Treatment and long-term outcome of breast cancer in very young women: nationwide population-based study

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Abstract

Background: The study aimed to assess the correlation between long-term survival and treatment in very young women with breast cancer.

Methods: Data on women with breast cancer were retrieved from the Taiwan Cancer Registry between 2004 and 2014. Patients who did not undergo surgery or who had stage 0 or IV disease were excluded. Survival analysis was conducted. The participants were divided into very young (20–29.9 years), young (30–39.9 years), and adult (40–50.0 years) groups.

Results: Among 104,115 women, 24,474 (572 very young, 5,565 young, and 18,337 adult) were eligible for the study. Median follow-up was 79.5 (range 24–158) months. The mortality rates in the very young, young, and adult groups were 12.9, 10.0, and 8.2 per cent respectively (P < 0.001). Very young patients had higher histological grade, unfavourable subtype, higher TNM stage, and received more chemotherapy than young and adult patients. Kaplan–Meier survival analysis showed that very young patients had the poorest long-term survival. Very young patients with stage II disease had the worst prognosis. In the multivariable regression model, radiotherapy was associated with decreased local recurrence but not with improved overall, cancer-specific, or disease-free survival for stage II disease in the very young group. Surgery type and chemotherapy were not associated with significant improvement in overall survival.

Conclusion: Very young patients with stage II disease had poor long-term outcomes. BCS had no detrimental effects on long-term outcomes.

Introduction

Breast cancer is the most common cancer in women worldwide and in Taiwan1,2. Its incidence has increased in recent decades probably owing to environmental factors, dietary habits, and advancements in diagnostic modalities3. In Taiwan, breast cancer usually occurs in individuals aged between 45 and 55 years4, about 10 years younger than in western countries, which may lead to significant excess costs in medical treatment and productivity loss. The absolute number of young women at risk of developing breast cancer is growing, making it a significant health issue for this population5. Breast tumours in younger women are more aggressive and advanced, are more likely to be caused by an inherited defective gene (such as breast cancer susceptibility gene (BRCA) mutation), and may respond differently to treatment than tumours in older women6,7. This population is usually faced with a variety of issues and psychosocial considerations, including fertility preservation, body image, and the impact of disease on family life, relationships, genetic counselling, career, and finances8,9,10.

Multimodal therapy has been recommended in the treatment of patients with breast cancer, including younger patients. Whether these treatment types offer optimal outcomes in younger patients as in older patients remains under debate. Conventionally, surgical treatments for breast cancer include breast-conserving surgery (BCS) and mastectomy10,11. The former option, with its restricted cosmetic alteration and improved quality of life, might prompt young patients to undergo limited therapy. A meta-analysis12 of registry and database studies conducted in 22,958 patients aged below 40 years suggested that BCS had disease-free and overall survival equivalent to those of mastectomy; however, a meta-analysis13 of studies including 3,531 young patients with locally advanced breast cancer after neoadjuvant therapy showed that BCS was associated with better disease-free and overall survival. Additionally, younger age (less than 35 years) has been considered a relative contraindication to BCS14. Local recurrence after BCS is a primary concern, so adjuvant radiotherapy should be administered to patients having this treatment.

Breast cancer is relatively rare in very young patients (aged less than 30 years). Although younger patients have been generally defined as those younger than 40 years, previous literature...
defined younger patients with breast cancer as those aged less than 50 years, 45 years, or 40 years. Studies of very young patients remain scarce, probably due to the limited number of patients. Hence, there are limited data regarding the characteristics, treatment patterns, and outcomes of very young patients with breast cancer. The aim of this study was to investigate the treatments and long-term survival of very young patients with breast cancer, and the differences in outcomes between very young patients and other young patients with breast cancer.

Methods

Study population

The target population was women aged 20.0–29.9 years with breast cancer registered in the Taiwan Cancer Registry (TCR). Candidates were patients with a C50 (breast cancer) code according to the ICD-O-3, diagnosed from January 2004 to December 2014. For comparison, women aged 30–50 years with breast cancer were also included. Patients who had stage 0 or IV disease, whose whose pathological report did not indicate ductal carcinoma (DC) or lobular carcinoma (LC), and those who did not undergo surgery were excluded. The TCR (from the Health Promotion Administration), which includes 85 per cent of patients with newly diagnosed breast cancer, contains prospectively collected data on patients, tumour characteristics, types of treatment, and follow-up. Data in the TCR were linked to the National Health Insurance Research Database (NHIRD, 2003–2014) and the Death Registry (2003–2014) to allow retrieval of independent variables and dependent variables. Enrolled patients were divided into three groups: very young (20.0–29.9 years), young (30.0–39.9 years), and adult (40.0–50.0 years).

