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The prognosis of early-stage breast cancer in extremely young female patients

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Abstract

Breast cancer at a young age is associated with poor outcomes. However, few reports have compared the outcomes of breast cancer between extremely young patients and elderly patients.

We retrospectively collected information on patients diagnosed with breast cancer before 30 years of age. This case-control study employed matched operative methods, stage, and subtypes with a case-to-control ratio of 1:3. The primary endpoint was disease-free survival, and the secondary endpoint was overall survival. We analyzed potential prognostic factors in univariate and multivariate analyses.

This analysis included 18 patients in the young group with a median age of 28.5 years and 54 patients in the control group with a median age of 71 years. The 5-year disease-free survival rate was 68.8% in the former group and 84.6% in the latter group (P = .080). The 5-year overall survival was 87.1% and 91.2% in the young and old groups, respectively (P = .483). Multivariate analysis showed that tumor size and triple-negative breast cancer was major prognostic factors of poorer disease-free survival in the young group.

Extremely young breast cancer patients had a trend to develop a poorer disease-free survival than old patients, but not a poorer overall survival. Aggressive treatment for young patients at early stages of disease would improve survival.

Abbreviations: 95% CI = 95% confidence interval, EIC = extensive intraductal component, LTE = lymphatic tumor emboli, HR = hazard ratio, HER2 = human epidermal growth factor receptor 2.

Keywords: breast cancer, disease-free survival, extremely young age, overall survival, prognosis

1. Introduction

Over the past several decades, the survival of female breast cancer patients has improved.[1] This improvement is attributed to the awareness of breast cancer,[2] the organization of multidisciplin-

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ary teams,[3] and newly available treatments.[4–6] All our efforts have focused on identifying prognostic predictors among breast cancer patients for possible tailored treatments. Although the incidence of breast cancer in patients younger than 40 years is less than 4%,[7] young age is an independent risk factor for inferior survival, particularly in those younger than 35 years.[8–10] The risk factors for developing breast cancer at a young age include higher body mass, the use of oral contraceptives, family history of breast cancer, and radiation exposure.[11] Furthermore, a recently published study shows that the biology of breast cancer exhibits racial differences, which contributes to the increasing breast cancer incidence of the young population in East Asia.[12] Breast cancer at a young age has the following characteristics: history of breast cancer in close relatives, particular lifestyle, a lower proportion of the luminal subtype, a more aggressive nature, higher rates of locoregional recurrence, and a greater risk of breast cancer-related death.[13–16]

In this study, we collected information on early stage breast cancer patients whose diseases were diagnosed before the age of 30 years. Our aim was to search for specific characteristics of extremely young patients and compare them with elderly matched controls. By conducting this study, we aimed to identify factors to improve diagnosis or outcomes in the future. A total of 18 young patients and 54 matched controls who received treatments at one medical center located in southern Taiwan were included.

2. Methods

2.1. Study design and patients

This was a case-control study with a case-to-control ratio of 1:3. The demographics, pathological reports, and clinical outcomes were collected by retrospective chart review. The study group

enrolled patients younger than 30 years of age. The control group comprised elderly patients matched according to operative methods, cancer stage, and intrinsic subtypes during a similar time period. The patients received neoadjuvant therapies followed by surgery or surgery followed by adjuvant treatments based on local practice guidelines. If chemotherapy was indicated, anthracycline-based chemotherapy regimens were generally prescribed. Taxane-containing chemotherapy was prescribed for breast cancer patients with axillary lymph node involvement or triple-negative breast cancer (TNBC). The administration of trastuzumab for the human epidermal growth factor receptor 2 (HER2)-positive subtype has only been reimbursed for patients with lymph node involvement since 2010. Endocrine treatment is mandatory for all patients with estrogen receptor and/or progesterone receptor (ER/PR)-positive breast cancer.

