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Article

ARTICLE

Incidence and Survival Among Young Women With Stage I–III Breast Cancer: SEER 2000–2015

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Abstract

Background: Although recent findings suggest that de novo stage IV breast cancer is increasing in premenopausal women in the United States, contemporary incidence and survival data are lacking for stage I–III cancer.
Methods: Women aged 20–29 (n = 3826), 30–39 (n = 34 585), and 40–49 (n = 126 552) years who were diagnosed with stage I–III breast cancer from 2000 to 2015 were identified from the Surveillance, Epidemiology, and End Results 18 registries database. Age-adjusted, average annual percentage changes in incidence and 5- and 10-year Kaplan-Meier survival curves were estimated by race and ethnicity, stage, and hormone receptor (HR) status and grade (low to well and moderately differentiated; high to poorly and undifferentiated) for each age decade.
Results: The average annual percentage change in incidence was positive for each age decade and was highest among women aged 20–29 years. Increased incidence was driven largely by HR+ cancer, particularly HR+ low-grade cancer in women aged 20–29 and 40–49 years. By 2015, incidence of HR+ low- and high-grade cancer each independently exceeded incidence of HR− cancer in each age decade. Survival for HR+ low- and high-grade cancer decreased with decreasing age; survival for HR− cancer was similar across age decades. Among all women aged 20–29 years, 10-year survival for HR+ high-grade cancer was lower than that for HR+ low-grade or HR− cancer. Among women aged 20–29 years with stage I cancer, 10-year survival was lowest for HR+ high-grade cancer.
Conclusions: HR+ breast cancer is increasing in incidence among premenopausal women, and HR+ high-grade cancer was associated with reduced survival among women aged 20–29 years. Our findings can help guide further evaluation of preventive, diagnostic, and therapeutic strategies for breast cancer among premenopausal women.

Breast cancer in premenopausal women, particularly younger premenopausal women, has been consistently associated with high risk of disease relapse and death (1). Premenopausal women often present with breast cancer that has aggressive molecular characteristics (2). For example, gene-expression profiling suggests proportionally more basal-like and HER2–enriched tumors occur in these women (3,4). Also, studies using receptor status and other histologic tumor features as indicators of disease biology report that young patients tend to have high-grade and highly proliferative breast tumors (2).

Additional factors appear to be associated with development and prognosis of breast cancer in premenopausal women. In particular, previous work observed that women younger than 40 years of age tend to present with higher stage cancer than older women (5–7). This finding may be attributable in part to disease biology described above; however, young premenopausal women, compared to perimenopausal or postmenopausal women, disproportionately experience clinical and social circumstances associated with care delays, including lack of screening, dense breast tissue, less access to care, or low clinician suspicion

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Table 1. Frequencies of patient and tumor characteristics among women aged 20–49 years diagnosed with stage I–III breast cancer, 2000–2015, SEER 18 registries*

Characteristic	20–29 years No. (%)	30–39 years No. (%)	40–49 years No. (%)
Analytic sample	3826	34 585	126 552
Race and ethnicity			
Non-Hispanic white	1921 (50.2)	19 272 (55.7)	79 781 (63.0)
Non-Hispanic black	687 (18.0)	4955 (14.3)	15 026 (11.9)
Non-Hispanic American Indian/Alaska Native	33 (0.9)	238 (0.7)	746 (0.6)
Non-Hispanic Asian/Pacific Islander	377 (9.9)	3868 (11.2)	12 964 (10.2)
Hispanic (all races)	792 (20.7)	6071 (17.6)	17 445 (13.8)
Non-Hispanic (unknown race)	16 (0.4)	181 (0.5)	590 (0.5)
Stage			
I	902 (23.6)	9961 (28.8)	53 207 (42.0)
II	2011 (52.6)	17 064 (49.3)	53 014 (41.9)
III	913 (23.9)	7560 (21.9)	20 331 (16.1)
Analytic subsample	3459	31 564	114 798
HR status and grade			
HR+ low grade	1002 (29.0)	11 759 (37.3)	62 848 (54.7)
HR+ high grade	1194 (34.5)	9823 (31.1)	27 437 (23.9)
HR−	1263 (36.5)	9982 (31.6)	24 513 (21.4)

