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ORIGINAL ARTICLE – BREAST ONCOLOGY

Adolescents and Young Adults with Breast Cancer have More Aggressive Disease and Treatment Than Patients in Their Forties

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ABSTRACT

Background. Adolescents and young adults (AYAs; age < 40 years) account for less than 2% of breast cancer patients. Therefore, little is known about the tumor characteristics and care provided to AYA patients. This study sought to describe demographic, tumor, and treatment variables among AYA patients.

Methods. The study identified patients ages 15 to 49 years with breast cancer between 2010 and 2015 from the National Cancer Database. Patient and tumor factors were compared using Chi-square tests. Multivariable logistic regression was used to model the effect of age group on treatment while adjusting for confounding variables.

Results. The study identified 46,265 AYA patients with stages 0 to 3 breast cancer and compared them with 169,423 breast cancer patients ages 40 to 49 years. A greater proportion of the AYA patients presented with clinical stage 2 or 3 disease than the adult patients 40 to 49 years old (stage 2 disease: 44.3% vs 29.9%, respectively; stage 3 disease: 14.0% vs 7.7%, respectively; both $p < 0.001$). A greater proportion of the AYA patients had triple-negative breast cancer (TNBC) or human epidermal growth factor receptor 2-positive (HER2+) cancer than the adult patients (TNBC: 21.2% vs 13.8%, respectively; HER2+: 26.0% vs 18.6%, respectively; both $p < 0.001$). Among the AYA patients, the very young (ages 15–29 years) had more advanced disease and TNBC or HER2+ disease than the older youth (ages 30 to 39 years). The multivariable analysis showed that the AYA patients were more likely to undergo mastectomy (odds ratio [OR] 2.1) and receive chemotherapy (OR 1.9) than patients in their forties (both $p < 0.001$).

Conclusion. A greater proportion of the AYA breast cancer patients had more advanced disease and TNBC and HER2+ disease. The AYA patients had higher rates of mastectomy and use of chemotherapy than the adult breast cancer patients, reflecting that more aggressive therapy is recommended or chosen for women in this age group.

Breast cancer is the most common non-skin malignancy diagnosed in females and the second leading cause of cancer-related death in the United States.[1] Breast cancer typically is diagnosed in women older than 60 years and rather rare in young patients, with 1.8% of the diagnoses for patients 20 to 34 years old and 8.7% for patients 35 to 44 years old.[1] Although young patients compose a small proportion of breast cancer diagnoses, these patients have been shown to have more aggressive disease than older patients.[2–4] Adolescent and young adult (AYA) patients are between the ages of 15 and 39 years. Breast cancer is the leading cause of cancer-related death among females in this age category.[1,5,6]

A study evaluating the California Cancer Registry from 2005 to 2009 showed that AYA patients have more aggressive disease, with greater proportions of hormone receptor (HR)-negative and human epidermal growth

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factor 2-positive (HER+) disease. Furthermore, AYA patients are more likely to have a diagnosis of higher-stage disease.[3]

Although surgical trends in the United States have been explored among patients younger than 45 years, little is known regarding the overall state of disease patterns and treatments for breast cancer in the AYA age group nationally.[7] Therefore, we sought to determine the current patient and treatment characteristics of AYA patients with a diagnosis of breast cancer in the United States using the National Cancer Database (NCDB).

METHODS

A retrospective review analyzed all patients 15 to 49 years old in the NCDB with a diagnosis of ductal carcinoma in situ (DCIS) or invasive breast cancer from January 2010 to December 2015. The primary analysis sample comprised patients with stages 0 to 3 breast cancer according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology codes 8000 to 8576, 8940 to 8950, and 8980 to 8981. However, interesting subgroups, specifically patients presenting with stage 4 disease and those with histology code 9020 disease (phyllodes) also were described separately.

As per NCDB recommendations, we excluded class of case 0 patients (i.e., those receiving no treatment at the reporting facility) as well as those with a sequence greater than 1 (i.e., patients whose breast cancer diagnosis was not their first primary cancer diagnosis). We also excluded patients with clinical stage cT0/cN0 disease (because the breast cancer was not diagnosed before surgery) and those coded as receiving radiation before surgery (because neoadjuvant radiation therapy is not standard care for breast cancer). Figure 1 details the derivation of the primary analysis sample, including the number of patients excluded for each of the aforementioned reasons.

The NCDB is a national cancer registry estimated to capture 70% of all cases of newly diagnosed cancer in the United States. It contains data from more than 1500 facilities approved by the Commission on Cancer and has more than 34 million historical records.[8]

Patient, tumor, and treatment factors were extracted from the NCDB participant user file (PUF). Estrogen receptor (ER) and progesterone receptor (PR) status were recorded as positive if 1% or more of the cells stained positive. Hormone receptor (HR)-positive tumors were defined as ER- and/or PR-positive. The HER2 receptor status was recorded from a summary of results including immunohistochemistry, fluorescent in situ hybridization, and chromogenic in situ hybridization when performed.