2.2. Tumor characteristics

The pathological information of all breast cancer specimens was confirmed by 2 pathologists, and at least 1 was a breast cancer pathology specialist. The data included histological types, tumor sizes, number of involved axillary lymph nodes, extensive intraductal components, lymphatic tumor emboli, tumor grades, and immunohistochemical staining of ER, PR, and HER2. The interpretation of ER, PR, and HER2 was based on the American Society of Clinical Oncology/College of American Pathologists guidelines.[17,18] The pathological stage conformed to the seventh edition of the American Joint Committee on Cancer Tumor, Node, Metastasis system (AJCC TNM).[19]

2.3. Procedures

All patients were regularly followed up every 3 to 6 months and underwent annual examinations, which included sonography, mammography, chest radiography, and serum tumor marker assessments. Computed tomography and bone scintigraphy were optional if the patients had abnormal symptoms. Recurrent breast cancer was defined as a breast cancer-specific event. Other primary malignancies or non-cancer-related deaths were defined as non-breast cancer events. Disease-free survival (DFS) was defined as the time from the operation until the date of one of the following events: recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, any distant metastasis, or death from breast cancer. Overall survival (OS) was defined as the time from surgery until the date of mortality.

2.4. Statistical analysis

The continuous variables were compared using the non-parametric Kruskal–Wallis test. The nominal variables were compared using the likelihood-ratio Chi-Squared test or Fisher exact test. A Kaplan–Meier survival curve was drawn, and the survival difference between the 2 groups was compared using the log-rank test. Factors with $P < .2$ were imported into a multivariate analysis using a Cox proportional hazards regression model of DFS. The results were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs) and corresponding two-tailed P values. A P value less than .05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The study group enrolled 18 female patients with breast cancer identified by the above criteria at the National Cheng Kung University Hospital from 2000 to 2017. The median age of these patients was 28.5 years. By matching operative methods, 54 patients with a median age of 71 years were included in the control group. All enrolled patients were Taiwanese. Patient characteristics are summarized in Table 1.

The young group had a smaller body mass index with a median of $21.8 \, kg/m^2$. Other basic information was similar between the 2 groups. Most patients in both groups underwent an operation first without neoadjuvant therapies, and modified radical mastectomy was the primary surgical procedure of choice. The most common histologic type was invasive ductal carcinoma,

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Table 1

Histological types and therapeutic methods of extremely young patients and the control group.

	Young (n = 18)	Control (n = 54)	P value
Age, years, median (range)	28.5 (23–30)	71 (40–82)	<.001
Body height, cm, median (range)	158 (146–169)	151 (136–165)	.002
Body weight, kg, median (range)	53.7 (46.1–78.5)	57.4 (36.7–84.3)	.387
Body mass index, median (range)	21.8 (17.8–28.5)	23.8 (16.9–36.3)	.015
Operation first	16 (89%)	48 (89%)	>.999
Neoadjuvant chemotherapy first	2 (11%)	6 (11%)	>.999
Histological type			.867
Invasive ductal carcinoma	15 (82%)	48 (88%)	
Micropapillary carcinoma	1 (6%)	3 (6%)	
Sarcoma	1 (6%)	2 (4%)	
Invasive carcinoma with medullary feature	1 (6%)	1 (2%)	
Operative method			.842
MRM	13 (71%)	33 (61%)	
TM + SLNB	1 (6%)	3 (6%)	
BCS + ALND	1 (6%)	6 (11%)	
BCS + SLNB	3 (17%)	11 (20%)	
BCS only	0	1 (2%)	

ALND = axillary lymph node dissection, BCS = breast-conserving surgery, MRM = modified radical mastectomy, SLNB = sentinel lymph node biopsy, TM = total mastectomy.

Table 2

Pathological information of breast cancer in extremely young patients and the control group.