*Because of rounding, percentages might not total 100. HR = hormone receptor, SEER = Surveillance, Epidemiology, and End Results.

for malignancy (8–10). Rather than an image-detected lesion, young women frequently present with a palpable mass, which has been associated with diagnostic delay and higher stage cancer at presentation (7, 8). Additionally, familial risk due to germline mutations remains a well-established risk factor for breast cancer diagnosis at a young age (11–14). Lastly, pregnancy-associated breast cancer, which by definition occurs in premenopausal women, appears to have distinct and more aggressive molecular characteristics (15) and has been associated with lower survival compared to nonpregnancy-associated breast cancer in young women (16).

Population-based studies of women diagnosed over a decade ago supported gradual increases in breast cancer incidence in young women (17–19), and a recent study reported an increased incidence of young women presenting with de novo stage IV breast cancer (20). Less is known about contemporary patterns of incidence and survival in earlier stage, operable breast cancer and how these patterns are changing by cancer subtype among premenopausal women. Improved understanding of these patterns could offer additional insight into the etiology of premenopausal breast cancer and ideally result in improved preventive, diagnostic, and therapeutic strategies. In this context, we characterized recent population-based data from the United States on incidence and survival among women aged 20–49 years diagnosed with stage I–III breast cancer.

Methods

Study Population

Our retrospective cohort study was approved by the University of Iowa Institutional Review Board. Data were obtained from the US Surveillance, Epidemiology, and End Results (SEER) 18 registries database (November 2017 submission, 2000–2015) from the National Cancer Institute. The 18 population-based cancer registries that provided data for the SEER program comprised approximately 28% of the total US population (21). Stage and grade for breast cancer diagnoses in the SEER 18 registries database were assigned using the American Joint Committee on Cancer adjusted 6th edition (22) and Bloom-Richardson criteria (23), respectively. For hormone receptor (HR) status, HR+ status was defined as having either positive or borderline estrogen receptor (ER) or progesterone receptor (PR) status, and HR− status was defined as having both ER− and PR− status. Women with borderline ER and PR status were grouped with ER+ and PR+, respectively, because of changes in assay interpretation guidelines that no longer allow for a borderline result and indicate a cutoff of 1% positive tumor cell nuclei be used, compared to historical cutoffs of up to 10% (24). The HER2 receptor status of the breast tumors was not included in analyses, as SEER began reporting this information in 2010; additional years will be needed to assess a comparable time period for incidence and survival using this characteristic.

We identified 181 663 women aged 20–49 years whose initial cancer diagnosis was breast cancer during 2000–2015. We excluded women whose diagnoses were not microscopically confirmed (n = 680); reported only from a nursing or convalescent home, hospice, autopsy, or death certificate (n = 24); and not stage I–III (n = 15 996), leaving 164 963 women in our analytic sample. Our analytic subsample excluded an additional 15 142 women if their breast cancer was of unknown HR status, or HR+ but of unknown grade, leaving 149 821 women. Completeness of staging (Supplementary Table 1, available online) and HR status and grade (Supplementary Table 2, available online) improved over time throughout the study period, but less so for staging. Distributions of age, race and ethnicity, and cancer stage did not differ appreciably between those with known and unknown classification of HR status and grade (data not shown).

