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## ORIGINAL STUDY

# Impact of menopausal status on risk of metastatic recurrence of breast cancer

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**Abstract**

***Objective:*** Menopausal status at diagnosis is an important factor for the management of breast cancer in younger women, and may affect the prognosis for these women. We aim to examine the association of menopausal status and risk of metastatic relapse for stage I-III breast cancer.

***Methods:*** We included women diagnosed with stage I-III breast cancer at 45 to 55 years in the Auckland and Waikato Breast Cancer Registers. Cumulative incidence of metastatic relapse was examined by age group and by menopausal status after stratifying by estrogen receptor (ER) and progesterone receptor (PR) status. Cox proportional hazards model was used to estimate the adjusted hazard ratio of metastatic relapse by menopausal status after adjustment for age, ethnicity, year of diagnosis, socioeconomic status, public/private hospital treatment, mode of detection, cancer stage, grade and human epidermal growth factor receptor 2 status.

***Results:*** We have identified 5,309 eligible women: 2,799 premenopausal, 929 perimenopausal, and 1,581 postmenopausal. There was significant difference in risk of metastatic recurrence between menopausal statuses for ER+ and/or PR+ cases, with a 10-year cumulative incidence of 11.2% for premenopausal, 12.4% for perimenopausal, and 15.6% for postmenopausal women. The adjusted hazard ratio of metastatic recurrence for postmenopausal compared to premenopausal women was 1.38 for ER+ and/or PR+ cases. Age did not affect the risk of metastatic relapse for ER+ and/or PR+ cases but affected the risk for ER- and PR- cases with a hazard ratio of 0.94 per year.

***Conclusions:*** Women with earlier age at menopause, and ER+ and/or PR+ stage I-III breast cancer were more likely to develop metastatic breast cancer. Age increased the risk of metastatic relapse for women with ER− and PR− disease, but not for ER+ and/or PR+ cancers.

***Key Words:*** Age – Breast cancer – Distant metastatic relapse – Menopausal status.

Breast cancer is the most commonly diagnosed cancer in New Zealand women.[1] Approximately 95% of patients have stage I to III disease at diagnosis.[2] Some of these patients may experience metastatic relapse after treatment for early stage disease. The risk of metastatic recurrence is associated with stage at primary diagnosis, biomarker subtype, age at diagnosis, ethnicity, and other factors.[3-5] For example, regional breast cancer (spread to regional lymph nodes or adjacent tissues, includes locally advanced disease) has more than three times the risk of developing metastatic disease compared to localized cancer (node-negative tumor confined to breast tissue).[3] Human epidermal growth factor receptor 2-positive (HER2+) non-luminal and triple negative breast cancers have a higher risk of metastatic relapse than other subtypes. A German study found that the 10-year cumulative incidence of metastatic relapse was 16.2% for HER2+ non-luminal stage I to III breast cancer and 13.8% for triple negative disease compared to 6.6% for hormone receptor positive luminal type breast cancer.[4] Hormone receptor positive cancers may receive signals from estrogen and/or progesterone that promote their growth, but hormone receptor negative cancers do not receive signals.[6]

The impact of menopausal status at diagnosis on breast cancer prognosis has not been investigated. Menopausal

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status has, however, been reported to affect the risk of breast cancer and the choice and effects of treatments for breast cancer.[7] Natural menopause usually occurs between the ages of 45 and 55 years. Women who experienced menopause after the age of 55 were found to have an increased risk of breast cancer.[8,9] That is probably because women who have late menopause have been exposed to more estrogen that may promote breast cancer.

Menopausal status at diagnosis is an important factor for the management of breast cancer in younger women, and may affect the prognosis for these women. This study aims to examine the impact of menopausal status on metastatic recurrence for women diagnosed with stage I-III breast cancer at the age of 45 to 55 years.

## METHODS

This study included women diagnosed with stage I-III breast cancer at the age of 45 to 55 years with recorded menopausal status at time of diagnosis in the Auckland and Waikato Breast Cancer Registers. The Auckland Register started collecting data prospectively from June 1, 2000, and the Waikato Register started collecting data prospectively from June 1, 2005 with data retrospectively added back to January 1, 1991. The study period was between June 1, 2000 and December 31, 2017 for the Auckland Breast Cancer Register and January 1, 1991 and December 31, 2017 for the Waikato Breast Cancer Register. All eligible women with a first primary breast cancer recorded in these two registers were included. According to the American Joint Committee Cancer Cancer Staging Manual,[10] women presenting with distant metastases at diagnosis or within 4 months of primary diagnosis are considered to have de novo metastatic breast cancer, whereas women who develop metastatic disease more than 4 months after a primary diagnosis have recurrent metastatic breast cancer. Therefore, women who developed metastatic breast cancer within 4 months after a primary diagnosis were excluded.