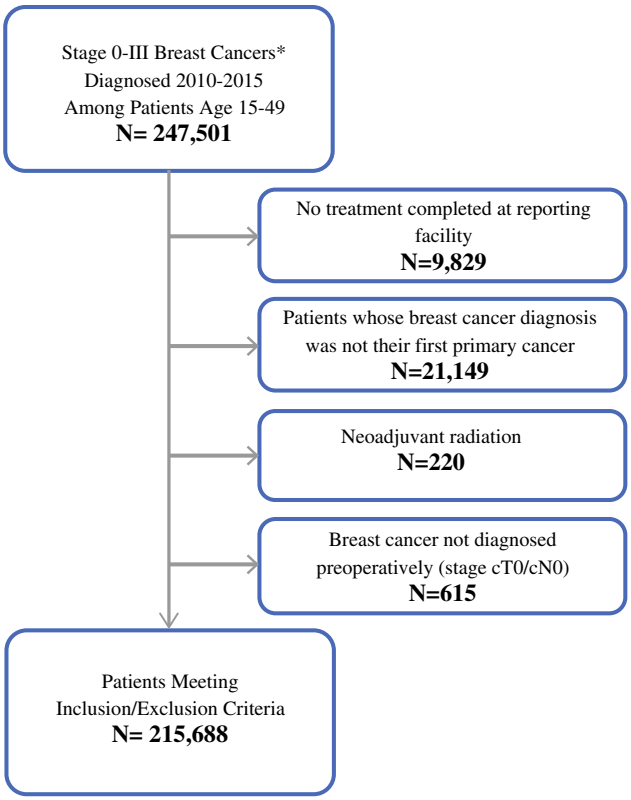

FIG. 1 Schematic detailing patient inclusion in the primary analysis sample. *International Classification of Diseases for Oncology, 3rd Edition (ICD-0-3) histology codes 8000-8576, 8940-8950, 8980-8981

Staging data were defined as per the American Joint Committee on Cancer (AJCC) Breast Cancer Staging System, seventh edition.[9]

If chemotherapy was started 30 days to 1 year before surgery, the patients were considered as having received neoadjuvant chemotherapy (NAC). The patients were classified as undergoing primary surgery if they did not undergo neoadjuvant systemic therapy (chemotherapy or hormone therapy). Breast surgery was classified as lumpectomy versus mastectomy based on the most definitive surgical procedure coded for the case.

Our Institutional Review Board deemed analysis of the NCDB PUF file to be exempt from review because it contains de-identified data.

Statistical Analysis

Patient, tumor, and treatment characteristics were compared between the AYA patients (ages 15–39 years) and the adults (ages 40–49 years), as well as within the AYA category between the very young (ages 15–29 years) and the young (ages 30–39 years) using Chi-square tests for univariate analysis. The patients presenting with stage 4 breast cancer were described but excluded from all other

TABLE 1 Patient and tumor characteristics stratified by age

	Age 15–29 years (n = 5058) n (%)	Age 30–39 years (n = 41,207) n (%)	Age 40–49 years (n = 169,423) n (%)	p value
Race				< 0.001[a,b]
Missing	59	500	1900	
White	3569 (71.4)	30,538 (75.0)	132,229 (78.9)	
Black	1015 (20.3)	6581 (16.2)	22,685 (13.5)	
Other	415 (8.3)	3588 (8.8)	12,609 (7.5)	
Spanish Hispanic				< 0.0001[a,c]
Missing	124	1196	5231	
Non-Spanish non-Hispanic	4370 (88.6)	35,426 (88.5)	149,538 (91.1)	
Spanish Hispanic	564 (11.4)	4585 (11.5)	14,654 (8.9)	
Charlson–Deyo score				< 0.0001[a,c]
0	4787 (94.6)	38,649 (93.8)	154,990 (91.5)	
1	251 (5.0)	2316 (5.6)	12,764 (7.5)	
2+	20 (0.4)	242 (0.6)	1669 (1.0)	
Sex				0.53[a]
Male	29 (0.6)	212 (0.5)	948 (0.6)	
Female	5029 (99.4)	40,995 (99.5)	168,475 (99.4)	
Primary payer				< 0.001[a,b]
Missing	122	990	3497	
Not insured	247 (5.0)	1747 (4.3)	5590 (3.4)	
Private insurance	3427 (69.4)	31,316 (77.9)	135,352 (81.6)	
Medicaid	1082 (21.9)	5719 (14.2)	17,811 (10.7)	
Medicare	80 (1.6)	829 (2.1)	4915 (3.0)	
Other government	100 (2.0)	606 (1.5)	2258 (1.4)	
Clinical stage				< 0.001[a,b]
Missing	335	2978	13,466	
0	430 (9.1)	4863 (12.7)	35,977 (23.1)	
1	1199 (25.4)	11,437 (29.9)	61,406 (39.4)	
2	2278 (48.2)	16,735 (43.8)	46,593 (29.9)	
3	816 (17.3)	5194 (13.6)	11,981 (7.7)	
Pathologic stage (among primary surgery cases)				< 0.001[a,b]
Missing	340	2575	11,547	
0	358 (11.1)	4136 (14.4)	29,604 (21.9)	
1	1079 (33.5)	9978 (34.9)	56,303 (41.6)	
2	1353 (42.0)	11,024 (38.5)	38,567 (28.5)	
3	428 (13.3)	3492 (12.2)	10,827 (8.0)	
Biologic subtype				< 0.001[a,b]
Missing	597	6271	39,852	
HER2+	1334 (29.9)	8901 (25.5)	24,060 (18.6)	
Triple-negative	1058 (23.7)	7295 (20.9)	17,930 (13.8)	
HR+/HER2–	2069 (46.4)	18,740 (53.6)	87,581 (67.6)	
Histology				< 0.001[a,b]
Ductal	4468 (88.3)	35,830 (87.0)	141,736 (83.7)	
Lobular	44 (0.9)	936 (2.3)	9853 (5.8)	
Mixed	98 (1.9)	1195 (2.9)	6457 (3.8)	
Other	448 (8.9)	3246 (7.9)	11,377 (6.7)	