Statistical Analysis

Age at breast cancer diagnosis was grouped into three age decades: 20–29, 30–39, and 40–49 years. Race and ethnicity were classified using SEER definitions into six mutually exclusive groups: non-Hispanic white, black, American Indian/Alaska Native, and Asian/Pacific Islander; Hispanic; and non-Hispanic (unknown race). Cancer stage was stratified as I, II, or III. HR status and

Table 2. AAPCs in incidence of patient and tumor characteristics for women aged 20–49 years diagnosed with stage I–III breast cancer, 2000–2015, SEER 18 registries

Characteristic	20–29 years AAPC (95% CI)	30–39 years AAPC (95% CI)	40–49 years AAPC (95% CI)
Analytic sample	1.62 (1.16 to 2.09)	0.31 (−0.07 to 0.69)	0.34 (0.18 to 0.51)
Race and ethnicity			
Non-Hispanic white	2.11 (1.52 to 2.69)	0.55 (0.19 to 0.91)	0.56 (0.41 to 0.72)
Non-Hispanic black	0.60 (−1.20 to 2.43)	0.28 (−0.31 to 0.87)	0.24 (−0.08 to 0.56)
Non-Hispanic Asian/Pacific Islander	1.87 (−0.32 to 4.10)	−0.02 (−0.81 to 0.76)	1.02 (0.61 to 1.44)
Hispanic (all races)*	1.07 (−0.08 to 2.23)	0.71 (−0.06 to 1.50)	0.39 (−0.04 to 0.83)
Stage			
I	1.88 (0.33 to 3.45)	−0.79 (−1.30 to -0.27)	0.43 (0.15 to 0.72)
II	1.77 (0.86 to 2.70)	1.41 (0.98 to 1.85)	0.78 (0.54 to 1.02)
III	1.02 (0.01 to 2.03)	−0.73 (−1.35 to -0.10)	−1.03 (−1.33 to -0.71)
Analytic subsample	2.26 (1.49 to 3.03)	0.88 (0.34 to 1.42)	0.97 (0.72 to 1.23)
HR status and grade			
HR+ low grade	5.67 (4.14 to 7.21)	2.67 (2.07 to 3.26)	2.84 (2.37 to 3.31)
HR+ high grade	3.83 (2.40 to 5.28)	2.69 (2.19 to 3.19)	1.34 (0.97 to 1.71)
HR−	−0.26 (−1.25 to 0.74)	−1.22 (−2.07 to -0.35)	−1.20 (−1.89 to -0.50)

*Women with breast cancer ascertained by the Alaska Native registry were excluded from incidence estimations for the Hispanic group because this registry only ascertains patients from the Native American and Alaska Native populations within the state. AAPC = average annual percentage change; CI = confidence interval; HR = hormone receptor; SEER = Surveillance, Epidemiology, and End Results.

grade were categorized as HR+ low-grade (well and moderately differentiated: grades 1–2), HR+ high-grade (poorly differentiated and undifferentiated: grades 3–4), and HR−.

We estimated incidence for each age decade as the number of annual breast cancer diagnoses per 100 000 women and age-adjusted to the 2000 US standard population by 5-year age groups using SEER*Stat Version 8.3.5 software (25). Average annual percent changes (AAPCs) in incidence and 95% confidence intervals (CIs) for 2000–2015 were estimated using Joinpoint Regression Program software, version 4.6.0.0 (26). We applied least-squares regression models with the natural logarithm of the age-adjusted rates as the outcome and diagnosis year as the predictor. Piecewise regression models also were assessed via a modified Bayesian information criterion model selection method (27) and fit using the Joinpoint software. Errors in the regression models were assumed to be normally distributed. Model assumptions were evaluated by examining the residuals, and no violations were observed.

We estimated survival for women diagnosed during 2000–2014. Women diagnosed in 2015 in the analytic sample (n = 10 469) and subsample (n = 10 094) were excluded because of lack of follow-up time, as were women diagnosed during 2000–2014 with no follow-up time (sample: n = 67; subsample: n = 44), leaving 154 427 and 139 683 women, respectively, for analysis. We generated Kaplan-Meier estimates and 95% CIs for 5- and 10-year survival using SEER*Stat; 10-year Kaplan-Meier curves were plotted using R Version 3.5.1 (28).