	Young (n = 18)	Control (n = 54)	P value
Tumor size, cm, median (range)	2.0 (0.5–12.5)	2.3 (0–4.7)	.630
Nuclear grade			>.999
Grade I + Grade II	9 (50%)	27 (50%)	
Grade III	9 (50%)	27 (50%)	
Extensive intraductal components	7 (41%)	17 (32%)	.562
Lymphatic tumor emboli	7 (39%)	19 (35%)	.784
Positive resection margin	8 (44%)	9 (17%)	.149
Axillary lymph node metastasis			>.999
Negative	10 (56%)	29 (54%)	
Positive	8 (44%)	25 (46%)	
Positive lymph node numbers	0 (0–44)	0 (0–14)	.854
Total resected lymph node numbers	19 (2–45)	19 (0–42)	.540
Extranodal extension	4 (22%)	14 (26%)	>.999
Nodal staging			.998
pN0	10 (55%)	29 (53%)	
pN1	3 (17%)	10 (19%)	
pN2	3 (17%)	9 (17%)	
pN3	2 (11%)	6 (11%)	
Tumor stage			.440
pTis	0 (0%)	2 (4%)	
pT1	10 (56%)	24 (44%)	
pT2	8 (44%)	28 (52%)	
AJCC TNM stage			.864
pStage 0	0	1 (2%)	
pStage I	8 (44%)	21 (39%)	
pStage II	5 (28%)	17 (31%)	
pStage III	5 (28%)	15 (28%)	
Estrogen receptor			>.999
Negative	4 (22%)	12 (22%)	
Positive	14 (78%)	42 (78%)	
Progesterone receptor			.586
Negative	7 (39%)	27 (50%)	
Positive	11 (61%)	27 (50%)	
Her-2/Neu receptor			.760
Negative	13 (72%)	41 (76%)	
Positive	5 (28%)	13 (24%)	
Intrinsic subtypes			.778
ER/PR-positive/HER2-negative breast cancer	9 (50%)	32 (59%)	
HER2-positive breast cancer	5 (28%)	13 (24%)	
Triple-negative breast cancer	4 (22%)	9 (17%)	

AJCC TNM stage = American Joint Committee on Cancer Tumor, Node, Metastasis stage; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.

which accounted for 82% (15/18) of the young group and 88% (48/54) of the control group. The pathological information of these patients' breast cancers is summarized in Table 2. The median tumor size was 2.0 cm in the young group, and 8 patients (44%) had lymph node metastasis. High-grade tumors were noted in half of these patients. In the control group, the median tumor size was 2.3 cm, and 25 patients (46%) had lymph node metastasis, with half of the tumors classified as high-grade. Pathologic AJCC TNM stages I, II, and III were classified in 44%, 28%, and 28% of patients in the young group and 39%, 31%, and 28% of patients in the control group, respectively. One patient from the control group had pStage 0 disease. Additionally, 50% of the patients had ER/PR-positive/HER2-negative diseases in the young group, followed by 28% with HER2-positive and 22% with triple-negative subtypes. In the control group, 59%, 24%, and 17% of patients displayed these breast cancer subtypes, respectively. All pathological factors were similar between the 2 groups.