TABLE 1 continued

	Age 15–29 years (n = 5058) n (%)	Age 30–39 years (n = 41,207) n (%)	Age 40–49 years (n = 169,423) n (%)	p value
Grade				< 0.001[a,b]
Missing	419	3306	15,504	
Well-differentiated	272 (5.9)	3295 (8.7)	27,275 (17.7)	
Moderately differentiated	1389 (29.9)	13,553 (35.8)	66,148 (43.0)	
Poorly differentiated/ undifferentiated	2978 (64.2)	21,053 (55.5)	60,496 (39.3)	

[a]Chi-square

[b]$p < 0.001$ for each pairwise comparison

[c]Only significant pairwise comparisons: ages 15–29 years versus 40–49 years and 30–39 years versus 40–49 years ($p < 0.001$)

statistical analyses. The analyses included both primary surgery and neoadjuvant patients unless otherwise specified.

Multivariable logistic regression was used to compare treatments between the AYA patients with breast cancer (ages 15–29 and 30–39 years separately) and the adult patients with breast cancer (ages 40–49 years), with adjustment for differences in confounding factors such as stage and tumor biology. The primary outcomes of interest were type of breast surgery (lumpectomy vs mastectomy) and use of chemotherapy. The secondary outcomes were extent of axillary surgery, timing of chemotherapy, receipt of hormone therapy, and receipt of radiation therapy.

The analyses were performed with meaningful subsets based on the indication for a given treatment (e.g., hormone therapy was assessed in the subset with hormone receptor-positive breast cancer), as detailed in the Results section. The adjustment for stage was performed using clinical staging variables (clinical tumor and clinical node category) in all the multivariable models, with the exception of the multivariable model for lumpectomy versus mastectomy among the primary surgery patients, for which we used pathologic staging variables. Evaluation of chemotherapy and/or hormone therapy included whether the therapy was ever received regardless of therapy duration. Logistic regression results were reported with odds ratios (ORs) and 95% confidence intervals (CIs).

A p value lower than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Stage 4 Breast Cancer

Both the very young patients and the young patients were significantly more likely than the patients in their forties to present with stage 4 disease, with 8.3% of those 15 to 29 years old and 5.6% of those 30 to 39 years old presenting with stage 4 disease versus 3.4% of those 40 to 49 years old ($p < 0.001$ for each pairwise comparison).

Stages 0 to 3 Breast Cancer

The primary analysis sample included 5058 patients 15 to 29 years old, 41,207 patients 30 to 39 years old, and 169,423 patients 40 to 49 years old. Patient and tumor characteristics stratified by age category are summarized in Table 1. A greater proportion of patients 15 to 29 years old were black (20.3%) compared with patients 30 to 39 years old (16.2%) and patients 40 to 49 years old (13.5%) ($p < 0.001$ for each pairwise comparison).

Tumor Characteristics (Table 1)

The AYA patients had higher clinical stage disease at presentation, with the very young patients having a higher stage of disease than the young patients. The rates of presentation with clinical stage 2 or 3 disease were respectively 48.2% and 17.3% for the patients 15 to 29 years old compared with 43.8% and 13.6% for the patients 30 to 39 years old and 29.9% and 7.7% for the patients 40 to 49 years old ($p < 0.001$ for each pairwise comparison). Although most of the patients in all the age groups had HR+/HER2– disease, triple-negative breast cancer (TNBC) and HER2+ breast cancer were more frequent in the young patients and most frequent in the very young patients ($p < 0.001$; Table 1).

Surgery: Primary Surgery

Among the patients treated with primary surgery, mastectomy was more common among the AYA patients (69.2%) than among the patients in their forties (49.5%).

