whom 3,137

(11.6%) had a diabetes classification on the VDR at the time of cancer diagnosis. The characteristics of these patients have been reported in our earlier publication.[12] Of the 22,964 patients with ER+/PR+ cancer, 14,632 (63.7%) had endocrine therapy (Table 1). Among the 3,995 patients with HER2+ disease, 2,577 (64.5%) had HER2-targeted therapy. Only 31% (8,291/26,968) of all patients had chemotherapy. The proportions of patients receiving endocrine therapy, HER2-targeted therapy and chemotherapy were all lower in the patients with diabetes than in the patients without diabetes, and the relative gaps were wider in the stage I and II cancers than in the stage III and IV cancers. For example, for stage I and II cancers the percentages of patients having chemotherapy in the diabetes group were approximately half of those in the non-diabetes group, and for the stage III and IV cancers the percentages in the diabetes group were around 30% lower than in the non-diabetes group.

The unadjusted OR of having endocrine therapy for ER+/PR+ cancers for patients with diabetes versus patients without diabetes was 0.85 (95% CI 0.78–0.92, Table 2). Most of this difference could be explained by adjustment for differences in age at diagnosis and comorbidity between these two groups. Women with diabetes were older and had more comorbidities.[12] When stratifying the patients by cancer stage, the fully adjusted OR for endocrine therapy for ER+/PR+ disease by diabetes status was ameliorated for stage I, II and IV cancers. In contrast, the difference between the two groups for stage III cancer magnified after adjustment for other factors, with endocrine therapy being more common for women with diabetes than women without diabetes (OR 1.66, 95% CI 1.16–2.36).

For HER2-targeted therapy, the ORs between patients with diabetes and patients without diabetes followed a similar pattern as for endocrine therapy, before and after adjustment for other factors (Table 3). The unadjusted OR of having HER2-targeted therapy for patients with diabetes compared with patients without diabetes was 0.64 (95% CI 0.51–0.79), and the fully adjusted OR was 1.04 (95% CI 0.80–1.35). Age, ethnicity and comorbidity accounted for most of the difference in receipt of HER2-targeted therapy by diabetes status. When stratifying the cancer patients by stage, the adjusted OR increased with cancer stage, from 0.85 (95% CI 0.51–1.42) for stage I cancer to 1.75 (95% CI 0.78–4.50) for stage IV cancer. Results for stage III and IV suggested more use of targeted therapy in the group for those with diabetes.

The OR of having chemotherapy for patients with diabetes compared with patients without diabetes was 0.54 (95% CI 0.50–0.59) before adjustment, and 0.85 (95% CI 0.75–0.97) after adjustment for other factors (Table 4). Age and comorbidity still had the most substantial impact on the estimated ORs. When stratifying patients by cancer stage, there was strong evidence in stage II disease for reduced treatment for those with diabetes (adjusted OR 0.71, 95% CI 0.59–0.86), but there was no strong evidence for the other cancer stages.

Finally, we considered the differences in treatment receipt by diabetes status separately for ethnic group (Table 5). The unadjusted OR of having endocrine therapy for women with diabetes compared with women without diabetes varied by ethnic group. The unadjusted ORs for Māori and Pacific peoples were higher than the ORs for Asian and European women (0.95 and 0.85 vs 0.68 and 0.79). After adjustment for other factors, the ORs of having endocrine therapy in different ethnic groups were all close to 1. When stratified by ethnicity, the unadjusted and adjusted OR of having HER2-targeted therapy for those with diabetes compared with those without diabetes followed a similar pattern. The unadjusted OR of having chemotherapy was approximately 0.5 for all ethnic groups, except for Pacific women (unadjusted OR 0.42, 95% CI 0.33–0.53). After adjustment for other factors, the OR of receiving chemotherapy for Pacific peoples with diabetes compared with Pacific peoples without diabetes was 0.70 (95% CI 0.51–0.94). Similar results were found in Asian people (adjusted OR 0.74, 95% CI 0.52–1.05).