Demographic information including jobs, family history of breast cancer, and pregnancy are presented in Figure 1A–C. Most of the young patients worked, and the majority of elderly patients stayed house-holding (Fig. 1A, $P < .001$). Family members who were at least second-degree relatives and had breast cancer were noted in 22% of patients in the young group and 8% of patients in the control group (Fig. 1B, $P = .018$). No history of pregnancy was recorded in 72% of the young patients and in only 6% of the old patients (Fig. 1C, $P < .001$). In the young group, the pathological stage was worse than the clinical stage in 11%, 39%, and 39% of patients according to the tumor, node, and TNM system classifications, respectively (Fig. 1D–F). These findings in the control group were 2%, 35%, and 24%, respectively. Thus, the consistency between the clinical and pathological stages was better in the old patients. The young patients tended to have an underestimated node and TNM stage preoperatively. However, the difference was minimal and not statistically significant. Preoperative examinations included
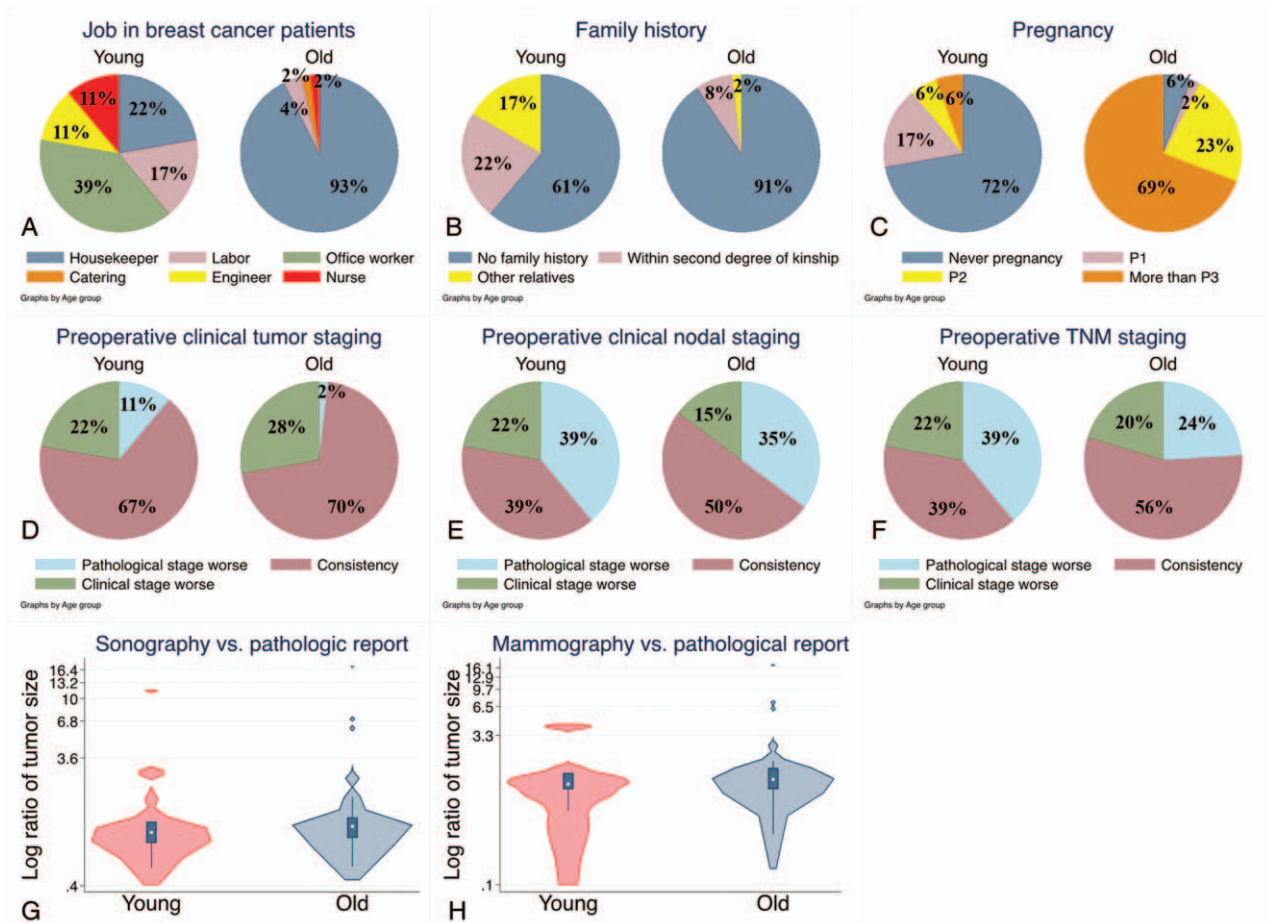
Figure 1. Demographics and preoperative exams for extremely young patients and the control group. (A) Proportion currently working. (B) Family history of breast cancer. (C) Personal history of pregnancy. (D) Preoperative clinical tumor stage. (E) Preoperative clinical nodal stage. (F) Preoperative clinical AJCC TNM stage. (G) Ratios of tumor size in sonography compared with the pathological tumor size (cm). The Y-axis is the logarithm transformation with base 10. (H) Ratios of tumor size in mammography compared with the pathological tumor size (cm). The Y-axis is the logarithm transformation with base 10.

ultrasonography and/or mammography. Sixteen young patients and 50 controls underwent sonography in our hospital, and the diagnostic rate was 100%. The measured tumor size in the sonography was similar to the tumor size in the pathological reports (Fig. 1G, $P = .603$). Diagnostic mammography was performed in 15 young patients and 52 controls. The accuracy rate was 93% in the young group and 90% in the control group. There was no difference between the measured tumor size in the mammography and in the pathological reports (Fig. 1H, $P = .585$).