The data we extracted from the Auckland and Waikato Registers included: (1) patient characteristics: age, ethnicity, menopausal status (premenopausal, perimenopausal, and postmenopausal), and socioeconomic status (deprivation quintile); (2) tumor information: diagnosis date, cancer stage, cancer grade, hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]), and human epidermal growth factor receptor 2 [HER2], and (3) outcomes: date of metastatic recurrence, date and cause of death. The menopausal status was recorded at date of diagnosis and used the same definition as the Breast Surgeons ANZ quality Audit[11]: (1) premenopausal: an individual who has not yet experienced menopause; (2) perimenopausal: an individual who is either in the period just before menopause or the subsequent 1 year of amenorrhea following menopause; and (3) postmenopausal: an individual who has experienced menopause and the occurrence of 12 months of spontaneous amenorrhea. As recommended in the St. Gallen Consensus, ER positive (ER+) or PR+ was assessed as immunohistochemistry positive (1+, >10% before 2001; and 1+, >1% from 2001).[12] HER2+ was defined as fluorescence in situ hybridization amplified or 3+ staining on immunohistochemistry according to the 2013 American Society of Clinical Oncology Guideline.[13]

Patient demographics and tumor characteristics were compared by menopausal status. Chi-square test was used to examine the subgroup differences. Cumulative incidence of distant metastatic relapse was examined with the Kaplan-Meier method by age group (45-49 and 50-55 years) and by menopausal status after stratifying the data by hormone receptor status (ER+ and/or PR+, ER− and PR−). The subgroup differences were examined with Log-rank test. Patients were considered to be censored by the date of death from any cause or the end of follow-up on December 31, 2017. Cox proportional hazards models were used to estimate the adjusted hazard ratio (HR) of developing recurrent metastatic breast cancer by menopausal status after adjustment for age, ethnicity, year of diagnosis, socioeconomic status, public/private hospital treatment, mode of detection, cancer stage, grade and HER2 status, for ER+ and/or PR+ cancers, and for ER− and PR− cancers. All data analyses were performed in IBM SPSS 25 (New York, NY). Ethics approval for the study was granted through the Northern A Health and Disability Ethics Committee, reference: 19/CEN/14/AM01.

## RESULTS

We identified 5,309 women diagnosed with stage I to III breast cancer at the age of 45 to 55 years with recorded menopausal status at diagnosis: 2,799 premenopausal, 929 perimenopausal, and 1,581 postmenopausal (Table 1). Only 83 eligible women did not have menopause status recorded. For women diagnosed at the age of 45 years, 91.6% of them were premenopausal, 5.9% perimenopausal, and 2.4% postmenopausal, compared to 8.7%, 11.8%, and 79.6% for women aged 55 years. The menopausal status differed by ethnicity. After adjustment for age, year of diagnosis, and deprivation quintile, Maori and Pacific women were more likely to be postmenopausal at diagnosis (adjusted odds ratio: 1.51 (95% confidence interval [CI]: 1.19-1.91, $P < 0.001$) for Maori women and 1.67 (95% CI: 1.25-2.24, $P < 0.001$) for Pacific women). After adjustment for age, year of diagnosis, and ethnicity, women with deprivation quintile 4 and 5 were more likely to be postmenopausal at diagnosis (adjusted odds ratio: 1.31 [95% CI: 1.04-1.66, $P = 0.024$] for deprivation quintile 4 and 1.26 [95% CI: 1.00-1.60, $P = 0.051$] for deprivation quintile 5).

Postmenopausal women were more likely to have grade 3 breast cancer than premenopausal and perimenopausal women (31.1% vs 24.7% and 27.1%, Table 1). Postmenopausal women were more likely to have ER− and PR− breast cancer than premenopausal and perimenopausal women (21.5% vs 16.5% and 17.0%), and were also more likely to have HER2+ disease than premenopausal and perimenopausal women (20.2% vs 14.6% and 19.5%).