Independent variables

Potential prognostic variables included patient characteristics (age and sex), comorbidity (Charlson Co-morbidity Index, diabetes mellitus, and hypertension), disease characteristics (laterality, tumour location, tumour size, histological grade of cell differentiation, molecular intrinsic subtype, pT, and pN), initial treatment type (BCS or mastectomy), and therapeutic characteristics (hormone therapy, chemotherapy, and radiotherapy). The specification of co-morbidity (Deyo version) by ICD-9 clinical modification code included 17 diseases. The molecular intrinsic subtypes included oestrogen receptor (ER)/progesterone receptor (PR)-positive (luminal A and luminal B), human epidermal growth factor receptor 2 (HER2/neu)-positive, luminal A and B, (including B1 and B2), and basal-like. Luminal A and B (including B1 and B2) were defined as ER/PR-positive. Additionally, luminal B1 and B2 were defined as ER/PR-positive with high cell grade or ER/PR-positive with HER2/neu-positive status respectively. HER2/neu overexpression was defined as HER2/neu-positive but ER/PR-negative breast cancer. Triple-negative breast cancer (TNBC) was an ER/PR-negative and HER2/neu-negative subtype. Hormone therapy included tamoxifen, letrozole, exemestane, and anastrozole. Chemotherapy included anthracyclines (doxorubicin and Lipo-Dox®) and taxanes (paclitaxel and docetaxel), whereas immunotherapy included trastuzumab. Data on co-morbidity (Charlson Co-morbidity Index, Deyo version), chemotherapy, and hormone therapy were retrieved from the NHIRD. Because the National Health Insurance system in Taiwan is a one-payer system (regulated by the National Health Insurance Administration), this database covers healthcare billing services of all patients. Therefore, accurate data on co-morbidity and medication could be retrieved.

Dependent variables

The primary endpoint was overall survival, which referred to the percentage of patients who were alive for a certain period of time after diagnosis of breast cancer. Secondary endpoints included cancer-specific and disease-free survival, and local recurrence-free rate. Cancer-specific survival referred to the percentage of patients who had not died from breast cancer-related causes for a certain period of time after diagnosis of breast cancer respectively. The Death Registry provides the date and cause of death, and survival outcomes (overall survival and cancer-specific survival) could be validated by linking the TCR to the 2011–2014 Death Registry (from the Ministry of Health and Welfare). The institutional review board at Taipei City Hospital approved this study and waived the requirement to obtain informed consent.

Statistical analysis

Demographic, clinical, pathological, and therapeutic variables are reported as numbers with percentages. The χ² test was used to compare categorical variables between very young patients (aged 20.0–29.9 years), young patients (aged 30.0–39.9 years), and adult patients (40.0–49.9 years). Kaplan–Meier plots were prepared to calculate survival estimates, and significance determined by means of the log rank test. Univariable and multivariable Cox proportional hazards models (using all potential but not highly correlated prognostic factors) were used to assess the crude and independent prognostic values of age and treatment modalities (including surgery, chemotherapy, and radiotherapy) on survival outcomes (overall, cancer-specific, and disease-free survival, and local recurrence-free rate). Hazard ratios (HRs) with 95 per cent confidence intervals are reported. SAS® version 9.2 (SAS Institute, Cary, NC, USA) was used for the initial database-merging process, and SPSS® version 21 (IBM, Armonk, NY, USA) for data management and inferential statistical analysis. All P values were two-sided, and the significance level was set at P < 0.05.

Results

Initially, 104115 women who were newly diagnosed with breast cancer between January 2004 and December 2014 were identified. Of these, 68 139 had breast DC or LC which was not stage 0 or IV. After excluding 7568 patients who did not undergo surgery and 36 097 who were not aged 20–50 years, a total of 24 474 women with breast cancer (DC: 23 574, 96.3 per cent; LC: 900, 3.7 per cent) were enrolled in this study (Fig. 1).