3.2. Clinical outcomes

Chemotherapy was administered based on local practice guidelines and agreed upon by the multidisciplinary team. Approximately 10% of the young patients and nearly 50% of the control group did not receive any chemotherapy (Fig. 2A). The major difference was that the control group was less exposed to adjuvant chemotherapy. There were no significant differences between the 2 groups regarding the percentages of patients who received adjuvant radiotherapy, target therapy, or endocrine therapy (Fig. 2B). Patient outcomes were analyzed according to DFS and OS. The median duration of follow-up was 55 months

(8–96 months) for all patients. The 5-year DFS was 68.8% in the young group and 84.6% in the old group. The 5-year OS was 87.1% in the young group and 91.2% in the old group. The median DFS or OS was not reached in either group. The HR for DFS of the young group compared with the control group was 2.697 (95% CI, 0.850–8.555; log-rank $P = .080$) (Fig. 2C). The HR for OS of the young group compared with the control group was 1.823 (95% CI, 0.332–10.005; log-rank $P = .483$) (Fig. 2D). There were 5 breast cancer-specific events in the young group and 7 such events in the control group. The recurrent sites are listed in Table 3. Some patients experienced recurrence in more than 1 organ. There were 2 deaths in the young group, both of which were breast cancer-related. Four deaths occurred in the old group, including 2 breast cancer-related events, 1 metastatic colon cancer event, and 1 unknown cause of death.

We analyzed several prognostic factors for recurrence in a univariate analysis using a Cox proportional hazard model, including age, tumor size, tumor size on mammography, body mass index, lymph node metastasis, nuclear grade, extensive intraductal component, lymphovascular tumor emboli, breast cancer subtypes, and chemotherapy. A forest plot of the univariate analysis is shown in Figure 3A. Larger tumor size, larger tumor size on mammography, and TNBC contributed to a
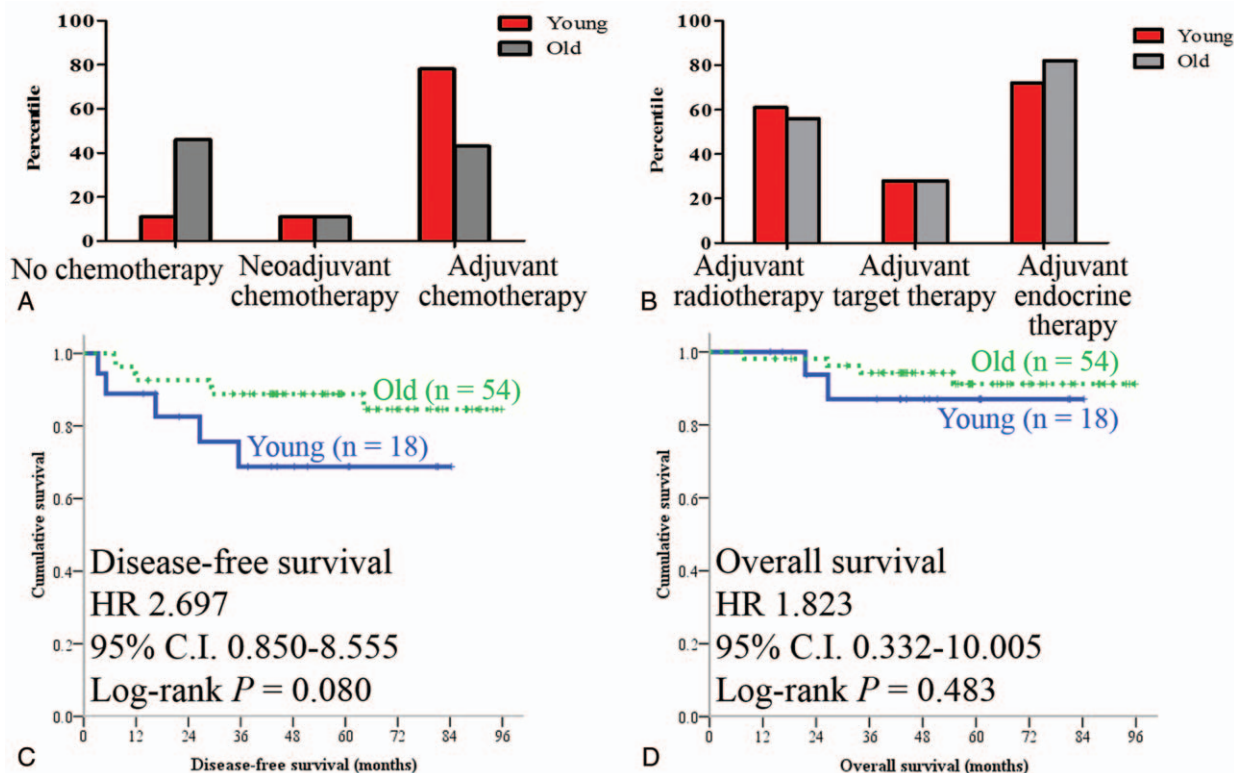
Figure 2. Multidisciplinary therapy and clinical outcomes for breast cancer patients in the extremely young group and control group. (A) Proportion of patients receiving chemotherapy. (B) Proportion of patients receiving radiotherapy, target therapy, and endocrine therapy. (C) Kaplan–Meier curve of disease-free survival. (D) Kaplan–Meier curve of overall survival. Extremely young patients have a trend of worse disease-free survival than the control group of older patients.