Discussion

Of those women eligible for endocrine therapy, two-thirds received treatment. Overall, only 60.4% of women with diabetes received endocrine therapy compared with 64.2% without diabetes. However, the difference in the use of endocrine therapy between the two groups can be explained by age, ethnicity and the presence of comorbidities, except for people with stage III breast cancer where diabetes was associated with an increased likelihood of having endocrine therapy after adjustment. The increased use of endocrine therapy for diabetic patients with stage III cancer is consistent with a Dutch study that showed women aged 35–64 years with diabetes were more likely to have endocrine therapy for breast cancer

than women without diabetes.[23] This is probably because of the high-risk nature of their breast cancer, combined with the fact that these women were often deemed unsuitable for adjuvant chemotherapy. Therefore, endocrine therapy may have been considered the most viable option to reduce the risk of cancer recurrence. In summary, while diabetes may have influenced treatment patterns, the clinical circumstances (high-risk cancer) played a more important role in deciding the treatment plan.

After adjustment for relevant factors, patients with diabetes were less likely to receive chemotherapy than patients without diabetes. A 2007 study from the Netherlands[23] also showed that patients with diabetes were less likely to have chemotherapy for breast cancer than patients without diabetes, and the difference was found to be greater in women aged 35–64 years than women aged 65 years or older.[23] The patterning of chemotherapy use by diabetes status for breast cancer is consistent with a systematic review showing that early breast cancer patients with comorbidities receive less chemotherapy than their counterparts without comorbidity.[11] Our dataset lacked information to determine whether the decision to forgo chemotherapy resulted from an active, informed discussion with the patient or if it was a passive choice made without patient involvement. The difference in chemotherapy between the two groups was most pronounced in patients with stage II breast cancer. In contrast, for those with stage III and IV disease after adjustment for other factors we could not show a difference, suggesting that for those with diabetes and a poorer breast cancer prognosis, the benefits of chemotherapy outweigh the harm; therefore, chemotherapy was offered to patients in both groups.

Treatment toxicity is a key reason for the reduced use of chemotherapy for breast cancer for patients with diabetes. A United States (US) based study showed that women with diabetes and breast cancer are at increased risk of chemotherapy-related toxicities compared with patients without diabetes, including higher odds of hospitalisation for toxicity.[24] Reduced treatment benefits of chemotherapy for patients with diabetes is another contributor to reduced use of chemotherapy. This US study also found that patients with and without diabetes who did not receive chemotherapy had similar breast cancer–specific mortality, but patients with diabetes who received chemotherapy had higher breast cancer–specific mortality than patients without diabetes receiving chemotherapy after adjustment for comorbidities and other confounding factors.[24] This is similar to what was found in chemotherapy for colon cancer,[25] where the benefit of chemotherapy in improving survival for colon cancer was greater for patients without diabetes than patients with diabetes.[25] However, patients with comorbidities can still benefit from chemotherapy if offered.[26]

Diabetes is strongly patterned by ethnicity in Aotearoa New Zealand. While the unadjusted results suggested differences in the use of chemotherapy, the adjusted results differed by ethnic groups. These suggested that there were ethnic differences in the likelihood of receiving chemotherapy depending on diabetes status. For example, it looked like the proportions of European women receiving chemotherapy were similar in both groups regardless of diabetes status. However, Pacific women with diabetes were 30% less likely to receive chemotherapy than their counterparts without diabetes. Our previous study found no survival differences between women with and without diabetes based on treatment variations.[27] Differences in survival between the two groups are attributed to age and the tendency for women with diabetes to present with more advanced disease at diagnosis.[12,27] This suggests that the differences in use of chemotherapy in women with diabetes do not have a major impact on survival.

This study found differences in systemic treatments between breast cancer patients with and without diabetes, but our other study[27] demonstrated that these treatment variations did not impact survival outcomes. Our future studies will examine whether breast cancer patients with substantial comorbidities can benefit from systemic treatment. Do the harms of adjuvant systemic therapy outweigh the benefits? Which patients with existing comorbidities are most likely to benefit from systemic anti-cancer treatment? These investigations will provide clearer guidance for optimising treatment strategies for patients with comorbidities.