Demographic, clinical, and interventional characteristics of patients in the very young (572, 2.3 per cent), young (5565, 22.7 per cent), and adult (18 337, 74.9 per cent) groups are summarized in Table S1. The mean(s.d.) age of the cohort at diagnosis was 43.0(5.3) years. Tumour laterality and location did not differ between the groups. Although the very young group had a higher incidence of carcinoma in situ (4.4 per cent) and a lower Charlson Co-morbidity Index score than the other two groups, these patients had tumours with a poorer histological grade (42.8 per cent versus cohort average 32.1 per cent) and a higher rate of tumours of 2–5 cm in size (52.1 per cent versus average 47.3 per
Women with breast cancer 2004-2014 assessed for eligibility
\(n = 104\,115\)

Excluded \(n = 35\,976\)
- Not DC or LC \(n = 74\,976\)
- Stage 0 \(n = 10\,956\)
- Stage IV \(n = 46\,747\)
- Unknown stage \(n = 12\,849\)

Stage I-III breast cancer
\(n = 68\,139\)

Excluded \(n = 43\,665\)
- No surgery \(n = 75\,686\)
- Age < 20 years or > 50 years \(n = 36\,097\)

Young women with stage I-III breast cancer
\(n = 24\,474\)

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**Fig. 1 Study flow chart**

DC, ductal carcinoma; LC, lobular carcinoma.

The percentage of patients in the very young group who underwent BCS as the first treatment (62.4 per cent) was higher than that of patients in the young group (50.5 per cent) and the adult group (45.1 per cent) (\(P < 0.001\)).

The very young group had a higher rate of HER2/neu overexpression (8.0 per cent versus average 6.4 per cent) and a higher incidence of the triple-negative subtype (18.1 per cent versus average 8.6 per cent). Similarly, the incidence of hormone-positive tumours was lower in the very young group (69.6 per cent versus average 82.0 per cent; \(P < 0.001\)). The very young group also had a higher proportion of late-stage tumours (stage II: 57.0 per cent versus average 50.9 per cent; stage III: 9.8 per cent versus average 8.6 per cent).

Neoadjuvant therapy was more frequently performed in younger patients than in older patients (very young 16.1 per cent, young 13.5 per cent, adult 9.5 per cent; \(P < 0.001\)), but this trend was not observed for overall chemotherapy (72.2, 75.9, and 73.4 per cent respectively; \(P < 0.001\)). Anthracyclines and/or taxanes were administered to 66.5 per cent of patients (anthracyclines 63.4 per cent; taxanes 33.0 per cent) as chemotherapy agents. The most frequently administered anthracycline and taxane for very young women were doxorubicin (47.7 per cent, 273 of 572) and docetaxel (32.2 per cent, 184 of 572) respectively. The very young (7.9 per cent, 45 of 572) and young (7.9 per cent, 441 of 5565) groups had higher percentages of trastuzumab administration than the adult group (7.0 per cent, 1275 of 18337). The very young group had a lower percentage of hormone therapy (69.6 per cent, 398 of 572), but a higher proportion of these patients underwent radiotherapy (61.0 per cent, 349 of 572) than in the young and adult groups (\(P < 0.001\)).

Median follow-up was 79.5 (range 24–158) months. Overall and cancer-related mortality rates for the cohort at the end of the study were 8.7 per cent (very young 12.9 per cent, young 10.0 per cent, adult 8.2 per cent; \(P < 0.001\)) and 7.5 per cent (very young 12.1 per cent, young 9.0 per cent, adult 6.8 per cent; \(P < 0.001\)) respectively. The overall cohort had a disease-free survival rate of 88.8 per cent (very young 84.3 per cent, young 86.7 per cent, adult 89.6 per cent; \(P < 0.001\)). Fig. 2 shows Kaplan–Meier survival plots according to age group (\(P < 0.001\), \(P < 0.001\), \(P < 0.001\), and \(P = 0.098\) for overall, cancer-specific, and disease-free survival, and local recurrence-free status respectively).

The \(P\) values for pairwise comparisons between any two groups (Fig. 2a–c) were less than 0.001, except those for overall survival (very young versus young; \(P = 0.036\)), cancer-specific survival (very young versus young; \(P = 0.021\)), and disease-free survival (very young versus young; \(P = 0.129\)). \(P\) values for local recurrence among very young versus young (\(P = 0.680\)) and young versus adult (\(P = 0.479\)) groups were not significant (Fig. 2d).