TABLE 2 Treatment characteristics stratified by age

	Age 15–29 (n = 5058) n (%)	Age 30–39 (n = 41,207) n (%)	Age 40–49 (n = 169,423) n (%)	p value
Surgery type				< 0.001[a,b]
Missing	224	1434	3936	
Lumpectomy	1108 (22.9)	11,758 (29.6)	80,205 (48.5)	
Mastectomy	3722 (77.0)	27,968 (70.3)	85,132 (51.4)	
Surgery NOS	Not reportable	47 (0.1)	150 (0.1)	
Axillary surgery				< 0.001[a,b]
Missing	69	590	1651	
No nodes removed	439 (8.8)	3671 (9.0)	24,778 (14.8)	
1–5 nodes	2356 (47.2)	20,767 (51.1)	94,821 (56.5)	
> 5 nodes	2194 (44.0)	16,179 (39.8)	48,173 (28.7)	
Reconstruction (among mastectomy cases)				0.03[a,c]
Missing	183	1521	5550	
No reconstruction	1229 (34.7)	9123 (34.5)	28,147 (35.4)	
Reconstruction	2310 (65.3)	17,324 (65.5)	51,435 (64.6)	
Removal of uninvolved contralateral (among mastectomy cases)				< 0.001[a,d]
Missing	418	3066	10,230	
No removal of uninvolved contralateral	1195 (36.2)	9532 (38.3)	35,149 (46.9)	
Removal of uninvolved contralateral	2109 (63.8)	15,370 (61.7)	39,753 (53.1)	
Chemotherapy treatment (among invasive cancer cases)				< 0.001[a,b]
Missing	74	695	2811	
None	524 (11.3)	6197 (17.1)	48,150 (36.6)	
Neoadjuvant chemotherapy	1260 (27.2)	8434 (23.3)	17,955 (13.6)	
Adjuvant chemotherapy	2578 (55.6)	19,539 (54.1)	60,596 (46.1)	
Unknown timing	275 (5.9)	1965 (5.4)	4862 (3.7)	
Hormone therapy treatment (among HR+ cases)				0.51[a]
Missing	141	1114	5124	
No	670 (20.2)	5943 (21.0)	27,293 (21.0)	
Yes	2653 (79.8)	22,393 (79.0)	102,714 (79.0)	
Breast radiation (among BCS cases)				< 0.001[a,b]
Missing	25	195	1103	
No	182 (16.8)	1402 (12.1)	8757 (11.1)	
Yes	901 (83.2)	10,161 (87.9)	70,345 (88.9)	
Axillary radiation (among 4+ node positive cases)				>0.99[a]
Missing	11	104	244	
No	205 (35.9)	1569 (35.9)	4355 (35.8)	
Yes	366 (64.1)	2807 (64.1)	7810 (64.2)	

[a] $p < 0.001$ for each pairwise comparison

[b] Chi-square

[c] Only significant pairwise comparison: ages 30–39 years versus 40–49 years ($p = 0.009$)

[d] $p < 0.02$ for each pairwise comparison

Among the AYA patients, mastectomy was more common in the very young group (75.4%) than in the young group [68.5% ($p < 0.001$ for each pairwise comparison)]. Among those treated with mastectomy, contralateral prophylactic mastectomy (CPM) rates showed the same pattern, with the highest rates for the very young compared with the young and the patients in their forties [63.8% vs 61.7% vs 53.1% ($p < 0.02$ for each pairwise comparison)]. Interestingly,

TABLE 3 Multivariable analysis of factors associated with mastectomy versus lumpectomy among patients undergoing primary surgery