worse DFS in the young group compared with the old group. All factors with a P value less than .2 were entered into the multivariate analysis. The variables without statistical significance were removed in the next analysis. Figure 3B shows the final results: a larger tumor size predicted an HR of 2.099 (95% CI, 1.094–4.029; $P = .026$). Compared with the ER/PR-positive/HER2-negative subtype, the HR was 0.965 (95% CI, 0.118–7.900; $P = .973$) for the HER2-positive subtype and 7.624 (95% CI, 1.394–41.697; $P = .019$) for TNBC. Therefore, tumor size and TNBC were major independent prognostic factors for poorer DFS.
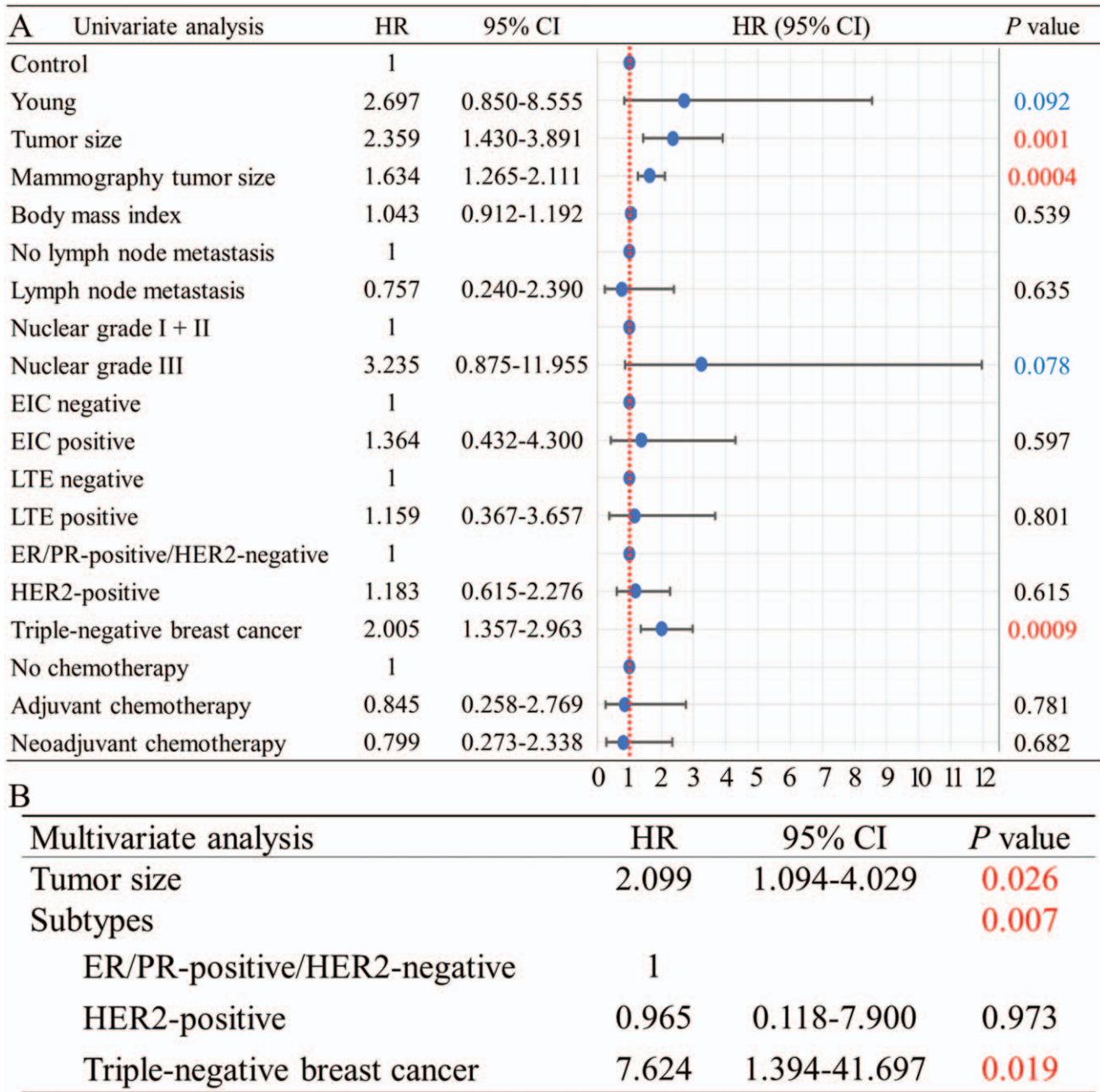
Table 3