The differences in cumulative incidence of metastatic recurrence was not significant between women aged 45 to 49 years and 50 to 55 years for either ER− and PR− cases (Fig. 1, $P = 0.093$) or ER+ and/or PR+ cases (Fig. 2, $P = 0.768$). The

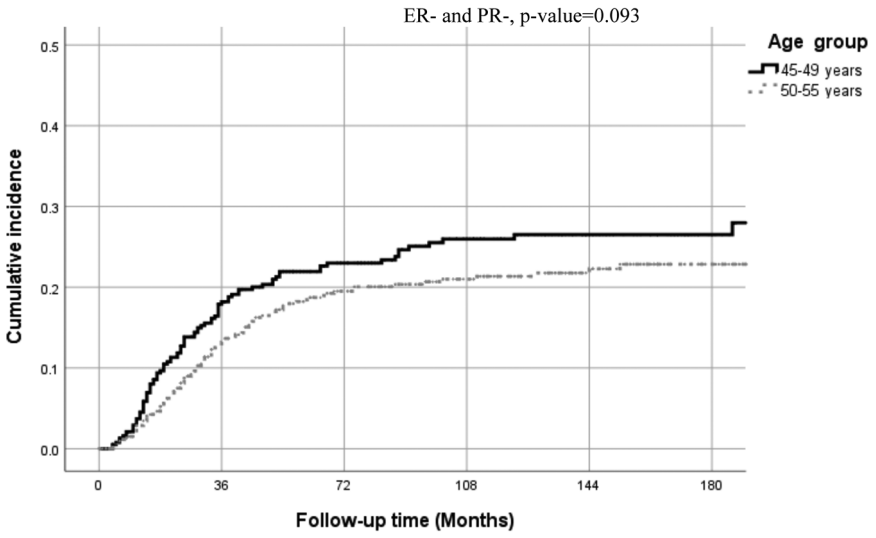
**TABLE 1.** *Demographics and tumor characteristics of the study population*

| Subgroup | Premenopausal | Perimenopausal | Postmenopausal | *P* | Total |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age (yr) | | | | | |
| 45 | 450 (91.6%) | 29 (5.9%) | 12 (2.4%) | <0.001 | 491 |
| 46 | 361 (86.8%) | 40 (9.6%) | 15 (3.6%) | | 416 |
| 47 | 394 (79.3%) | 63 (12.7%) | 40 (8.0%) | | 497 |
| 48 | 313 (69.9%) | 80 (17.9%) | 55 (12.3%) | | 448 |
| 49 | 381 (68.4%) | 100 (18.0%) | 76 (13.6%) | | 557 |
| 50 | 275 (51.4%) | 133 (24.9%) | 127 (23.7%) | | 535 |
| 51 | 229 (48.0%) | 111 (23.3%) | 137 (28.7%) | | 477 |
| 52 | 176 (33.4%) | 136 (25.8%) | 215 (40.8%) | | 527 |
| 53 | 122 (26.4%) | 104 (22.5%) | 236 (51.1%) | | 462 |
| 54 | 62 (12.8%) | 84 (17.4%) | 337 (69.8%) | | 483 |
| 55 | 36 (8.7%) | 49 (11.8%) | 331 (79.6%) | | 416 |
| Ethnicity | | | | | |
| European | 1,885 (52.2%) | 658 (18.2%) | 1,071 (29.6%) | <0.001 | 3,614 |
| Māori | 282 (48.1%) | 103 (17.6%) | 201 (34.3%) | | 586 |
| Pacific | 198 (53.5%) | 49 (13.2%) | 123 (33.2%) | | 370 |
| Asian | 353 (59.2%) | 98 (16.4%) | 145 (24.3%) | | 596 |
| Others | 50 (64.9%) | 9 (11.7%) | 18 (23.4%) | | 77 |
| Unknown | 31 (47.0%) | 12 (18.2%) | 23 (34.8%) | | 66 |
| Deprivation quintile | | | | | |
| 1 (Least deprived) | 627 (56.5%) | 191 (17.2%) | 292 (26.3%) | 0.007 | 1,110 |
| 2 | 527 (55.3%) | 160 (16.8%) | 266 (27.9%) | | 953 |
| 3 | 491 (51.3%) | 179 (18.7%) | 288 (30.1%) | | 958 |
| 4 | 436 (49.6%) | 154 (17.5%) | 289 (32.9%) | | 879 |
| 5 (Most deprived) | 532 (49.7%) | 182 (17.0%) | 357 (33.3%) | | 1,071 |
| Unknown | 186 (55.0%) | 63 (18.6%) | 89 (26.3%) | | 338 |
| Year of diagnosis | | | | | |
| 1991-1999 | 105 (41.2%) | 31 (12.2%) | 119 (46.7%) | <0.001 | 255 |
| 2000-2009 | 1,227 (51.0%) | 405 (16.8%) | 775 (32.2%) | | 2,407 |
| 2010-2017 | 1,467 (55.4%) | 493 (18.6%) | 687 (26.0%) | | 2,647 |
| Public/private | | | | | |
| Private | 1,209 (55.0%) | 372 (16.9%) | 616 (28.0%) | 0.007 | 2,197 |
| Public | 1,584 (51.0%) | 557 (17.9%) | 965 (31.1%) | | 3,106 |
| Unknown | 6 | | | | 6 |
| Mode of detection | | | | | |
| Symptomatic | 1,526 (54.8%) | 487 (17.5%) | 771 (27.7%) | 0.001 | 2,784 |
| Screen detected | 1,273 (50.4%) | 442 (17.5%) | 810 (32.1%) | | 2,525 |
| Tumor characteristic | | | | | |
| Cancer stage | | | | | |
| 1 | 1,354 (53.2%) | 425 (16.7%) | 764 (30.0%) | 0.439 | 2,543 |
| 2 | 1,077 (52.2%) | 386 (18.7%) | 600 (29.1%) | | 2,063 |
| 3 | 368 (52.3%) | 118 (16.8%) | 217 (30.9%) | | 703 |
| Cancer grade | | | | | |
| 1 | 712 (54.5%) | 236 (18.1%) | 358 (27.4%) | <0.001 | 1,306 |
| 2 | 1,310 (54.3%) | 421 (17.4%) | 683 (28.3%) | | 2,414 |
| 3 | 663 (48.2%) | 244 (17.7%) | 469 (34.1%) | | 1,376 |
| Unknown | 114 (53.5%) | 28 (13.1%) | 71 (33.3%) | | 213 |
| ER/PR status | | | | | |
| Both negative | 451 (48.3%) | 155 (16.6%) | 328 (35.1%) | <0.001 | 934 |
| Either positive | 2,281 (53.8%) | 756 (17.8%) | 1,199 (28.3%) | | 4,236 |
| Unknown | 67 (48.2%) | 18 (12.9%) | 54 (38.8%) | | 139 |
| HER2 status | | | | | |
| Negative | 1,986 (55.6%) | 615 (17.2%) | 968 (27.1%) | <0.001 | 3,569 |
| Positive | 340 (46.3%) | 149 (20.3%) | 245 (33.4%) | | 734 |
| Unknown | 473 (47.0%) | 165 (16.4%) | 368 (36.6%) | | 1,006 |
| Total | **2,799** (52.7%) | **929** (17.5%) | **1,581** (29.8%) | | **5,309** |