Variable	Level	Lumpectomy (n = 84,911) n (%)	Mastectomy (n = 96,700) n (%)	Univariate OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Age group (years)	15–29	876 (24.6)	2682 (75.4)	3.13 (2.90–3.38)	< 0.001	2.81 (2.59–3.04)	< 0.001
	30–39	9821 (31.5)	21,384 (68.5)	2.22 (2.17–2.28)	< 0.001	2.00 (1.95–2.06)	< 0.001
	40–49	74,214 (50.5)	72,634 (49.5)	1.0 reference		1.0 reference	
Race	White	65,096 (45.9)	76,819 (54.1)	1.0 reference		1.0 reference	
	Black	12,035 (50.9)	11,630 (49.1)	0.82 (0.80–0.84)	< 0.001	0.71 (0.69–0.73)	< 0.001
	Other	6730 (48.1)	7273 (51.9)	0.92 (0.88–0.95)	< 0.001	0.92 (0.88–0.95)	< 0.001
	Unknown	1050 (51.8)	978 (48.2)	0.79 (0.72–0.86)	< 0.001	0.77 (0.71–0.85)	< 0.001
Pathologic tumor category	T0	1373 (36.3)	2408 (63.7)	1.88 (1.75–2.01)	< 0.001	1.90 (1.77–2.04)	< 0.001
	Tis	20,892 (55.7)	16,641 (44.3)	0.85 (0.83–0.87)	< 0.001	1.45 (1.39–1.51)	< 0.001
	T1	43,704 (51.7)	40,859 (48.3)	1.0 reference		1.0 reference	
	T2	15,595 (36.0)	27,718 (64.0)	1.90 (1.86–1.95)	< 0.001	1.49 (1.45–1.53)	< 0.001
	T3	635 (9.7)	5915 (90.3)	9.96 (9.17–10.83)	< 0.001	6.08 (5.57–6.62)	< 0.001
	T4	63 (9.0)	640 (91.0)	10.87 (8.39–14.08)	< 0.001	7.11 (5.43–9.31)	< 0.001
	Unknown	2649 (51.3)	2519 (48.7)	1.02 (0.96–1.08)	0.553	4.66 (4.32–5.02)	< 0.001
Pathologic nodal category	N0	55,986 (48.5)	59,430 (51.5)	1.0 reference		1.0 reference	
	N1	12,535 (34.8)	23,521 (65.2)	1.77 (1.72–1.81)	< 0.001	1.59 (1.55–1.64)	< 0.001
	N2	1834 (20.8)	6966 (79.2)	3.58 (3.39–3.77)	< 0.001	2.59 (2.44–2.73)	< 0.001
	N3	540 (15.4)	2971 (84.6)	5.18 (4.73–5.68)	< 0.001	3.04 (2.76–3.35)	< 0.001
	Unknown	14,016 (78.6)	3812 (21.4)	0.26 (0.25–0.27)	< 0.001	0.15 (0.14–0.15)	< 0.001
Biologic subtype	HR+/HER2–	44,751 (46.6)	51,195 (53.4)	1.0 reference		1.0 reference	
	HER2+	9242 (37.7)	15,268 (62.3)	1.44 (1.40–1.49)	< 0.001	1.32 (1.28–1.37)	< 0.001
	Triple-negative	7731 (43.7)	9980 (56.3)	1.13 (1.09–1.17)	< 0.001	0.96 (0.93–1.0)	0.043
	Unknown	23,187 (53.4)	20,257 (46.6)	0.76 (0.75–0.78)	< 0.001	1.27 (1.22–1.32)	< 0.001
Histology	Ductal	73,936 (48.3)	79,172 (51.7)	1.0 reference		1.0 reference	
	Lobular	3031 (32.0)	6453 (68.0)	1.99 (1.90–2.08)	< 0.001	1.82 (1.73–1.91)	< 0.001
	Mixed	2477 (36.6)	4297 (63.4)	1.62 (1.54–1.70)	< 0.001	1.45 (1.37–1.53)	< 0.001
	Other	5467 (44.6)	6778 (55.4)	1.16 (1.12–1.20)	< 0.001	1.14 (1.09–1.18)	< 0.001
Grade	Well-differentiated	16,463 (56.8)	12,496 (43.2)	1.0 reference		1.0 reference	
	Moderately differentiated	33,132 (46.7)	37,796 (53.3)	1.50 (1.46–1.54)	< 0.001	1.25 (1.22–1.29)	< 0.001
	Poorly differentiated/ undifferentiated	27,595 (41.9)	38,292 (58.1)	1.83 (1.78–1.88)	< 0.001	1.35 (1.31–1.40)	< 0.001
	Unknown	7721 (48.8)	8116 (51.2)	1.38 (1.33–1.44)	< 0.001	1.31 (1.25–1.37)	< 0.001

OR odds ratio, *CI* confidence interval

reconstruction rates showed little variation across the three groups (65.3% vs 65.5% vs 64.6%), and only the pairwise comparison between the patients 30 to 39 years old and those 40 to 49 years old was statistically significant (p = 0.009). The types of treatment stratified by age category are summarized in Table 2.

In the multivariable analysis, adjusting for other factors including the AYA patients undergoing primary surgery remained more likely to be treated with mastectomy than the patients in their forties (OR 2.1; 95% CI 2.0–2.1; $p < 0.001$). Further stratification showed that mastectomy was more likely to be performed for the very young patients (ages 15–29 years; OR 2.8) and the young patients (ages 30–39 years; OR 2.0) than for the patients 40 to 49 years old ($p < 0.001$), after control was used for other factors including race, pathologic tumor/nodal category, biologic subtype, histology, and grade (Table 3).

Surgery: Neoadjuvant Chemotherapy

A separate analysis restricted to patients treated with neoadjuvant chemotherapy showed similar effects on the likelihood of mastectomy, with 81.7% of the patients 15 to 29 years old, 77.3% of the patients 30 to 39 years, and 67.6% of the patients 40 to 49 years old undergoing mastectomy. The adjusted ORs within this subset were 2.4 (95% CI 2.0–2.8) for the patients 15 to 29 years old versus the patients 40 to 49 years old and 1.8 (95% CI 1.7–2.0) for the patients 30 to 39 years old versus the patients 40 to 49 years old (each $p < 0.001$).

Surgery: Axillary Surgery

In the primary surgery cohort, axillary surgery also was more extensive for the AYA patients. It was more extensive for the very young patients than for the young patients among the clinically node-negative patients, but similar for those with clinically node-positive disease. Among the cN0 primary surgery patients, more than five lymph nodes were removed for 31.5% of the very young patients, 26.5% of the young patients, and 19.1% of the patients in their forties ($p < 0.001$ for each pairwise comparison). Among the cN+ primary surgery patients, there was no difference across age groups ($p = 0.92$), with 77.0% to 77.5% having more than five nodes removed in each age category. Among the neoadjuvant chemotherapy patients, however, no significant difference was observed regarding extent of axillary surgery regardless of clinical node status. Among the groups 15 to 29 years, 30 to 39 years, and 40 to 49 years of age, more than five lymph nodes were removed from respectively 29.2%, 27.7%, and 27.4% in the cN0 subgroup ($p = 0.66$) and from respectively 67.9%, 68.4%, and 67.9% in the cN+ subgroup ($p = 0.80$).