Stratifying by age decade, we used the analytic sample to describe patient race and ethnicity and cancer stage and compare incidence and survival by these characteristics. Because of sparse numbers, we did not examine incidence and survival for non-Hispanic American Indian/Alaska Native women or non-Hispanic women of unknown race. We used our analytic subsample to describe HR status and grade frequencies and compare incidence and survival by this characteristic. Because the women in our sample may have a relatively high prevalence of germline mutations (29), we assessed whether a second primary malignancy confounded our survival estimates by conducting a subanalysis to remove women later diagnosed with a second primary malignancy from the analytic sample (n = 16 552 [10.7%]) and subsample (n = 14 605 [10.5%]).

Results

Our analytic sample comprised 3826 women aged 20–29 years, 34 585 women aged 30–39 years, and 126 552 women aged 40–49 years (Table 1). The proportion of stage III breast cancer decreased with age, with the opposite pattern observed for stage I and II cancer. Stage III cancer tended to be higher among non-Hispanic blacks and Hispanics compared to non-Hispanic whites and Asian/Pacific Islanders with the opposite observed for stage I cancer; proportions for stage II cancer tended to be similar among racial and ethnic groups (Supplementary Table 3, available online). In our analytic subsample, the proportion of HR+ high-grade and HR− cancer each decreased with age, whereas that for HR+ low-grade cancer increased with age (Table 1).

Incidence

Using our analytic sample, the overall incidence of stage I–III breast cancer increased during 2000–2015 among women in each age decade studied, particularly those aged 20–29 years (Table 2). In each decade, incidence increased among non-Hispanic whites but was rather stable among non-Hispanic blacks (Table 2, Figure 1). Incidence also increased among non-Hispanic Asian/Pacific Islanders aged 20–29 and 40–49 years but remained stable among those aged 30–39 years. Patterns among Hispanics were similar or lesser in magnitude than those among non-Hispanic whites. Stratifying overall incidence by stage revealed positive AAPCs for stage I cancer among women aged 20–29 and 40–49 years, but negative among those aged 30–39 years. The AAPCs for stage II and III cancer decreased with age, being negative for women aged 30–49 years with stage III cancer (Table 2, Figure 2).

Examining incidence by HR status and grade using our analytic subsample, we observed that the increased incidence