Among the 24,474 patients with stage I–III breast cancer, 3-, 5-, and 10-year overall survival rates in the very young group were 95.2, 90.2, and 81.8 per cent respectively. The 3-, 5-, and 10-year cancer-specific survival rates in this group were 95.3, 90.5, and 87.6 per cent respectively. The 3-, 5-, and 10-year disease-free survival rates in the very young group were 93.7, 89.0, and 79.1 per cent. The very young group had the worst overall, cancer-specific, and disease-free survival rates, followed by the young group.

Univariable Cox regression analysis of all cohorts showed that age at diagnosis was a prognostic factor (Table S2). The adult (HR 0.76, 95 per cent c.i. 0.66 to 0.87, \(P = 0.001\)) and young (HR 0.79, 0.69 to 0.89, \(P = 0.001\)) groups had better overall survival than the very young group. Other prognostic factors included tumour behaviour, tumour size, histological grade, surgery type, resection margin, TNM stage, co-morbidity, radiotherapy, chemotherapy, and hormone therapy. Except for local recurrence-free rate, survival outcomes in the very young group differed from those of the young and adult groups among patients with stage II disease (Table 1). In the multivariable Cox regression model, the adult (HR 0.68, 0.54 to 0.86; \(P = 0.002\)) and young (HR 0.80, 0.62 to 1.02; \(P = 0.067\)) groups were associated with better overall survival than the very young group. Similarly, cancer-specific survival was better in the adult (HR 0.62, 0.48 to 0.79; \(P < 0.001\)) and young (HR 0.77, 0.60 to 0.99; \(P = 0.043\)) groups. No significant intergroup differences were
observed in the HRs for disease-free survival and local recurrence-free rate, except for disease-free survival in the adult group versus very young group (HR 0.72, 0.58 to 0.89; P = 0.003) (Table 2).

Additional stage-specific analyses of the multivariable Cox regression model showed that surgery type (mastectomy versus BCS) was not significantly associated with overall, cancer-specific, or disease-free survival, or local recurrence in very young patients with stage I, II, or III disease (Table 3). Although chemotherapy might decrease the local recurrence rate among patients with stage I, II, and III disease in the adult and young groups, it was not associated with significantly better overall survival or less local recurrence in very young patients with stage I and II disease. Radiotherapy was associated with improved overall and cancer-specific survival in the adult (stage II and III) and young (stage I and III) groups, but not in the very young group. It was associated with decreased local recurrence (HR 0.14, 0.03 to 0.72; P = 0.018) of stage II disease in the very young group. Hormone therapy was associated with improved overall, cancer-specific, and disease-free survival, and the local recurrence-free rate in the adult (stages II and III) and young (stage III) groups, but not in the very young group.

Discussion
This study evaluated four long-term outcomes and the effect of treatment in very young patients with breast cancer. Except for local recurrence, women in their 20s and 30s had higher all-cause and cancer-specific mortality and progression rates than those in their 40s. Before the age of 50 years, age at breast cancer diagnosis showed an inverse correlation with outcomes; that is, the younger the patient, the poorer the prognosis. Higher histological grade, higher stage, and unfavourable molecular subtype probably contributed to this. On closer inspection, the very young group had poorer prognosis than other groups among patients with stage II disease. Notwithstanding, BCS was recommended for patients with stage II disease, as it did not decrease overall survival in this group. Chemotherapy did not provide a significant improvement in the survival of very young patients.

Several studies recently reported that very young (aged less than 30 years) and young (30–40 years) patients accounted for about 20–25 per cent of patients with breast cancer aged less than 50 years. In a retrospective review of 215 688 patients (aged 15–49 years) with stage 0–III breast cancer in the National Cancer Database (NCDB) from 2010 to 2015, Murphy and colleagues noted that very young patients accounted for 2.3 per cent of the patients (aged 15–49 years) with stage 0–III breast cancer in the National Cancer Database (NCDB) from 2010 to 2015, Murphy and colleagues noted that very young patients accounted for 2.3 per cent of the patients. In a study of 30 793 Korean patients (aged 20–49 years) with stage I–III breast cancer in the Korean Breast Cancer Registry (KBCR) between 2003 and 2010, 2.6 per cent of the patients were reported to be very young. The percentages of high histological grade and triple-negative tumours in the very young groups in the NCDB (64.2 and 23.7 per cent respectively) and KBCR (47.0 and 29.8 per cent) were obviously larger than their counterparts in the TCR.
The increased use of mastectomy in Asia has been reported in several studies. The rates of BCS in Asian settings have traditionally been lower than that in the USA and Europe. The prevalence of young women with breast cancer treated with mastectomy remains high in Asian countries, and patients who had BCS appear to have survival rates similar to those of patients who underwent mastectomy.