Radiation Therapy

Among the patients who underwent lumpectomy, use of breast radiation was less common among the AYA patients (87.5%) than among the patients in their forties (88.9%), and less common among the very young (83.2%) than among the young (87.9%) ($p < 0.001$ for each pairwise comparison). These differences persisted after multivariable adjustment, with an OR of 0.47 (95% CI 0.40–0.55) for the very young patients and an OR of 0.75 (95% CI 0.71–0.80) for young patients, each compared with patients in their forties.

Among the patients undergoing mastectomy, the AYA patients were more likely to receive post-mastectomy radiation (27.9%) than the patients in their forties (21.5%) ($p < 0.001$; with an adjusted OR of 1.10 [95% CI 1.06–1.14], $p < 0.001$). Among the AYA patients, the very young patients (29.7%) and the young patients (27.6%) differed slightly ($p = 0.01$). Among the patients with four or more positive lymph nodes (LNs), no age effect for LN radiation was observed in either the univariate analysis (15- to 29-year-olds [64.1%] vs 30- to 39-year-olds [64.1%] or 40- to 49-year-olds [64.2%]; $p > 0.99$) or the multivariable analysis ($p = 0.98$).

Chemotherapy

Among the patients with invasive disease, the AYA patients were more likely to be treated with chemotherapy (83.5%) than the patients in their forties (63.4%) ($p < 0.001$). In the AYA group, a small but statistically significant difference was observed between the patients 15 to 29 years old (88.7%) and those 30 to 39 years old (82.9%) ($p < 0.001$). In the multivariable analysis, with adjustment for race, stage, grade, histology, and biologic subtype, AYA patients were more likely to receive chemotherapy compared to patients in their forties with an OR of 1.9 (95% CI 1.8–2.0). With the AYA group split into those 15 to 29 years old and those 30 to 39 years old, the multivariable adjusted OR was 2.4 (95% CI 2.2–2.7) for the 15- to 29-year-olds and 1.9 (95% CI 1.8–1.9) for the 30- to 39-year-olds, each relative to the 40- to 49-year-olds (Table 4). Among the patients receiving chemotherapy, a greater proportion of the very young patients (32.8%) and the young patients (30.2%) received chemotherapy in the neoadjuvant setting than the patients in their forties (22.9%) ($p < 0.001$ for all pairwise comparisons). This increased likelihood of neoadjuvant versus adjuvant chemotherapy for the AYA patients persisted after multivariable adjustment, with an OR of 1.3 (95% CI 1.2–1.4) for the 15- to 29-year-olds and an OR of 1.3 (95% CI 1.2–1.3) for the 30- to 39-year-olds, each compared with the 40- to 49-year-olds ($p < 0.001$).

Hormone Therapy

Among the patients with HR+ breast cancer, use of hormone therapy was similar across the age groups in the univariate analysis: 79.8% of the patients 15 to 29 years old, 79.0% of those 30 to 39 years old, and 79.0% of those 40 to 49 years old were treated with hormone therapy ($p = 0.51$). However, the multivariable analysis showed that the AYA patients were less likely to receive hormone therapy, with an adjusted OR of 0.78 (95% CI 0.71–0.86) for those 15 to 29 years old and 0.80 (95% CI 0.77–0.83) for those 30 to 39 years old, than those 40 to 49 years old (each $p < 0.001$).

TABLE 4 Multivariable analysis of factors associated with chemotherapy use among patients with invasive breast cancer