Disease-free survival events and number of deaths.

	Young (n = 18)	Control (n = 54)	P value
Disease-free survival events	13 (72%)	45 (83%)	
Breast cancer-specific events	5 (28%)	7 (13%)	.160
Lung metastasis	4 (22%)	3 (6%)	.061
Bone metastasis	3 (17%)	2 (4%)	.096
Liver metastasis	1 (6%)	1 (2%)	.440
Brain metastasis	1 (6%)	1 (2%)	.440
Locoregional recurrence	2 (11%)	5 (9%)	>.999
Non-breast cancer events	0	2 (4%)	>.999
Metastatic colon cancer	0	1 (2%)	>.999
Unknown	0	1 (2%)	>.999
Breast cancer-related deaths	2 (11%)	2 (4%)	.259

4. Discussion

Breast cancer diagnosis at a young age has an overwhelming impact on a patients life. In addition to the issue of survival, young women face other problems, including endocrine symptoms, anxiety, and unemployment.[20,21] In East Asian women, the incidence of breast cancer in younger patients is increased disproportionally compared with rates in American women.[12] There are few data providing survival outcomes in breast cancer patients younger than 30 years old.[22,23] Most studies have focused on patients younger than 40 years of age.[24] To the best of our knowledge, this is the first report focusing on the comparison of extremely young patients and matched elderly patients with early stage breast cancer. Except for body mass index and pregnancy status, there were no significant differences in the baseline characteristics of the 2 groups. The young group had a more relevant family history of breast cancer. Regardless of receiving adjuvant chemotherapy much more frequently, young patients had a poorer DFS compared with older patients (HR = 0.371). The difference in DFS was not statistically significant because of the minimal number of patients in the present study. Furthermore, there was no difference in the OS between the groups after a median follow-up of 55 months. Our hospital is a tertiary referral medical center in Taiwan. Most patients were referred with suspicious breast masses, which had higher diagnostic rates with mammography and breast sonography. The prognosis of patients in this cohort may not completely represent the outcomes of similar populations because of the rarity of extremely young patients and the selection bias from a referral hospital.