Several studies investigating the trends in surgical management of breast cancer in the USA and Europe have highlighted that an increasing number of younger patients undergo mastectomy. The rates of BCS in Asian settings have traditionally been very low compared with those in Europe and the USA. The increased use of mastectomy in Asia has been reported in several studies. This attitude is based on the increased incidence of tumour recurrence after BCS in young women with breast cancer. However, increased local recurrence does not necessarily indicate a low survival rate.

Based on a study conducted in 536 patients in the Netherlands, Bantema-Joppe and co-workers concluded that, although the rate of local recurrence significantly affected the rate of distant metastases or death, the increased risk of local recurrence after BCS compared with mastectomy did not lead to worse distant metastasis or death rates in patients aged less than 40 years. Another study from the UK investigating 3024 patients aged 40 years and 34 per cent in those aged over 40 years.

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Recently, a study of 1331 young patients (aged under 40 years) with early breast cancer diagnosed between 1997 and 2010 reported that local control and overall prognosis improved significantly in patients who underwent BCS, especially after 2005, the year after trastuzumab was introduced into routine clinical practice. The prevalence of young women with breast cancer treated with mastectomy remains high in Asian countries, and patients who had BCS appear to have survival rates similar to those of patients who underwent mastectomy.

The present study showed that adjuvant chemotherapy was associated with less local recurrence and better overall and cancer-specific survival in the young group, but not among the very young. A pooled analysis of 480 patients aged 40 years or less demonstrated that younger patients with hormone receptor-positive tumours benefit less from adjuvant systemic chemotherapy than those with hormone receptor-negative tumours. However, adjuvant chemotherapy appears to be a very important component of a successful treatment regimen in young women with ER-negative breast cancer. Even in the neoadjuvant setting, the GeparTrio study suggested that younger age is consistently associated with greater benefit from preoperative anthracycline–taxane-based chemotherapy. In patients with triple-negative tumours, the pathological complete response rates were as high as 57 per cent among those aged under 40 years and 34 per cent in those aged over 40 years.

Neoadjuvant chemotherapy for breast cancer has been advocated and popularized in recent decades. A study of 315 264 patients with breast cancer registered in the NCDB in 2010–2015 showed significant increases in the administration of neoadjuvant chemotherapy in all biological subtypes, with the greatest increase in patients with TNBC and HER2-positive tumours. The present study (between 2004 and 2014) had comparable findings, and the rate of neoadjuvant chemotherapy (10.6 per cent) was lower than the 20.2 per cent reported in the abovementioned study, possibly because the proportion of chemotherapy administered as treatment for breast cancer in the neoadjuvant setting has increased since 2010, it is most commonly administered to patients with triple-negative breast cancer and HER2-positive tumours. It is worth mentioning that the overall chemotherapy rate in very young patients was lower, whereas the neoadjuvant therapy rate was higher, than those in older patients. Because of the occurrence of premature menopause and infertility following chemotherapy, younger women (aged under 40 years) with early-stage hormone receptor-positive breast cancer might refuse to undergo adjuvant chemotherapy or hormone therapy.

This study also indicated that very young patients with stage II disease had a poorer prognosis than those with stage III tumours. This finding was partially supported by the results of a
study by Fu and colleagues. Their stratified analysis indicated that differences in cancer-specific survival in younger patients compared with those aged under 40 years were worse for earlier-stage disease. The only difference between their results and the present findings was that this was not observed in patients with stage I disease. Although worse outcome has been noted in younger patients, drugs that specifically target cancer cells with genetic alterations that inhibit DNA repair are already being used in the clinical setting and may improve the long-term outcomes of patients with cancer.