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

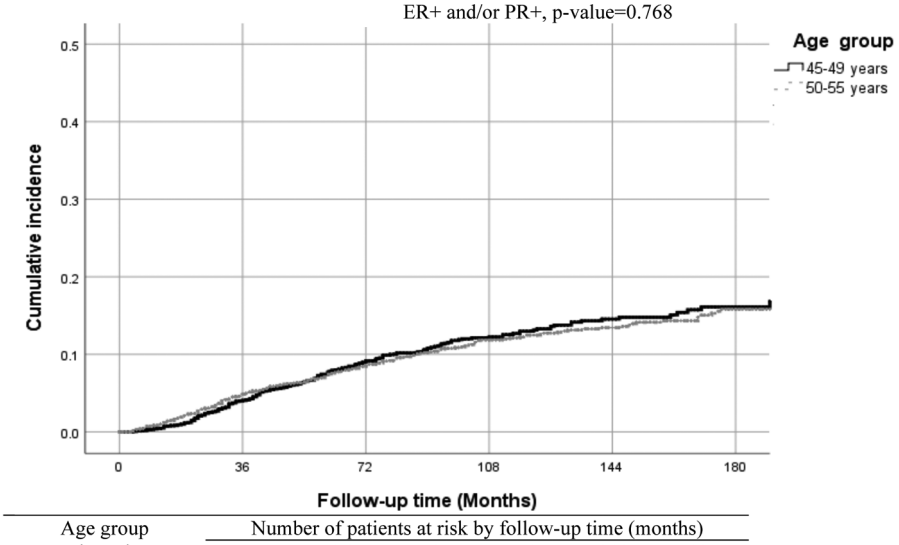
difference was significant between different menopausal status for ER+ and/or PR+ cases ($P = 0.047$), with a 10-year cumulative incidence of metastatic recurrence of 11.2% (95% CI: 9.6-12.9) for premenopausal women, 12.4% (95% CI: 9.4-15.3) for perimenopausal women, and 15.6% (95% CI: 13.0-18.1) for postmenopausal women. When stratifying the ER+ and/or PR+ cases by age group, the difference was not significant between different menopausal status ($P = 0.061$ for women aged 45-49 years and $P = 0.060$ for women aged 50-55 years, Fig. 3).