Variable	Level	No chemotherapy (n = 54,871) n (%)	Chemotherapy (n = 117,464) n (%)	Univariate OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Age group (years)	15–29	524 (11.3)	4113 (88.7)	4.53 (4.13–4.97)	< 0.001	2.42 (2.18–2.70)	< 0.001
	30–39	6197 (17.1)	29,938 (82.9)	2.79 (2.71–2.87)	< 0.001	1.87 (1.80–1.94)	< 0.001
	40–49	48,150 (36.6)	83,413 (63.4)	1.0 reference		1.0 reference	
Race	White	44,108 (33.1)	89,137 (66.9)	1.0 reference		1.0 reference	
	Black	5738 (23.4)	18,736 (76.6)	1.62 (1.57–1.67)	< 0.001	0.98 (0.94–1.02)	0.315
	Other	4337 (34.0)	8421 (66.0)	0.96 (0.92–1.0)	0.041	0.83 (0.79–0.87)	< 0.001
	Unknown	688 (37.0)	1170 (63.0)	0.84 (0.77–0.93)	< 0.001	0.68 (0.60–0.77)	< 0.001
Clinical tumor category	T0	22 (8.4)	239 (91.6)	9.57 (6.18–14.82)	< 0.001	1.56 (0.99–2.47)	0.056
	Tis	3364 (67.1)	1650 (32.9)	0.43 (0.41–0.46)	< 0.001	0.33 (0.31–0.35)	< 0.001
	T1	37,502 (46.8)	42,556 (53.2)	1.0 reference		1.0 reference	
	T2	7948 (14.2)	48,176 (85.8)	5.34 (5.20–5.49)	< 0.001	3.07 (2.97–3.16)	< 0.001
	T3	688 (5.1)	12,726 (94.9)	16.30 (15.08–17.62)	< 0.001	6.70 (6.15–7.30)	< 0.001
	T4	152 (3.4)	4365 (96.6)	25.31 (21.51–29.77)	< 0.001	5.95 (4.99–7.09)	< 0.001
	Unknown	5195 (40.1)	7752 (59.9)	1.31 (1.27–1.37)	< 0.001	0.97 (0.92–1.03)	0.368
Clinical nodal category	N0	49,191 (40.9)	71,184 (59.1)	1.0 reference		1.0 reference	
	N1	1724 (5.2)	31,266 (94.8)	12.53 (11.92–13.17)	< 0.001	6.44 (6.10–6.80)	< 0.001
	N2	134 (2.7)	4823 (97.3)	24.87 (20.94–29.54)	< 0.001	9.85 (8.22–11.79)	< 0.001
	N3	64 (2.1)	2913 (97.9)	31.45 (24.55–40.30)	< 0.001	8.51 (6.58–11.02)	< 0.001
	Unknown	3758 (34.1)	7278 (65.9)	1.34 (1.28–1.39)	< 0.001	1.72 (1.61–1.83)	< 0.001
Biologic subtype	HR+/HER2–	2876 (8.9)	29,342 (91.1)	1.0 reference		1.0 reference	
	HER2+	1419 (5.5)	24,280 (94.5)	8.09 (7.77–8.42)	< 0.001	5.48 (5.23–5.73)	< 0.001
	Triple-negative	45,718 (44.2)	57,688 (55.8)	13.56 (12.84–14.33)	< 0.001	5.18 (4.88–5.51)	< 0.001
	Unknown	4858 (44.1)	6154 (55.9)	1.0 (0.96–1.04)	0.846	0.85 (0.80–0.89)	< 0.001
Histology	Ductal	41,420 (29.7)	98,043 (70.3)	1.0 reference		1.0 reference	
	Lobular	4725 (44.8)	5825 (55.2)	0.52 (0.50–0.54)	< 0.001	0.95 (0.91–1.00)	0.053
	Mixed	2912 (38.4)	4679 (61.6)	0.68 (0.65–0.71)	< 0.001	1.02 (0.96–1.08)	0.476
	Other	5814 (39.5)	8917 (60.5)	0.65 (0.53–0.67)	< 0.001	0.72 (0.68–0.75)	< 0.001
Grade	Well-differentiated	18,141 (69.5)	7967 (30.5)	1.0 reference		1.0 reference	
	Moderately differentiated	25,238 (38.7)	39,940 (61.3)	3.60 (3.49–3.72)	< 0.001	2.45 (2.37–2.54)	< 0.001
	Poorly differentiated/ undifferentiated	7147 (10.3)	62,226 (89.7)	19.83 (19.12–20.55)	< 0.001	7.28 (6.98–7.59)	< 0.001
	Unknown	4345 (37.2)	7331 (62.8)	3.84 (3.67–4.02)	< 0.001	2.02 (1.91–2.13)	< 0.001

OR odds ratio, *CI* confidence interval

Phyllodes Tumors

Although not included in our primary analysis sample, a substantial portion of the breast cancer reported for the patients 15 to 19 years old was malignant phyllodes. Phyllodes tumors made up 32.1% (17/36) of the reported breast cancer cases among the 15- to 19-year-olds, 1.5% (84/5490) of the cases among the 20- to 29-year-olds, 0.4% (195/43,763) of the cases among the 30- to 39-year-olds, and 0.2% (364/175,772) of the cases among the 40- to

49-year-olds ($p < 0.001$ for each pairwise comparison). The histologic grade of the phyllodes was missing for 57% of the patients, but when recorded, it was poorly differentiated/undifferentiated for 80% of those 15 to 19 years of age, 57.1% of those 20 to 29 years of age, 45.0% of those 30 to 39 years of age, and 46.7% for those 40 to 49 years of age ($p = 0.13$). The phyllodes tumor was larger than 5 cm in 58.8% of those 15 to 19 years of age, 41.3% of those 20 to 29 years of age, 47.9% of those 30 to 39 years of age, and 48.6% of those 40 to 49 years of age ($p = 0.52$).

DISCUSSION

Adolescent and young adults with breast cancer have more aggressive tumor biology, present with later-stage disease, are more likely to undergo mastectomy, and are more likely to receive chemotherapy than breast cancer patients in their forties. Furthermore, among the AYA patients in our study, these findings were significantly more common in the very young (ages 15–29 years) than in the young (ages 30–39 years). Whereas previous studies have reported on AYA patients, to our knowledge, our study is one of the first to evaluate differences between very young and young patients at a national level.