Table 2 Multivariable Cox regression analyses of impact of age, tumour, and treatment variables on overall, cancer-specific, disease-free survival, and local recurrence-free status in patients with breast cancer aged 20–50 years

| Variable                  | Overall survival | Cancer-specific survival | Disease-free survival | Local recurrence-free |
|---------------------------|------------------|--------------------------|-----------------------|-----------------------|
| **Hazard ratio**          | Hazard ratio     | Hazard ratio             | Hazard ratio          | Hazard ratio          |
| Age (years)               |                  |                          |                       |                       |
| 20.0–29.9                 | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| 30.0–39.9                 | 0.80 (0.64, 1.02)| 0.67                     | 0.043                 | 0.312                 |
| 40.0–50.0                 | 0.68 (0.54, 0.86)| 0.002                    | 0.001                 | 0.003                 |
| Surgery type              |                  |                          |                       |                       |
| BCS                       | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Mastectomy                | 1.52 (1.36, 1.70)| 1.57 (1.39, 1.78)        | 1.11 (1.01, 1.22)     | 0.74 (0.64, 0.84)     |
| Laterality                | 0.430            | 0.414                    | 0.069                 | 0.018                 |
| Right                     | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Left                      | 0.96 (0.88, 1.04)| 0.313                    | 0.256                 | 0.449                 |
| Not specified             | 1.37 (0.61, 3.06)| 0.443                    | 0.529                 | 0.033                 |
| Tumour behaviour          |                  |                          |                       |                       |
| Carcinoma in situ         | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Invasive                  | 2.85 (1.67, 4.86)| 6.15 (2.54, 14.88)       | 3.01 (1.99, 4.57)     | 2.55 (1.61, 4.05)     |
| Differentiation           |                  |                          |                       |                       |
| Well or moderate           | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Poor or none              | 1.38 (1.25, 1.52)| 1.45 (1.30, 1.61)        | 1.32 (1.21, 1.45)     | 1.21 (1.06, 1.39)     |
| Not specified             | 1.06 (0.90, 1.25)| 0.455                    | 1.09 (0.91, 1.30)     | 0.819                 |
| Resection margin          |                  |                          |                       |                       |
| Positive                  | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Negative                  | 0.71 (0.61, 0.82)| 0.066                    | 0.66 (0.56, 0.77)     | 0.044                 |
| Co-morbidity              |                  |                          |                       |                       |
| Location                  |                  |                          |                       |                       |
| Lateral, superior quadrant| 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Medial, upper quadrant    | 1.13 (0.99, 1.30)| 0.074                    | 1.10 (0.95, 1.28)     | 0.206                 |
| Central breast and nipple | 1.01 (0.85, 1.20)| 0.951                    | 0.90 (0.74, 1.09)     | 0.294                 |
| Inferior breast           | 1.02 (0.89, 1.17)| 0.800                    | 0.99 (0.85, 1.15)     | 0.867                 |
| Overriding/unknown        | 1.11 (0.99, 1.23)| 0.064                    | 1.10 (0.98, 1.23)     | 0.094                 |
| TNM stage                 |                  |                          |                       |                       |
| I                         | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| II                        | 2.01 (1.78, 2.27)| < 0.001                  | 2.29 (2.00, 2.63)     | < 0.001               |
| III                       | 6.12 (5.30, 7.06)| < 0.001                  | 7.45 (6.35, 8.74)     | < 0.001               |
| Radiotherapy              | 0.274            | 0.170                    | 1.00 (reference)      | 1.00 (reference)      |
| No                        | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Yes                       | 0.95 (0.86, 1.04)| 0.93 (0.84, 1.03)        | 0.71 (0.65, 0.77)     | 0.47 (0.41, 0.53)     |
| Chemotherapy/immunotherapy| 0.727            | 0.271                    | < 0.001               |                       |
| No                        | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Yes                       | 1.02 (0.90, 1.16)| 1.09 (0.94, 1.23)        | 0.75 (0.68, 0.83)     | 0.55 (0.48, 0.62)     |
| Hormone therapy           |                  |                          |                       |                       |
| No                        | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Yes                       | 0.83 (0.74, 0.93)| 0.84 (0.75, 0.95)        | 0.84 (0.76, 0.94)     | 0.69 (0.59, 0.81)     |
| Molecular subtype         |                  |                          |                       |                       |
| Luminal A                 | 1.00 (reference) | 1.00 (reference)         | 1.00 (reference)      | 1.00 (reference)      |
| Luminal B                 | 1.52 (1.16, 2.00)| 0.003                    | 1.64 (1.21, 2.22)     | 0.002                 |
| HER2/neu type             | 1.87 (1.29, 2.72)| 0.001                    | 2.26 (1.52, 3.36)     | < 0.001               |
| Basal (triple-negative)   | 3.74 (2.77, 5.05)| < 0.001                  | 4.13 (2.96, 5.75)     | < 0.001               |
| Not specified             | 2.02 (1.63, 2.52)| < 0.001                  | 2.16 (1.68, 2.77)     | < 0.001               |