After adjustment for age, ethnicity, year of diagnosis, socioeconomic status, public/private hospital treatment, mode of detection, cancer stage, and grade and HER2 status, the HR of having metastatic recurrence for postmenopausal women compared to premenopausal women was 1.38 (95% CI: 1.05-1.81) for ER+ and/or PR+ cases (Table 2). For ER− and PR− cases, menopausal status did not have a significant impact on risk of metastatic relapse. On the contrary, age did not affect the risk of metastatic relapse for ER+ and/or




A

| Age group (years) | Number of patients at risk by follow-up time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 36 | 72 | 108 | 144 | 180 |
| 45-49 | 391 | 276 | 214 | 156 | 97 | 56 |
| 50-55 | 543 | 381 | 299 | 229 | 155 | 88 |




B

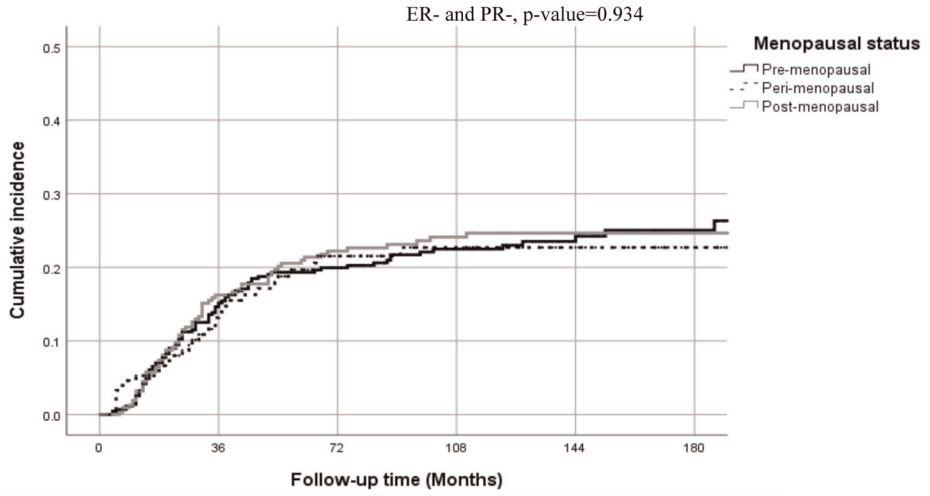
| Age group (years) | Number of patients at risk by follow-up time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 36 | 72 | 108 | 144 | 180 |
| 45-49 | 1954 | 1501 | 1038 | 670 | 374 | 172 |
| 50-55 | 2282 | 1692 | 1202 | 822 | 540 | 282 |

**FIG. 1.** Cumulative incidence of recurrent metastatic breast cancer by age group: **(A)** ER− and PR−; **(B)** ER+ and/or PR+. ER, estrogen receptor; PR, progesterone receptor.

PR+ cases but did affect the risk for ER− and PR− cases with an adjusted HR of 0.94 per year (95% CI: 0.89-1.00, $P = 0.044$). There was no significant difference between HER2+ and HER2− disease for the development of metastatic cancer in either ER+ and/or PR+ cases or ER− and PR− cases.

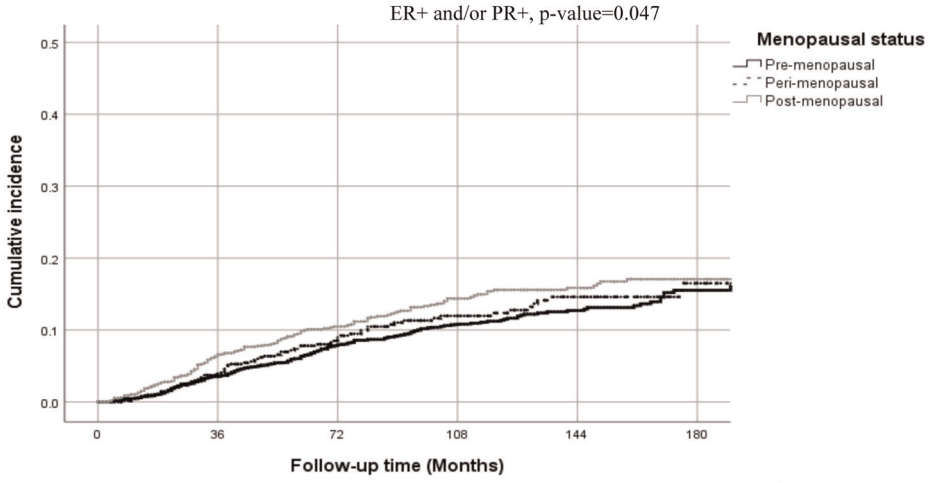
## DISCUSSION

This study found that overall, the metastatic recurrence rate decreased with increasing age, yet was increased for women who were postmenopausal at diagnosis and had ER+ and/or PR+ breast cancers. This suggested that younger women who had early menopause had the highest risk of metastatic relapse of breast cancer. Menopausal status at diagnosis had great impact on metastatic recurrence for ER+ and/or PR+ breast cancer but no impact on ER− and PR− disease. Postmenopausal women diagnosed with ER+ and/or PR+ breast cancer had 39% higher risk of metastatic relapse than premenopausal women. These findings have not been reported before, but are important for guiding clinical practice and predicting prognosis of young women diagnosed with breast cancer.