We found that the very young patients (ages 15 to 29 years) and the young patients (ages 30 to 39 years) with breast cancer were more often black than the patients 40 to 49 years old. This finding has been previously reported in other studies, which found women younger than 40 years to be of the black race more commonly than older women.[3,10–13] It is interesting that very young breast cancer patients have an even greater proportion of non-whites with a diagnosis of breast cancer than patients in the young category. The reasons for the increased prevalence of breast cancer in this patient population are speculated to be associated with differences in childbearing without breastfeeding and a corresponding increased prevalence of TNBC.[10,14,15]

The higher proportion of patients with aggressive tumor biologic subtypes (TNBC and HER2+ breast cancers) among AYA than among patients in their forties has been observed before among women younger than 40 years of age.[2–4,11,16,17] We further found a difference in the proportion of patients with more aggressive biologic subtypes between the very young and young patient categories as well, although HR+ disease remained the most common subtype across all age groups. This is in keeping with a recent analysis of combined data from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results (SEER) Program, which also showed that HR+ tumors compose the greatest proportion of tumors across patients of all ages (ages 20–49 years).[10] After HR+, the most common tumor biologies in that analysis were TNBC and HR+/HER2+, and the least common was HR–/HER2+.[10]

Among the very young patients, a greater proportion of patients presented with clinical stages 2, 3 and 4 disease, and a smaller proportion of patients presented with clinical stage 0 or 1 disease than either the young patients or the patients in their forties with breast cancer. This likely was because these patients had tumors of the more aggressive biologic subtypes and were below the recommended age for routine screening for average-risk women. Unfortunately, we were unable to evaluate for genetic mutations or significant family history in our data set.

Previous studies also have reported similar findings, with AYA women more likely to have their disease diagnosed at a higher stage, to have lymph node-positive disease, and to have bilateral breast cancer.[3,4,11,17,18] Therefore, imaging including axillary ultrasound for patients with invasive breast cancer to evaluate the extent of disease in the breast and the nodes is important in the workup of AYA patients with breast cancer.

Previous studies have shown that patients younger than 40 years are more likely to undergo mastectomy for treatment,[11,17] and that patients younger than 45 years are more likely to undergo CPM.[7] We also found that the very young patients were more likely than the young patients to undergo mastectomy and also CPM. The very young patients and the young patients with cN0 disease also were more likely to have more extensive axillary surgery than the adult patients. Interestingly, both the very young patients and the young patients were less likely to receive radiation after lumpectomy than the patients in their forties. The reasons for this finding are unclear. However, the reluctance of young women to pursue radiation also may be a factor influencing the mastectomy rate.

Both the very young patients and the young patients were more likely to receive chemotherapy, and when treated with chemotherapy, were more likely to receive it in the neoadjuvant setting than the patients in their forties. This likely was due in part to the more aggressive tumor biologic subtypes and the higher-stage disease present in these age groups, as well as the greater use of neoadjuvant chemotherapy for these tumor subtypes.[19] However, this age effect persisted in the multivariable analysis, even after adjustment for disease characteristics, suggesting that AYA patients are treated more aggressively. Therefore, the more aggressive treatment of very young patients may be overtreatment stemming from patient age rather than appropriate treatment focused on tumor stage and biology. However, we were unable to evaluate whether the higher rate of aggressive therapy (chemotherapy and mastectomy) were predominantly due to physician recommendation,

patient preference, or both. With improvements in genomic assessment of tumors and an individualized approach based more on tumor biology and less on demographics, this potential overtreatment should decrease in future years.

In the univariate analysis, we found no significant difference across the three age categories regarding the use of hormonal therapy. However, in the multivariable analysis adjusted for other factors, the findings showed that the AYA patients were less likely to receive hormonal therapy. One explanation for this might be that young women may not want to undergo hormonal therapy that may influence future pregnancy. We were unable to evaluate for breast cancer-specific survival and could therefore not assess the effect of the lower rate of hormonal therapy use in this patient population. Evaluation of the utility and efficacy of hormonal therapy for very young patients requires further research.

Although overall prognosis and local disease control has improved for young patients with breast cancer during the past two decades, younger patients continue to have a worse prognosis than older patients.[2,11,20–22] Findings also have shown that short-term survival varies by breast cancer subtypes for both AYA patients and adult patients.[23] A limitation of our study was its inability to evaluate granular data such as genetic mutations, family history, and breast-cancer specific survival.

CONCLUSIONS

In this study, both the very young patients and the young patients with breast cancer presented with a greater proportion of patients having more advanced disease and more often having triple-negative and HER2+ disease than the patients in their forties with breast cancer. These patients also showed higher rates of mastectomy, a greater number of lymph nodes removed, and a greater use of chemotherapy than the breast cancer patients in their forties when control was used for tumor biology and stage. This may reflect recommendations and/or patient preferences for more aggressive treatment based on age rather than tumor biology.

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