The strengths of this study include: 1) utilisation of the comprehensive NBCR recording detailed data on patient demographics and tumour characteristics as well as treatment, 2) the use of a national prevalent diabetes database to establish diabetes status, and 3) the linkage of data to the comprehensive PHARMS dataset. This enabled us to examine the association of diabetes with breast cancer treatments. These data were linked to other health data to allow

for adjustment for the impact of comorbidities when estimating the impact of diabetes on breast cancer treatment. This study also has limitations. The VDR dataset does not differentiate between type 1 and type 2 diabetes; therefore, we could not examine the differences between type 1 diabetes and type 2 diabetes on the impact of cancer treatment. This is a retrospective study, and there may still be uncontrolled confounding factors that could impact the results. These confounding variables, which were not accounted for in the analysis, may introduce biases that affect the validity of the findings. Additionally, the treatment patterns have changed over the 16-year period covered by the study, which could further complicate the interpretation of the results.

Conclusions

Most of the difference in probability of women with breast cancer having any form of systemic treatment between those with diabetes and those without diabetes can be explained by age, comorbidity and ethnicity. However, even after adjustment for these factors, women with diabetes are less likely to receive chemotherapy for their breast cancer than women without diabetes, and the difference is greatest in Pacific women. The lower usage of endocrine therapy and HER2-targeted therapy in patients with diabetes could also be explained by the older age at diagnosis and more comorbidities. We are not able to determine from these data whether these differences are active decisions made by the women and their healthcare providers, taking into account the risks of treatment in the context of diabetes and comorbidity. These differences need to be taken into account when considering factors that may impact on overall outcomes for women with breast cancer and diabetes. This is especially true for those ethnic groups who have a high prevalence of diabetes and who have poorer outcomes from breast cancer, such as Māori and Pacific women.

Table 1: Proportion of patients receiving systemic treatment between the diabetes and non-diabetes groups.

Cancer stage	Endocrine therapy (For ER+ or PR+ cancers)			HER2-targeted therapy (For HER2+ cancers)			Chemotherapy (For all cancers)		
	No diabetes	Diabetes	Total	No diabetes	Diabetes	Total	No diabetes	Diabetes	Total
Number of patients eligible for treatment									
I	9,901	1,144	11,045	1,309	89	1,398	11,241	1,259	12,500
II	7,151	1,069	8,220	1,349	181	1,530	8,554	1,253	9,807
III	2,330	332	2,662	650	73	723	2,856	394	3,250
IV	865	172	1,037	298	46	344	1,180	231	1,411
Total	20,247	2,717	22,964	3,606	389	3,995	23,831	3,137	26,968
Number of patients receiving treatments									
I	5,274	573	5,847	739	37	776	1,602	89	1,691
II	5,410	724	6,134	943	100	1,043	3,683	292	3,975
III	1,824	250	2,074	455	44	499	1,768	177	1,945
IV	483	94	577	227	32	259	597	83	680
Total	12,991	1,641	14,632	2,364	213	2,577	7,650	641	8,291
Proportion of patients receiving treatments									
I	53.3%	50.1%	52.9%	56.5%	41.6%	55.5%	14.3%	7.1%	13.5%
II	75.7%	67.7%	74.6%	69.9%	55.2%	68.2%	43.1%	23.3%	40.5%
III	78.3%	75.3%	77.9%	70.0%	60.3%	69.0%	61.9%	44.9%	59.8%
IV	55.8%	54.7%	55.6%	76.2%	69.6%	75.3%	50.6%	35.9%	48.2%
Total	64.2%	60.4%	63.7%	65.6%	54.8%	64.5%	32.1%	20.4%	30.7%

HER2 = human epidermal growth factor receptor 2; ER = estrogen receptor; PR = progesterone receptor.