A

| Menopausal status | Number of patients at risk by follow-up time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 36 | 72 | 108 | 144 | 180 |
| Pre-menopausal | 451 | 319 | 252 | 183 | 108 | 66 |
| Peri-menopausal | 155 | 112 | 79 | 58 | 37 | 18 |
| Post-menopausal | 328 | 226 | 182 | 144 | 107 | 60 |

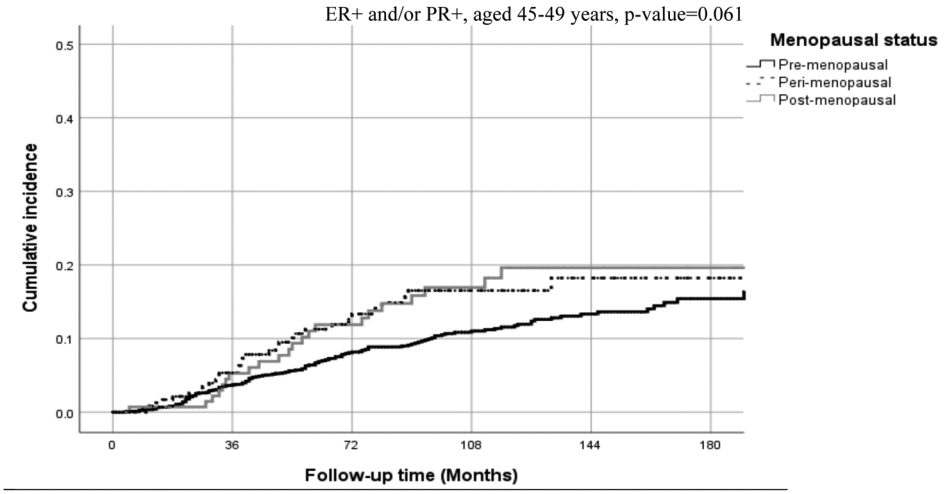



B

| Menopausal status | Number of patients at risk by follow-up time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 36 | 72 | 108 | 144 | 180 |
| Pre-menopausal | 2281 | 1717 | 1195 | 774 | 440 | 206 |
| Peri-menopausal | 756 | 579 | 379 | 255 | 166 | 82 |
| Post-menopausal | 1199 | 897 | 666 | 463 | 308 | 166 |

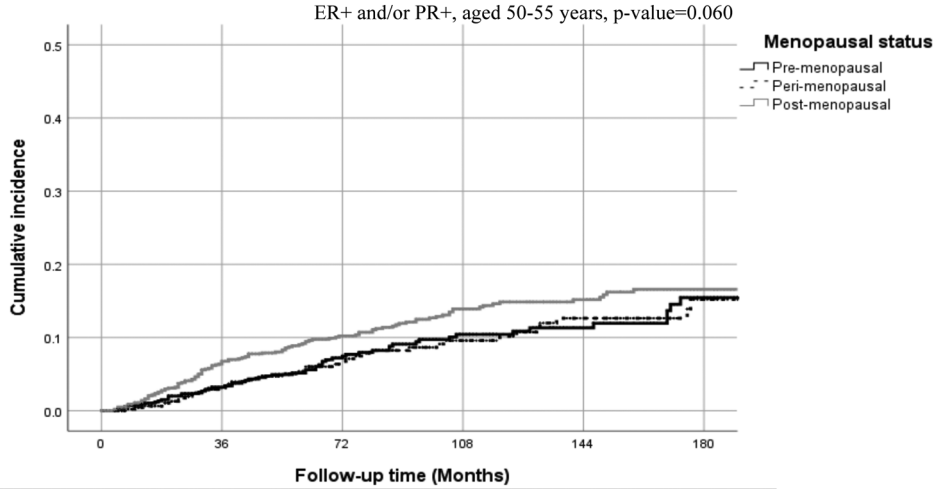
**FIG. 2.** Cumulative incidence of recurrent metastatic breast cancer by menopausal status: **(A)** ER− and PR−; **(B)** ER+ and/or PR+. ER, estrogen receptor; PR, progesterone receptor.