Values in parentheses are 95% confidence intervals. *According to sixth edition of AJCC classification of breast cancer. BCS, breast-conserving surgery; HER2, human epidermal growth factor receptor 2.

stage I disease. Although worse outcome has been noted in younger patients, drugs that specifically target cancer cells with genetic alterations that inhibit DNA repair are already being used in the clinical setting and may improve the long-term outcomes of patients with cancer.
Table 3 Multivariable Cox regression analyses of impact of surgery type and adjuvant therapies in patients with breast cancer according to patient age

| Age 20.0–29.9 years | Overall survival | Cancer-specific survival | Disease-free survival | Local recurrence-free |
|----------------------|------------------|--------------------------|----------------------|----------------------|
|                      | Hazard ratio     | P                         | Hazard ratio         | P                     | Hazard ratio     | P                     |
| Surgery type (mastectomy versus BCS) |                |                           |                      |                       |                     |                       |
| Stage I              | 0.94 (0.58, 1.52) | 0.797                     | 0.91 (0.54, 1.52)    | 0.713                 | 0.52 (0.36, 0.75)  | < 0.001              |
| Stage II             | 1.58 (1.20, 2.08) | 0.001                     | 1.62 (1.21, 2.18)    | 0.001                 | 1.10 (0.86, 1.40)  | 0.435                 |
| Stage III            | 1.76 (1.06, 2.92) | 0.029                     | 1.74 (1.03, 2.92)    | 0.038                 | 1.57 (1.00, 2.45)  | 0.048                 |
| Chemotherapy (yes versus no) |                |                           |                      |                       |                     |                       |
| Stage I              | 1.11 (0.71, 1.73) | 0.651                     | 1.16 (0.72, 1.87)    | 0.538                 | 0.61 (0.40, 0.91)  | 0.017                 |
| Stage II             | 1.57 (1.23, 2.00) | < 0.001                   | 1.57 (1.21, 2.03)    | 0.001                 | 1.00 (0.79, 1.27)  | 0.987                 |
| Stage III            | 1.61 (1.13, 2.29) | 0.008                     | 1.63 (1.13, 2.34)    | 0.008                 | 1.13 (0.80, 1.59)  | 0.485                 |
| Radiotherapy (yes versus no) |            |                           |                      |                       |                     |                       |
| Stage I              | 0.46 (0.28, 0.74) | 0.001                     | 0.36 (0.21, 0.61)    | < 0.001               | 0.24 (0.17, 0.35)  | < 0.001               |
| Stage II             | 0.93 (0.72, 1.20) | 0.059                     | 0.87 (0.67, 1.14)    | 0.032                 | 0.65 (0.52, 0.82)  | < 0.001               |
| Stage III            | 0.65 (0.46, 0.92) | 0.015                     | 0.66 (0.46, 0.94)    | 0.022                 | 0.59 (0.43, 0.81)  | 0.001                 |
| Hormone therapy (yes versus no) |            |                           |                      |                       |                     |                       |
| Stage I              | 0.85 (0.52, 1.39) | 0.509                     | 0.77 (0.45, 1.29)    | 0.313                 | 1.00 (0.66, 1.52)  | 0.994                 |
| Stage II             | 0.76 (0.58, 1.00) | 0.051                     | 0.81 (0.60, 1.08)    | 0.143                 | 0.95 (0.74, 1.23)  | 0.711                 |
| Stage III            | 0.63 (0.44, 0.90) | 0.012                     | 0.62 (0.43, 0.90)    | 0.012                 | 0.62 (0.45, 0.87)  | 0.005                 |

