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Survival Outcomes in Young Women with Early-Stage Breast Cancer: Insights from an International Multicenter Cohort Study

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Abstract

Breast cancer incidence is rising among young Asian women, who are still underrepresented in international datasets. We examined the epidemiology and clinical outcomes of Asian patients under 40 years of age across various breast cancer subtypes to highlight their unmet clinical needs. We evaluated women aged 20 years and older diagnosed with early-stage breast cancer from the prospective Asian Breast Cancer Cooperative Group (ABCCG) cohort. For reference, data from the SEER cancer registry were included. Patients were divided into three age categories: young (<40 years), likely premenopausal mid-age (40–49 years), and likely postmenopausal (≥50 years). Survival analyses were conducted using multivariable Cox proportional hazards models, adjusting for tumor subtype, T stage, lymph node involvement, histologic grade, and study site. This study analyzed 45,021 breast cancer patients from Asian centers, alongside 496,332 SEER-White and 18,279 SEER-Asian patients. The median age at diagnosis was notably lower in the Asian cohort (51 years) compared with SEER-Asians (58 years; $P < 0.0001$) and SEER-Whites (62 years). In the young-age subgroup, HR+/HER2− breast cancers were more frequently observed among Asians and SEER-Asians than SEER-Whites (61.2% and 59.8% vs. 54.7%). Within the Asian cohort, young women with HR+/HER2− tumors had poorer overall survival relative to the mid-age group (6-year OS: 94.4% vs. 96.6%; HR 0.62; $P < 0.001$). A similar pattern was seen in SEER-Whites, where younger patients experienced an earlier drop in survival compared with those aged 40–49 (89.1% vs. 94.0%; $P < 0.001$).Among ABCCG-Asian patients under 40 with HR+/HER2− breast cancer, survival outcomes were worse compared with those in the mid-age group. These findings emphasize the adverse prognosis in younger patients and highlight the importance of personalized treatment strategies, including ovarian function suppression, with consideration of ethnic-specific factors.

Keywords: Young, Asian, HR+/HER2− breast cancer, Survival, Prevalence

Introduction

Breast cancer is the leading malignancy among women worldwide. Screening is generally recommended for women aged over 40 years (NCCN Guidelines Version 1.2022, Breast Cancer Diagnosis and Screening) [1]. Despite this, the incidence of breast cancer in women under 40 has been rising in the United States, according to SEER data [2, 3]. A similar upward trend has been observed in Asia, particularly among women younger than 40 years [4-7].

Breast cancer represents a biologically diverse group of diseases, each with unique clinical behaviors and therapeutic implications. Clinical classification relies on the expression of progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2), while molecular profiling further subdivides tumors into luminal A, luminal B, HER2-positive, basal-like, and normal breast-like subtypes [8, 9]. Evidence suggests that ER-positive tumors increase with age in American women, and Asian women aged 40–49 are more likely to present with ER-positive disease [10]. Younger women tend to develop more aggressive tumor types [11]. However, detailed data on survival outcomes of young Asian women across different breast

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cancer subtypes are limited. This study aimed to characterize the clinicopathologic features and survival outcomes of young Asian patients with early-stage breast cancer.

Materials and Methods

Patients and study design

Female patients aged 20 years and older diagnosed with early-stage breast cancer between 1 January 2005 and 31 December 2015 were included from five academic centers participating in the Asian Breast Cancer Cooperative Group (ABCCG): Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Samsung Medical Center, National Taiwan University Hospital, Singapore General Hospital/National Cancer Centre Singapore and Seoul National University Hospital (SNUH) [10]. For external validation, data were obtained from the SEER 18 cancer registry, focusing on four ethnic groups—Whites (including Hispanic individuals, SEER-Whites), Japanese, Chinese, and Korean (SEER-Asians)—with stage I–III unilateral breast cancer.