It has been reported that women who go through menopause later in life have an increased risk of breast cancer compared to women who go through menopause earlier.[7] This is believed to be a result of a lower lifetime exposure to cyclical estrogen levels.[14] Our study, however, found that women who had early menopause had a higher risk of metastatic relapse of breast cancer (for ER+ and/or PR+ cancers). This may be related to some confounding include the BRCA1 status, strong family history of breast cancer, and being a carrier for fragile X syndrome. Although being a carrier for fragile X (for <1% of women) is generally considered to be associated with a lower overall risk of breast cancer, the risk of progression is greater if breast cancer occurs.[15] The hypothesis generated by this study about the risk of metastatic recurrence in young postmenopausal women needs to be tested in a dataset where the potential confounding factors are available. We have also found that the proportion of women diagnosed with breast cancer before menopause has increased over time (41.2% in 1991-1999 to 55.4% in 2010-2017). This was mainly because of the national breast cancer screening program, which commenced in New Zealand since December 1998 and the increasing uptake of




A

| Menopausal status | Number of patients at risk by follow-up time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 36 | 72 | 108 | 144 | 180 |
| Pre-menopausal | 1564 | 1182 | 818 | 531 | 292 | 127 |
| Peri-menopausal | 247 | 196 | 122 | 72 | 42 | 22 |
| Post-menopausal | 143 | 123 | 98 | 67 | 40 | 23 |




B

| Menopausal status | Number of patients at risk by follow-up time (months) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 36 | 72 | 108 | 144 | 180 |
| Pre-menopausal | 717 | 535 | 377 | 243 | 148 | 79 |
| Peri-menopausal | 509 | 383 | 257 | 183 | 124 | 60 |
| Post-menopausal | 1056 | 774 | 568 | 396 | 268 | 143 |

**FIG. 3.** Cumulative incidence of recurrent metastatic breast cancer by menopausal status: **(A)** ER− and/or PR−, aged 45 to 49 years; **(B)** ER+ and/or PR+, aged 50 to 55 years. ER, estrogen receptor; PR, progesterone receptor.

breast cancer screening over time.[16] In July 2004, the eligible age for breast screening was extended from 50 to 64 years to 45 to 69 years including more premenopausal women.[16] The better survival in the postmenopausal group could be partly attributed to lead time (earlier detection by screening than clinical presentation) and length time bias (the cancer cases at the same stage identified by screening are likely to be less aggressive than those presented clinically). A higher proportion of women were diagnosed by screening in the postmenopausal group than in the premenopausal group: 51% versus 45%.

Māori and Pacific, and more deprived women were more likely to go through earlier menopause. This is consistent with findings from a systematic review by Schoenaker et al[17] showing that age at natural menopause varies by populations, socioeconomic positions, and lifestyle factors. Lower education, lower occupation levels, smoking, adverse socioeconomic circumstances in childhood, and adulthood were associated with an earlier age at natural menopause.[17-19] Women in the postmenopausal group were less likely to have ER+ and/or PR+ disease than women in the premenopausal group. This might be related to menopause. Women in the