Table 2: The odds ratio of having endocrine therapy for ER+ or PR+ cancers for patients with diabetes versus patients without diabetes.

Adjusted factors	Stage I	Stage II	Stage III	Stage IV	All stages
Unadjusted	0.88 (0.78–1.00)*	0.68 (0.59–0.78)***	0.85 (0.65–1.11)	0.95 (0.69–1.32)	0.85 (0.78–0.92)***
Period of diagnosis	0.88 (0.78–1.00)*	0.72 (0.62–0.83)***	0.91 (0.69–1.19)	0.92 (0.66–1.28)	0.87 (0.80–0.95)***
Age	0.98 (0.86–1.10)	0.89 (0.76–1.03)	1.05 (0.79–1.40)	0.73 (0.52–1.04)	1.00 (0.92–1.09)
Menopausal status	0.98 (0.86–1.11)	0.89 (0.76–1.04)	1.06 (0.80–1.41)	0.73 (0.52–1.04)	1.00 (0.92–1.09)
Ethnicity	0.94 (0.83–1.07)	0.93 (0.80–1.09)	1.24 (0.92–1.65)	0.70 (0.49–1.00)*	0.99 (0.91–1.08)
Deprivation quintile	0.92 (0.81–1.04)	0.94 (0.80–1.10)	1.25 (0.93–1.68)	0.70 (0.49–1.00)	0.98 (0.89–1.07)
Mode of detection	0.92 (0.81–1.05)	0.93 (0.80–1.09)	1.24 (0.92–1.66)	0.71 (0.50–1.02)	0.97 (0.89–1.07)
Comorbidities	0.99 (0.87–1.13)	1.06 (0.90–1.25)	1.38 (1.02–1.88)*	0.69 (0.47–1.00)*	1.06 (0.97–1.17)
Stage, grade, subtype	0.97 (0.85–1.12)	1.14 (0.95–1.37)	1.66 (1.16–2.36)**	0.67 (0.44–1.01)	1.05 (0.96–1.16)

ER = estrogen receptor; PR = progesterone receptor.
*<0.05
**<0.01
***<0.001

Table 3: The odds ratio of having targeted therapy for HER2+ cancers for patients with diabetes versus patients without diabetes.

Adjusted factors	Stage I	Stage II	Stage III	Stage IV	All stages
Unadjusted	0.55 (0.36–0.85)**	0.53 (0.39–0.73)***	0.65 (0.40–1.07)	0.72 (0.36–1.41)	0.64 (0.51–0.79)***
Period of diagnosis	0.53 (0.34–0.82)**	0.48 (0.35–0.66)***	0.59 (0.35–0.99)*	0.72 (0.36–1.43)	0.60 (0.49–0.75)***
Age	0.70 (0.44–1.10)	0.66 (0.47–0.94)*	0.90 (0.52–1.55)	0.96 (0.47–1.99)	0.84 (0.67–1.06)
Menopausal status	0.68 (0.43–1.08)	0.65 (0.46–0.93)*	0.86 (0.50–1.49)	0.98 (0.47–2.06)	0.83 (0.66–1.05)
Ethnicity	0.70 (0.44–1.12)	0.82 (0.57–1.18)	1.11 (0.63–1.97)	1.23 (0.56–2.67)	0.95 (0.75–1.21)
Deprivation quintile	0.73 (0.46–1.18)	0.86 (0.59–1.19)	1.13 (0.63–2.01)	1.20 (0.55–2.64)	0.98 (0.77–1.24)
Mode of detection	0.74 (0.46–1.18)	0.86 (0.59–1.26)	1.10 (0.62–1.98)	1.21 (0.55–2.67)	0.98 (0.77–1.24)
Comorbidities	0.84 (0.52–1.37)	1.02 (0.68–1.51)	1.61 (0.85–3.06)	2.04 (0.83–5.03)	1.15 (0.89–1.48)
Stage, grade, subtype	0.85 (0.52–1.41)	0.99 (0.66–1.51)	1.56 (0.80–3.07)	1.89 (0.75–4.77)	1.04 (0.80–1.35)

HER2 = human epidermal growth factor receptor 2.
*<0.05
**<0.01
***<0.001

Table 4: The odds ratio of having chemotherapy for patients with diabetes versus patients without diabetes.