A Univariate analysis	HR	95% CI	HR (95% CI)	P value
Control	1			
Young	2.697	0.850-8.555		0.092
Tumor size	2.359	1.430-3.891		0.001
Mammography tumor size	1.634	1.265-2.111		0.0004
Body mass index	1.043	0.912-1.192		0.539
No lymph node metastasis	1			
Lymph node metastasis	0.757	0.240-2.390		0.635
Nuclear grade I + II	1			
Nuclear grade III	3.235	0.875-11.955		0.078
EIC negative	1			
EIC positive	1.364	0.432-4.300		0.597
LTE negative	1			
LTE positive	1.159	0.367-3.657		0.801
ER/PR-positive/HER2-negative	1			
HER2-positive	1.183	0.615-2.276		0.615
Triple-negative breast cancer	2.005	1.357-2.963		0.0009
No chemotherapy	1			
Adjuvant chemotherapy	0.845	0.258-2.769		0.781
Neoadjuvant chemotherapy	0.799	0.273-2.338		0.682

0 1 2 3 4 5 6 7 8 9 10 11 12

B Multivariate analysis	HR	95% CI	P value
Tumor size	2.099	1.094-4.029	0.026
Subtypes			0.007
ER/PR-positive/HER2-negative	1		
HER2-positive	0.965	0.118-7.900	0.973
Triple-negative breast cancer	7.624	1.394-41.697	0.019

Figure 3. Cox proportional survival analysis of recurrent predictors in extremely young breast cancer patients and the control group. (A) Forest plot of the univariate analysis of disease-free survival in the present study. (B) Multivariate analysis of disease-free survival. 95% CI = 95% confidence interval, EIC = extensive intraductal component, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, LTE = lymphatic tumor emboli.

Genetic testing for young patients with breast cancer has been thoroughly discussed and supported.[25,26] The 2 findings of the present study support the indication for genetic counseling. First, 22% of the young patients had a family history of breast cancer in this cohort. Second, the DFS of young patients was still worse after aggressive treatment, particularly in those with TNBC, which is the subtype of breast cancer required for identifying hereditary cancer.[27] Unlike a previous study that reported that the ER/PR-positive/HER2-negative subtype contributed to a poorer recurrence-free survival in breast cancer patients aged 40 years or younger,[25] the strong correlation between TNBC and worse DFS in our cohort highlighted underlying differences in genetic background. However, it was difficult to provide genetic testing information because it was not reimbursed by the government or insurance systems. The genetic background of these extremely young patients, particularly those with BRCA1/2 status, should be emphasized in future studies.[25,26]

In contrast with the DFS results, patients younger than 30 years had a stable survival curve 2 years after diagnosis. Therefore, the OS of the young group was not significantly different from that of the old group, which had a median age of 71 years. Eighty percent of recurrent events caused visceral diseases in the young group, but only half of those diseases resulted in patient death. This finding supports the reality that young breast cancer patients are

treated aggressively for the best chance of survival. Controlling breast cancer at early stages is the best method for extremely young patients before the development of recurrence or metastasis. We should communicate with our patients about facing the disease with a positive attitude, abiding treatment guidelines, and even seeking opportunities for clinical trials.[28]

We should put all our efforts into providing effective, low toxicity, and affordable treatments. Many young breast cancer patients were still working in our study. Thus, the physical and financial toxicities associated with breast cancer-related procedures might push these patients away from treatments.[29] Young women will suffer from overwhelming impacts once advanced diseases or metastatic diseases develop. Since no effective screening tool has been developed for young women to detect breast cancer at early stages, we can only attempt early intervention for those whose disease has not yet reached the advanced stage.

Acknowledgments

Author contributions

WPC and HPH designed the research, analyzed the results, and participated in the manuscript writing and editing. KTL, YPC, and YTH analyzed the data and participated in the study coordination. ZJL and CCH collected the data. HPH supervised the project. All authors have read and approved the final manuscript.

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Writing – original draft: Wei-Pang Chung.
Writing – review & editing: Hui-Ping Hsu.

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