**TABLE 2.** *Adjusted hazard ratio of metastatic recurrence*

| | ER− and PR− | | | ER+ and/or PR+ | | |
|---|---|---|---|---|---|---|
| Subgroup | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Age (continuous) | 0.94 | (0.89-1.00) | 0.044 | 0.99 | (0.95-1.03) | 0.496 |
| Ethnicity | | | | | | |
| European | Ref | | | Ref | | |
| Māori | 0.99 | (0.63-1.56) | 0.980 | 0.94 | (0.69-1.29) | 0.704 |
| Pacific | 0.64 | (0.34-1.20) | 0.162 | 1.28 | (0.89-1.84) | 0.177 |
| Asian | 0.59 | (0.35-1.01) | 0.052 | 0.72 | (0.49-1.08) | 0.107 |
| Others | - | - | - | 0.65 | (0.21-2.05) | 0.466 |
| Unknown | 0.63 | (0.15-2.59) | 0.524 | - | - | - |
| Menopausal status | | | | | | |
| Premenopausal | Ref | | | Ref | | |
| Perimenopausal | 1.14 | (0.74-1.77) | 0.556 | 1.10 | (0.83-1.47) | 0.509 |
| Postmenopausal | 1.19 | (0.81-1.75) | 0.365 | 1.38 | (1.05-1.81) | 0.021 |
| Year of diagnosis | | | | | | |
| 1991-1999 | Ref | | | Ref | | |
| 2000-2009 | 1.11 | (0.64-1.92) | 0.701 | 0.78 | (0.52-1.17) | 0.234 |
| 2010-2017 | 0.60 | (0.31-1.17) | 0.134 | 0.67 | (0.43-1.06) | 0.088 |
| Deprivation quintile | | | | | | |
| 1 (Least deprived) | Ref | | | Ref | | |
| 2 | 0.94 | (0.57-1.57) | 0.828 | 0.88 | (0.62-1.25) | 0.489 |
| 3 | 1.12 | (0.67-1.87) | 0.667 | 0.92 | (0.66-1.28) | 0.615 |
| 4 | 1.44 | (0.88-2.35) | 0.146 | 1.24 | (0.90-1.70) | 0.193 |
| 5 (Most deprived) | 0.98 | (0.58-1.67) | 0.953 | 1.18 | (0.86-1.61) | 0.313 |
| Unknown | 0.30 | (0.04-2.25) | 0.241 | 0.13 | (0.02-0.93) | 0.042 |
| Public/private | | | | | | |
| Private | Ref | | | Ref | | |
| Public | 1.45 | (1.04-2.01) | 0.028 | 1.45 | (1.16-1.81) | <0.001 |
| Unknown | - | - | - | 6.68 | (1.63-27.46) | 0.008 |
| Mode of detection | | | | | | |
| Symptomatic | Ref | | | Ref | | |
| Screen detected | 0.56 | (0.37-0.85) | 0.006 | 0.56 | (0.44-0.71) | <0.001 |
| Cancer stage | | | | | | |
| 1 | Ref | | | Ref | | |
| 2 | 1.71 | (1.09-2.68) | 0.020 | 1.93 | (1.49-2.51) | <0.001 |
| 3 | 5.86 | (3.72-9.24) | <0.001 | 3.83 | (2.86-5.13) | <0.001 |
| Cancer grade | | | | | | |
| 1 | Ref | | | | Ref | |
| 2 | 4.17 | (0.56-31.04) | 0.163 | 2.71 | (1.89-3.89) | <0.001 |
| 3 | 4.16 | (0.56-30.66) | 0.162 | 3.91 | (2.64-5.80) | <0.001 |
| Unknown | 4.92 | (0.63-38.57) | 0.130 | 4.23 | (2.24-7.99) | <0.001 |
| HER2 status | | | | | | |
| Negative | Ref | | | | | |
| Positive | 0.90 | (0.64-1.26) | 0.527 | 0.87 | (0.65-1.18) | 0.371 |
| Unknown | 0.78 | (0.52-1.18) | 0.239 | 0.79 | (0.61-1.03) | 0.088 |

Adjusted for the factors in the table. Interaction between age and menopausal status was not significant; therefore, the interaction was not included in the models.

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PR, progesterone receptor.

postmenopausal group were more likely to have HER2+ disease compared to women in the premenopausal group. This is partly because a higher proportion of Māori and Pacific who were more likely to have HER2+ breast cancer,[20] were in the postmenopausal group.

Age did not have significant impact on the risk of metastatic relapse for ER+ and/or PR+ breast cancer. The risk of metastatic relapse, however, decreased by 6% per year gained by age for ER− and PR− breast cancer. Previous studies have shown that age is a powerful prognostic indicator of risk of distant metastases in patients with breast cancer.[21,22] Women who developed breast cancer at a younger age may have more aggressive disease (eg, more triple negative and ER/PR−, HER2+ breast cancers) and have an increased risk of recurrence.[21]

The strength of this work is that it is a population-based study with relatively complete data. The number of eligible women was reasonably large. The detailed patient demographics including menopausal status at diagnosis and tumor characteristics including biomarker status were collected. This is also the first study examining the impact of menopausal status on risk of metastatic relapse of breast cancer for women who were diagnosed at the age range when menopause occurs. One of the weaknesses is that some of the women who experience premature menopause did so because of oophorectomy. We did not have data on oophorectomy before the diagnosis of breast cancer to differentiate the effect of premature menopause caused by surgery or medications from natural menopause. There might also be some random errors in the menopausal data which might reduce the accuracy of the results. We did not have information on obesity, which may have an interaction with menopausal status.[23] We have not examined treatment effects on development of

metastatic disease. The use of different types of treatments are influenced by cancer stage, grade, biomarkers, menopausal status, and patients' comorbidities, and these factors have been included in the Cox regression model and therefore the treatment effects have been partly accounted for. For example, the similar prognosis between HER2+ and HER2− cancers was because the use of trastuzumab though it was not included in the model. Considering the importance of the treatment effect, we have decided to explore it further and are planning to report the findings separately.

## CONCLUSIONS

Menopausal status has an impact on the risk of metastatic recurrence for women diagnosed with ER+ and/or PR+ stage I-III breast cancer at the age of 45 to 55 years, but no impact on those with ER− and PR− disease. Women with earlier age at menopause, and ER+ and/or PR+ stage I-III breast cancer were more likely to develop metastatic breast cancer. On the contrary, age is an important factor, increasing risk of metastatic relapse for women with ER− and PR− disease, but not for ER+ and/or PR+ cancers.

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