Adjusted factors	Stage I	Stage II	Stage III	Stage IV	All stages
Unadjusted	0.46 (0.37–0.57)***	0.40 (0.35–0.46)***	0.50 (0.41–0.62)***	0.55 (0.41–0.73)***	0.54 (0.50–0.59)***
Period of diagnosis	0.46 (0.37–0.57)***	0.41 (0.36–0.47)***	0.51 (0.41–0.63)***	0.55 (0.41–0.73)***	0.55 (0.51–0.61)***
Age	0.66 (0.53–0.83)***	0.68 (0.58–0.79)***	0.83 (0.65–1.05)	0.79 (0.58–1.09)	0.86 (0.78–0.95)**
Menopausal status	0.65 (0.52–0.82)***	0.66 (0.57–0.77)***	0.78 (0.61–1.00)*	0.77 (0.56–1.06)	0.85 (0.77–0.94)**
Ethnicity	0.70 (0.56–0.88)**	0.72 (0.61–0.84)***	0.97 (0.76–1.25)	0.84 (0.60–1.17)	0.87 (0.78–0.96)**
Deprivation quintile	0.71 (0.56–0.89)**	0.72 (0.61–0.85)***	0.99 (0.77–1.28)	0.79 (0.56–1.10)	0.87 (0.78–0.96)**
Mode of detection	0.72 (0.57–0.90)**	0.72 (0.62–0.85)***	0.96 (0.75–1.25)	0.84 (0.60–1.17)	0.87 (0.79–0.96)**
Comorbidities	0.76 (0.60–0.96)*	0.81 (0.69–0.96)*	1.19 (0.91–1.57)	1.12 (0.79–1.60)	0.96 (0.87–1.07)
Stage, grade, subtype	0.83 (0.63–1.11)	0.71 (0.59–0.86)***	1.15 (0.87–1.52)	1.09 (0.76–1.57)	0.85 (0.75–0.97)*

*<0.05
**<0.01
***<0.001

Table 5: The odds ratios of having systemic treatments for patients with diabetes versus patients without diabetes by ethnic group.

Systemic treatment	Odds ratio	Māori	Pacific	Asian	European/Others
Endocrine therapy	Unadjusted	0.95 (0.77–1.17)	0.85 (0.68–1.07)	0.68 (0.53–0.86)**	0.79 (0.71–0.88)***
	Adjusted†	1.10 (0.87–1.42)	1.02 (0.77–1.35)	0.90 (0.67–1.22)	1.04 (0.91–1.18)
HER2-targeted therapy	Unadjusted	0.98 (0.59–1.63)	0.71 (0.43–1.15)	0.58 (0.32–1.05)	0.53 (0.39–0.73)***
	Adjusted†	1.44 (0.74–2.79)	0.95 (0.49–1.85)	0.86 (0.40–1.84)	1.02 (0.69–1.49)
Chemotherapy	Unadjusted	0.52 (0.42–0.65)***	0.42 (0.33–0.53)***	0.47 (0.37–0.61)***	0.51 (0.44–0.58)***
	Adjusted†	0.87 (0.65–1.16)	0.70 (0.51–0.94)*	0.74 (0.52–1.05)	0.90 (0.76–1.08)

HER2 = human epidermal growth factor receptor 2.
*<0.05
**<0.01
***<0.001
†Adjusted for period of diagnosis, age, menopausal status, deprivation quintile, mode of detection, comorbidities, cancer stage, grade and biomarker subtype.

COMPETING INTERESTS
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DATA AVAILABILITY
The data used for this study are not publicly available because of the ethics for patient information. They can be accessed through the National Breast Cancer Register and the Ministry of Health with appropriate ethics approval.

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