| Age 30.0–39.9 years | Overall survival | Cancer-specific survival | Disease-free survival | Local recurrence-free |
|----------------------|------------------|--------------------------|----------------------|----------------------|
| Surgery type (mastectomy versus BCS) |                |                           |                      |                       |                     |                       |
| Stage I              | 0.93 (0.67, 1.29) | 0.652                     | 0.87 (0.58, 1.29)    | 0.481                 | 0.41 (0.32, 0.52)  | < 0.001              |
| Stage II             | 1.67 (1.40, 2.00) | < 0.001                   | 1.77 (1.46, 2.15)    | < 0.001               | 1.23 (1.05, 1.44)  | 0.011                 |
| Stage III            | 1.97 (1.38, 2.82) | < 0.001                   | 2.23 (1.50, 3.30)    | < 0.001               | 1.67 (1.22, 2.30)  | 0.001                 |
| Chemotherapy (yes versus no) |            |                           |                      |                       |                     |                       |
| Stage I              | 1.49 (1.13, 1.95) | 0.004                     | 1.56 (1.13, 2.16)    | 0.007                 | 0.65 (0.50, 0.85)  | 0.002                 |
| Stage II             | 1.15 (0.99, 1.34) | 0.071                     | 1.22 (1.04, 1.44)    | 0.017                 | 0.90 (0.78, 1.05)  | 0.187                 |
| Stage III            | 1.11 (0.89, 1.38) | 0.063                     | 1.16 (0.95, 1.46)    | 0.197                 | 0.90 (0.72, 1.12)  | 0.257                 |
| Radiotherapy (yes versus no) |            |                           |                      |                       |                     |                       |
| Stage I              | 0.75 (0.54, 1.03) | 0.079                     | 0.79 (0.53, 1.18)    | 0.247                 | 0.35 (0.28, 0.45)  | < 0.001               |
| Stage II             | 1.17 (1.01, 1.37) | 0.041                     | 1.22 (1.04, 1.44)    | 0.018                 | 0.97 (0.84, 1.12)  | 0.661                 |
| Stage III            | 0.74 (0.60, 0.90) | 0.003                     | 0.71 (0.57, 0.87)    | 0.001                 | 0.61 (0.51, 0.74)  | < 0.001               |
| Hormone therapy (yes versus no) |            |                           |                      |                       |                     |                       |
| Stage I              | 0.73 (0.53, 1.00) | 0.051                     | 0.74 (0.51, 1.08)    | 0.117                 | 0.77 (0.59, 1.01)  | 0.061                 |
| Stage II             | 0.71 (0.60, 0.83) | < 0.001                   | 0.67 (0.56, 0.79)    | < 0.001               | 0.76 (0.65, 0.89)  | < 0.001               |
| Stage III            | 0.68 (0.55, 0.84) | < 0.001                   | 0.73 (0.58, 0.91)    | 0.006                 | 0.80 (0.65, 0.98)  | 0.035                 |

Values in parentheses are 95 per cent confidence intervals. Tumours were staged according to sixth edition of AJCC classification of breast cancer. Estimates were adjusted for breast laterality, tumour cell grade, tumour behaviour, co-morbidity, and tumour location. BCS, breast-conserving surgery.

The major strengths of this study are the population-based design and large study population with complete follow-up data, making the results generally applicable. Data regarding death date and causes of death were primarily obtained from the Death Registry, not solely from the TCR, to avoid missing data or outdated information. Furthermore, the data were registered and regularly updated in the TCR by well trained registrars using a standardized coding manual.

The present results should be interpreted with consideration of some limitations. First, the analyses of tumour laterality, histological grade, tumour size, location, resection margin, and molecular subtype were limited by missing data for some tumours. In addition, the registry had no data on ER and PR status from 2007 to 2009, although this information might be important for the prognosis of patients with breast cancer. To overcome this, data on administration of hormone therapy agents (tamoxifen,
letrozole, exemestane, and anastrozole) for individual patients were used as surrogate data.

Second, many patients had no data on HER2/neu status as the TCR did not provide this information until 2011, let alone information on genetic (BRCA1/2) mutation testing, which was likely to be more common in the younger groups. In addition, Olaparib, a poly-ADP-ribose polymerase (PARP) inhibitor, has been reimbursed by the National Health Insurance for patients with terminal TNBC whose genetic assay indicates BRCA1/2 mutation only since November 2020. PARP inhibitor offers a promising role either combined with or without other agents to combat cell proliferation in BRCA1/2 mutation tumours. Therefore, it was not possible to control for the tumour characteristics with HER2/neu, BRCA mutation, and use of a PARP inhibitor in the multivariable survival analyses owing to a large amount of unknown data.

Third, the effect of chemotherapy in very young patients with stage III disease cannot be overexaggerated as the sample size was only 56. Fourth, the age definition of ‘very young’ is arbitrary. It was not possible to determine whether the age of 30 years was the best cut-off value. However, classifying patients as very young or young needs to be explored further. Other classifications of patients should not be overlooked. Finally, the TCR is a national cancer registry that records only 85 per cent of all patients with newly diagnosed cancer annually in Taiwan.

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Supplementary material
Supplementary material is available at BJS Open online.

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