Early-stage disease was defined as pathologic stage I–III based on the 5th, 6th, or 7th editions of the AJCC TNM system, while clinical staging was applied for patients treated with neoadjuvant therapy. Tumor characteristics, including PR, ER, and HER2 status, were confirmed via surgical or core biopsy pathology reports according to ASCO-CAP guidelines [12-14]. In 2010, the cutoff for ER and PR positivity was updated from 10% to 1% [14]. HER2 testing followed the 2007 and 2014 ASCO-CAP criteria and was performed in CAP-accredited or nationally certified laboratories. Patients with incomplete clinical or pathological information were excluded from the study.

Statistical analyses

Categorical data were presented as counts and percentages. Continuous data were reported using medians along with their ranges. Comparisons between groups for continuous data employed the Mann–Whitney U test, whereas categorical data were analyzed with the chi-square test or Fisher's exact test, depending on the situation.

Survival analysis was conducted via a multivariable Cox regression model, controlling for confounders including age, hormone receptor status, HER2 expression, histological grade, tumor stage, lymph node involvement, and participating centers.

Overall survival (OS) represented the duration from breast cancer diagnosis until death due to any reason. Survival probabilities were plotted using the Kaplan–Meier approach. In cases where patients were still alive at the final assessment, their data were censored at the last known follow-up date without recorded death. A log-rank test p-value below 0.05 indicated statistical significance.

To standardize follow-up periods, individuals diagnosed from 2005 to 2015 had their data censored at the longest follow-up duration seen in the 2010–2015 diagnosis cohort, equating to 6 years.

Consent to participate and ethics approval

The research protocol received approval from the Institutional Review Board at Seoul National University Hospital (IRB number H1509-047-702) as well as from the ethics committees of all collaborating institutions. All clinical information was de-identified and anonymized prior to any data analysis.

Results and Discussion

Ethnic variations in breast cancer epidemiology

Between 2005 and 2015, a total of 45,007 women were diagnosed with stage I–III breast cancer across several Asian countries: South Korea (n = 17,376), Singapore (n = 11,237), Japan (n = 7,623) and Taiwan (n = 8,771). For comparison, the SEER database provided data on 496,332 White patients (SEER-Whites) and 18,279 Asian-American patients (SEER-Asians).

In the Asian Breast Cancer Cooperative Group (ABCCG) cohort, the median age at diagnosis was 51 years—significantly younger than the 58 years in SEER-Asians ($P < 0.0001$) and 62 years observed in SEER-Whites.

Infiltrating ductal carcinoma was the predominant histologic type in ABCCG-Asians (84.88%), exceeding the rates seen in SEER-Whites (72.05%) and SEER-Asians (77.55%).

The majority of cases across all groups presented at stage II or III, with approximately 60% of patients being lymph node-negative.

The prevalence of hormone receptor-positive/HER2-positive (HR+/HER2+) subtype was comparable among the three populations. However, the HR+/HER2− subtype was more frequent in SEER-Asians (73.38%) and SEER-Whites (75.89%) than in ABCCG-Asians (65.75%).

In contrast, triple-negative breast cancer (TNBC) and HER2-positive subtypes were more prevalent among ABCCG-Asians (14.32% and 9.38%, respectively) compared with SEER-Whites (3.96% and 10.21%, respectively) and SEER-Asians (5.74% and 10.0%, respectively; **Table 1**).

Table 1. Epidemiological characteristics of patients with stage I–III early breast cancer

Characteristic	Total (N = 559,632)	SEER-White (N = 496,332)	SEER-Asian (N = 18,279)	ABCCG-Asian (N = 45,021)
Age at Diagnosis				
Patients, n	559,618	496,332	18,279	45,007
Median (range), years	61 (2–117)	62 (2–117)	58 (20–108)	51 (17–97)
Histologic Grade				
Patients, n	547,267	496,332	18,279	32,656
Grade I, n (%)	123,225 (22.52%)	113,675 (22.90%)	3,967 (21.70%)	5,583 (17.10%)
Grade II, n (%)	228,224 (41.7%)	206,437 (41.59%)	7,606 (41.61%)	14,181 (43.43%)
Grade III, n (%)	159,330 (29.11%)	141,037 (28.42%)	5,402 (29.55%)	12,891 (39.48%)
Unknown/Other, n (%)	36,488 (6.67%)	35,183 (7.09%)	1,304 (7.13%)	1 (0.00%)
Histologic Subtype				
Patients, n	559,632	496,332	18,279	45,021
Invasive ductal carcinoma, n (%)	409,981 (73.26%)	357,590 (72.05%)	14,176 (77.55%)	38,215 (84.88%)
Invasive lobular carcinoma, n (%)	49,912 (8.92%)	47,089 (9.49%)	983 (5.38%)	1,840 (4.09%)
Other subtypes, n (%)	99,739 (17.82%)	91,653 (18.47%)	3,120 (17.07%)	4,966 (11.03%)
Stage				
Patients, n	420,634	365,765	13,567	41,302
Stage I, n (%)	172,390 (40.98%)	149,972 (41%)	5,713 (42.11%)	16,705 (40.45%)
Stage II, n (%)	184,128 (43.77%)	160,757 (43.95%)	6,151 (45.34%)	17,220 (41.69%)
Stage III, n (%)	64,116 (15.24%)	55,036 (15.05%)	1,703 (12.55%)	7,377 (17.86%)
T Stage				
Patients, n	536,730	477,178	17,637	41,915
T0, n (%)	1,414 (0.26%)	807 (0.17%)	28 (0.16%)	579 (1.38%)
T1, n (%)	339,556 (63.26%)	304,167 (63.74%)	11,170 (63.33%)	24,219 (57.78%)
T2, n (%)	154,106 (28.71%)	134,238 (28.13%)	5,237 (29.69%)	14,631 (34.91%)
T3, n (%)	26,963 (5.02%)	24,275 (5.09%)	815 (4.62%)	1,873 (4.47%)
T4, n (%)	14,691 (2.74%)	13,691 (2.87%)	387 (2.19%)	613 (1.46%)
N Stage				
Patients, n	544,934	483,538	17,831	43,565
N0, n (%)	382,240 (70.14%)	343,010 (70.94%)	13,007 (72.95%)	26,223 (60.19%)
N1, n (%)	118,346 (21.72%)	102,684 (21.24%)	3,608 (20.23%)	12,054 (27.67%)
N2, n (%)	28,586 (5.25%)	24,466 (5.06%)	811 (4.55%)	3,309 (7.60%)
N3, n (%)	15,762 (2.89%)	13,378 (2.77%)	405 (2.27%)	1,979 (4.54%)
Breast Cancer Subtype				
Patients, n	305,881	258,102	9,902	37,877

HR+/HER2−, n (%)	228,049 (74.55%)	195,877 (75.89%)	7,266 (73.38%)	24,906 (65.75%)
HR+/HER2+, n (%)	31,110 (10.17%)	25,661 (9.94%)	1,078 (10.89%)	4,371 (11.54%)
HR−/HER2+, n (%)	14,339 (4.69%)	10,218 (3.96%)	568 (5.74%)	3,553 (9.38%)
Triple-negative, n (%)	32,383 (10.59%)	26,346 (10.21%)	990 (10%)	5,047 (13.32%)

HER2, human epidermal growth factor receptor 2; ABCCG, Asian Breast Cancer Cooperative Group; SEER, Surveillance, End Results Program and Epidemiology; HR, hormone receptor.

Variations in breast cancer subtype distribution across age groups

However, the distribution of molecular subtypes showed notable differences among younger Asian patients under 40 years old. In the ABCCG cohort, the percentage of HR+/HER2− breast cancers was markedly higher compared to SEER-White patients but comparable to SEER-Asian patients (61.2% vs. 54.7% vs. 59.8%, respectively; **Figure 1 and Table 2**). Within this young age group, the rates of triple-negative breast cancer (TNBC) were similar between ABCCG-Asian and SEER-White patients but elevated relative to SEER-Asian patients (18.3% and 19.8% vs. 14.2%, respectively). The proportions of HER2-positive breast cancers remained comparable across all groups in this younger age category.

In the 40–49 age group, SEER-Asian patients exhibited the highest proportion of HR+/HER2− breast cancer, while ABCCG-Asian and SEER-White patients showed similar rates. For patients aged 50 years and older, the proportion of TNBC rose among ABCCG-Asian individuals, accompanied by a decline in HR+/HER2− cases. In this older age group, SEER-White patients displayed a higher percentage of HR+/HER2− breast cancer and a lower percentage of TNBC compared to the other cohorts **(Figure 1 and Table 2**).

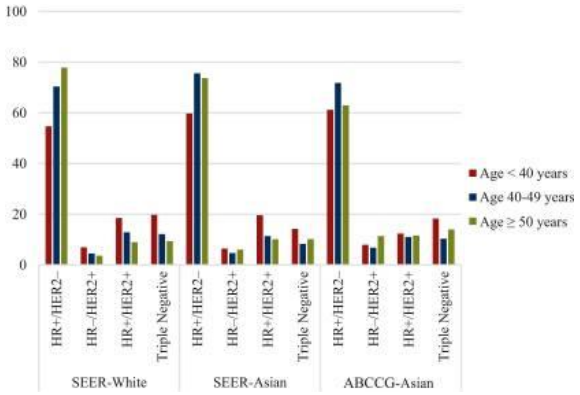


Figure 1. Breast cancer subtype distribution across age groups

This figure illustrates the percentages of breast cancer patients with different molecular subtypes—HR+/HER2+, HR+/HER2−, HR−/HER2− and HR−/HER2+ (triple-negative)—in the SEER-Asian, SEER-White, and ABCCG-Asian cohorts. The data are stratified by three age categories: presumed premenopausal middle-aged patients (40–49 years), young patients (<40 years), and presumed postmenopausal patients (≥50 years).

HER2: human epidermal growth factor receptor 2; ABCCG: Asian Breast Cancer Cooperative Group; SEER: Surveillance, Epidemiology, and End Results Program; HR: hormone receptor.

Table 2. Breast cancer subtype distribution by age group

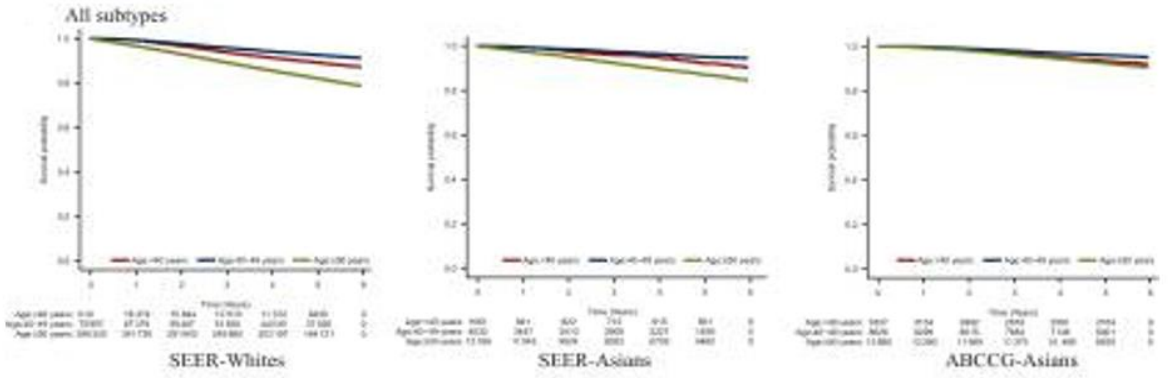
Subtype	Total	<40 years	40–49 years	≥50 years
SEER-White				
Patients with subtype data, n	496 332	21 010	75 997	399 325
HR+/HER2−, n (%)	195,877 (75.87%)	5,792 (54.7%)	26,232 (70.4%)	163,853 (77.9%)
HR+/HER2+, n (%)	25,661 (9.94%)	1,963 (18.5%)	4,810 (12.9%)	18,888 (9.0%)
HR−/HER2+, n (%)	10,218 (3.96%)	736 (7.0%)	1,684 (4.5%)	7,798 (3.7%)
Triple-negative, n (%)	26,346 (10.21%)	2,098 (19.8%)	4,559 (12.2%)	19,689 (9.4%)
SEER-Asian				
Patients with subtype data, n	18 279	1081	4032	13 166

HR+/HER2−, n (%)	7,266 (73.38%)	324 (59.8%)	1,611 (75.6%)	5,331 (73.7%)
HR+/HER2+, n (%)	1,078 (10.89%)	106 (19.6%)	242 (11.4%)	730 (10.1%)
HR−/HER2+, n (%)	568 (5.74%)	35 (6.5%)	101 (4.7%)	432 (6.0%)
Triple-negative, n (%)	990 (10.00%)	77 (14.2%)	176 (8.3%)	737 (10.2%)
ABCCG-Asian				
Patients with subtype data, n	45007	5890	14873	24244
HR+/HER2−, n (%)	24,887 (65.7%)	2,956 (61.2%)	9,073 (71.8%)	12,857 (63.0%)
HR+/HER2+, n (%)	4,354 (11.5%)	600 (12.4%)	1,393 (11.0%)	2,361 (11.6%)
HR−/HER2+, n (%)	3,570 (9.43%)	387 (8.0%)	858 (6.8%)	2,324 (11.4%)
Triple-negative, n (%)	5,066 (13.37%)	885 (18.3%)	1,317 (10.4%)	2,864 (14.0%)

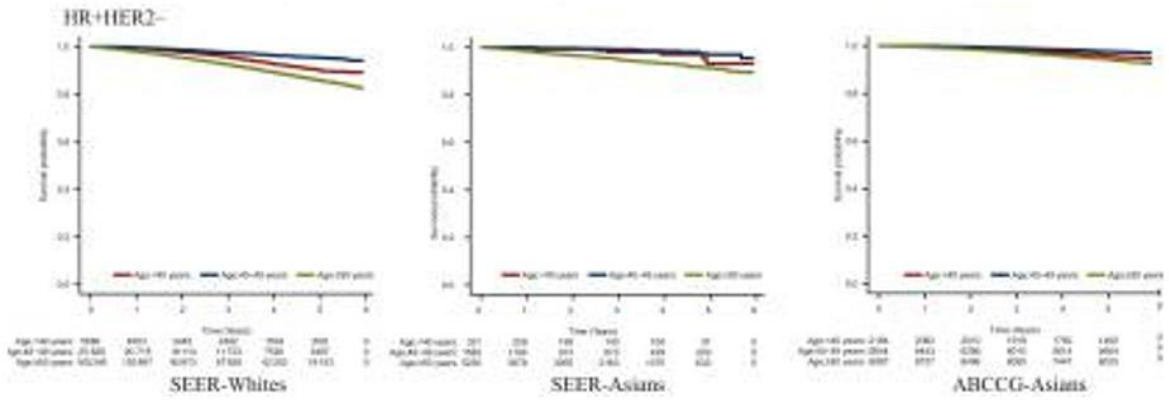
HER2, human epidermal growth factor receptor 2; ABCCG, Asian Breast Cancer Cooperative Group; SEER, Surveillance, Epidemiology, and End Results Program; HR, hormone receptor.

Survival

Survival outcomes were evaluated in 24,361 patients from the ABCCG cohort, 195,877 SEER-White patients, and 7,266 SEER-Asian patients. Across all populations, patients aged 40–49 years demonstrated the most favorable survival, whereas those aged 50 years and older had the poorest outcomes **(Figure 2).**



a)



b)

Figure 2. Six-year survival rates in SEER-Asians, SEER-Whites, and ABCCG-Asians

Survival rates were compared across three age categories—presumed premenopausal mid-age (40–49 years), young (<40 years), and presumed postmenopausal (≥50 years)—for all breast cancer

subtypes (A) and for HR+/HER2− tumors (B) in SEER-Asians, SEER-Whites, and ABCCG-Asians. HER2, human epidermal growth factor receptor 2; ABCCG, Asian Breast Cancer Cooperative Group; SEER, Surveillance, End Results Program and Epidemiology; HR, hormone receptor.

Subgroup analyses by age and subtype revealed distinct patterns across the cohorts. In ABCCG-Asian patients, those aged 40–49 years with HR+/HER2− tumors had significantly better overall survival (OS) compared with younger patients under 40 (6-year OS: 96.6% vs. 94.4%; adjusted hazard ratio [HR] 0.62, 95% CI 0.48–0.80; P < 0.001; **Figure 1 and Table 3**). This survival disadvantage for younger ABCCG-Asian patients persisted at 15 years of follow-up **(Figure 2)**. A similar trend was observed in SEER-White patients, where the younger group showed an earlier decline in survival compared with the mid-age group (89.1% vs. 94.0%; P < 0.001). By contrast, survival among younger SEER-Asian patients was comparable to the mid-age group (92.4% vs. 95.0%; P = 0.448).

For HR+/HER2+ breast cancer, six-year OS was similar between the young and mid-age groups across all populations, although ABCCG-Asian data suggested slightly lower long-term survival in the younger group at 15 years **(Figure 2).** In patients with HER2-positive or triple-negative breast cancer (TNBC), OS was largely similar between young and mid-age patients in all cohorts. Across all subtypes, patients aged ≥50 years consistently had the poorest outcomes in both ABCCG-Asian and SEER-White populations.

Comparisons by subtype also indicated that ABCCG-Asian patients with HR+/HER2− tumors and TNBC had better prognosis than their SEER-White and SEER-Asian counterparts. For HR+/HER2− tumors, the hazard ratios were 0.22 for ABCCG-Asians versus 0.819 for SEER-Whites and 0.891 for SEER-Asians. For TNBC, the corresponding hazard ratios were 0.826 for ABCCG-Asians, compared with 0.713 and 0.751 for SEER-Whites and SEER-Asians, respectively.

Table 3. Survival outcomes of early breast cancer by subtype, age group, and ethnicity

Subtype	Cohort	Age Group	Adjusted Hazard Ratio	95% Confidence Interval	P-value
HR+/HER2−	SEER-White	40–49 years	0.65	0.57–0.76	<0.001
		≥50 years	2.36	2.08–2.67	<0.001
	SEER-Asian	40–49 years	0.71	0.30–1.71	0.45
		≥50 years	3.49	1.64–7.42	0.001
	ABCCG-Asian	40–49 years	0.62	0.48–0.80	<0.001
		≥50 years	1.29	1.04–1.61	0.02
HR+/HER2+	SEER-White	40–49 years	1.01	0.72–1.41	0.96
		≥50 years	3.93	2.96–5.21	<0.001
	SEER-Asian	40–49 years	0.91	0.08–10.03	0.94
		≥50 years	6.82	0.93–49.80	0.06
	ABCCG-Asian	40–49 years	0.87	0.51–1.50	0.62
		≥50 years	1.96	1.22–3.16	0.01
HR−/HER2+	SEER-White	40–49 years	1.36	0.91–2.04	0.13
		≥50 years	3.23	2.27–4.60	<0.001
	SEER-Asian	40–49 years	0.69	0.17–2.84	0.61
		≥50 years	1.10	0.33–3.63	0.88
	ABCCG-Asian	40–49 years	0.92	0.57–1.49	0.74
		≥50 years	1.01	0.66–1.55	0.96
Triple-negative	SEER-White	40–49 years	0.99	0.85–1.16	0.92
		≥50 years	1.64	1.43–1.87	<0.001
	SEER-Asian	40–49 years	0.65	0.31–1.35	0.25
		≥50 years	0.94	0.51–1.74	0.85
	ABCCG-Asian	40–49 years	0.85	0.65–1.11	0.22
		≥50 years	0.82	0.65–1.04	0.10

Histologic grade, Adjusted with age, N stage, T stage, HER2 status, HR status, and study centers.

SEER, Surveillance, End Results Program and Epidemiology; CI, confidence interval; ABCCG, Asian Breast Cancer Cooperative Group; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

The results of this study reveal several key insights: (i) patients in the ABCCG-Asian cohort were diagnosed with early-stage breast cancer at younger ages than those in the SEER-White and SEER-Asian groups; (ii) younger ABCCG-Asian patients had a greater proportion of HR+/HER2− tumors; and (iii) patients younger than 40 years showed higher mortality rates compared to those in the middle-age category. These observations align with existing research indicating that breast cancer often presents earlier in Asian women. Unlike patterns in Western populations, where incidence increases with advancing age, breast cancer rates in Asian women typically peak around age 50 before decreasing [5].

A detailed analysis stratified by age and molecular subtype revealed that HR+/HER2− breast cancer was more common among younger ABCCG-Asian patients than among SEER-White patients. Notably, the proportion of HR+/HER2− tumors in SEER-Asian patients more closely mirrored that of SEER-White patients than ABCCG-Asian patients, pointing to possible influences from environmental factors. The increasing rates of estrogen-driven cancers, such as breast and gynecologic malignancies, have been associated with adoption of Western lifestyles, including higher body mass index, earlier onset of menarche, later age at first birth, and fewer children [15-17]. In addition, low fertility rates driven by family planning policies in various Asian countries have led to notable birth cohort effects [18-20]. Higher mammographic breast density, especially in premenopausal Asian women, has also been suggested as a factor that independently impairs the effectiveness of mammography screening [21, 22].

Differences in HR+/HER2− tumor prevalence between young SEER-Asian and SEER-White patients suggest underlying racial and biological contributions [10]. Genomic analyses have shown that ER-positive tumors in Asian patients more frequently harbor TP53 somatic mutations [23]. Compared to data from The Cancer Genome Atlas, premenopausal Asian women tend to have a higher incidence of luminal B subtypes, reduced ESR1 expression, and elevated rates of germline pathogenic variants in BRCA1 or BRCA2 [24]. Ethnic differences in the tumor microenvironment have also been identified, including greater tumor-infiltrating lymphocyte presence and lower transforming growth factor-beta signaling.

In Asian patients under 40 years, HR+/HER2− tumors were more prevalent, and these young patients experienced inferior survival outcomes relative to their middle-aged counterparts. illustrates that, over a 15-year follow-up period, survival for HR+/HER2− patients deteriorated more quickly, with the youngest age group showing a particularly sharp early drop, accounting for their worse prognosis. This trend is consistent with prior reports that younger patients with luminal tumors generally fare worse, whereas age has less impact on outcomes in HER2-positive or triple-negative breast cancer [25, 26]. Clinical trials such as HERA, NCCTG N9831, and NSABP B-31 found that age did not significantly predict survival in HR-negative, HER2-positive disease [27, 28].

Moreover, the 21-gene recurrence score (Oncotype DX, Genomic Health) reveals that high-risk scores are most common in women under 40, irrespective of nodal involvement [29]. Recent updates from the SOFT and TEXT trials indicate that premenopausal women who do not experience chemotherapy-induced menopause gain additional benefits from ovarian function suppression [30]. Since patients in the current study were diagnosed prior to these guideline updates, many likely did not receive optimal ovarian suppression. This highlights the importance of identifying young Asian women with HR+/HER2− breast cancer as a high-risk group and rapidly adopting contemporary treatment recommendations.

Several limitations should be acknowledged. The retrospective nature of the study and its dependence on registry data limited access to comprehensive details on adjuvant endocrine therapies (e.g., aromatase inhibitors, tamoxifen, and ovarian suppression), as well as chemotherapy and targeted treatments. Information on therapies for metastatic disease, which may influence survival, was also unavailable. Furthermore, patients with missing clinical data were excluded from the analysis. Despite these shortcomings, the results remain in agreement with earlier findings from East Asian cohorts.

Conclusion

Young Asian women under 40 years diagnosed with HR+/HER2− breast cancer, unlike those with HER2-positive or triple-negative subtypes, demonstrated significantly poorer survival compared to their middle-aged counterparts. This study emphasizes the importance of prolonged follow-up and the urgent need to develop targeted therapeutic approaches for this specific subtype in young patients to improve long-term outcomes.

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