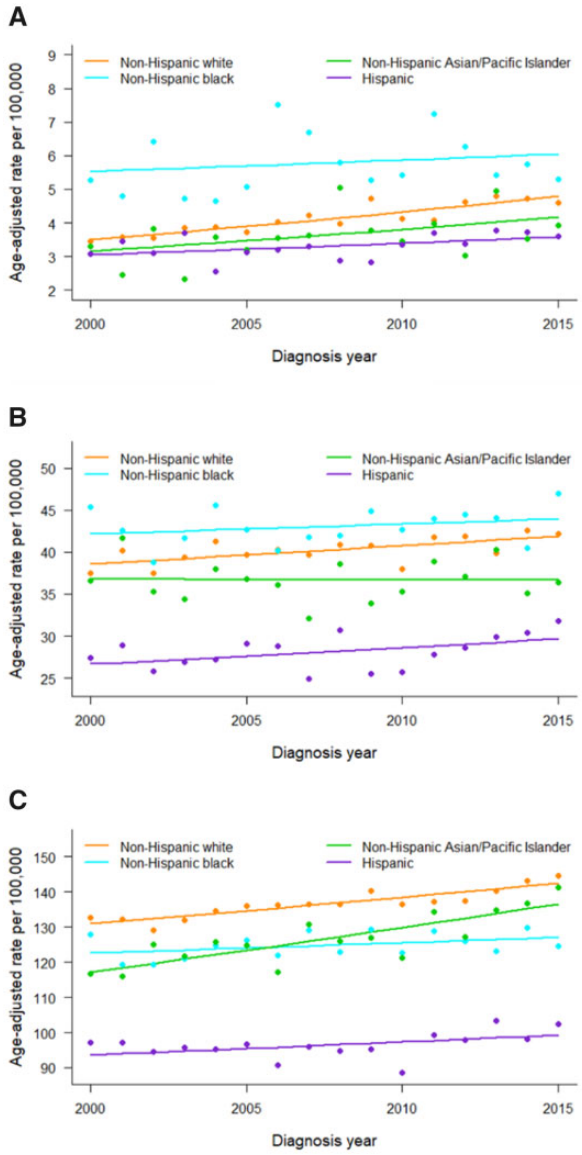

Figure 1. Breast cancer incidence rate by race and ethnicity for women aged 20–49 years diagnosed with stage I–III breast cancer, 2000–2015, SEER 18 registries. **A)** Women ages 20–29 years. **B)** Women ages 30–39 years. **C)** Women ages 40–49 years. Rates were calculated using the analytic sample. Women with breast cancer ascertained by the Alaska Native registry were excluded from incidence estimations for the Hispanic group because this registry only ascertains patients from the Native American and Alaska Native populations within the state. SEER = Surveillance, Epidemiology, and End Results.

among women in each age decade was driven by HR+ cancer (Table 2, Figure 2). Among women aged 20–29 and 40–49 years, the largest AAPCs were for HR+ low-grade cancer; among women aged 30–39 years, the AAPCs for HR+ low- and high-grade cancer were similar (Table 2). By 2015, the incidence of HR+ low- and high-grade cancer each exceeded the incidence of HR− cancer in each age decade (Figure 2). These incidence patterns tended to persist across each racial and ethnic group (Supplementary Figure 1, available online). A decrease in HR- cancer was observed for each age decade (Table 2). The pattern of highest AAPCs among women aged 20–29 years persisted among each race and ethnicity, cancer stage, and receptor subtype. Improved completeness of classification for HR status and grade over time throughout the study period (Supplementary Table 2, available online) may have positively biased AAPC estimates for the analytic subsample; however, comparing AAPCs for each age decade between the analytic sample and subsample suggested the impact of this bias was modest (Table 2). Results of piecewise regression models were not substantively different from those of unsegmented regression models (data not shown).

Survival

Overall survival varied by age at diagnosis, with women aged 20–29 years having the lowest survival (Table 3). Survival also varied by race and ethnicity, being lower among non-Hispanic blacks and Hispanics compared to non-Hispanic whites and Asian/Pacific Islanders (Table 3, Figure 3). In particular, among women aged 20–29 years, survival was markedly lower among non-Hispanic blacks compared to non-Hispanic whites. Survival tended to be similar across age decades for stage I and II cancer, but lower for women aged 20–29 years with stage III cancer compared to the other age decades (Table 3, Figure 4).

Stratifying by HR status and disease grade, 10-year survival estimates for HR+ low- and high-grade cancer decreased with decreasing age; estimates for HR− cancer were similar across age decades (Table 3, Figure 4). Ten-year survival for women aged 20–29 years with HR+ high-grade cancer was lower than that for women with either HR+ low-grade or HR− cancer; this pattern persisted across each racial and ethnic group (Supplementary Figure 2, available online). Among women aged 20–29 years, the largest declines in survival after 5 years were observed for those with HR+ low- and high-grade cancer; this pattern tended to be similar but of lesser magnitude among women aged 30–49 years. Notably, 10-year survival among women aged 20–29 years with stage I HR+ high-grade cancer (79.8%) was lower than that for women with stage I HR− cancer (89.3%) (Supplementary Table 4, available online). Median follow-up times for the analytic sample and subsample were 83 months and 80 months, respectively. Removing women first diagnosed in 2000–2014 with a second primary malignancy did not substantively alter the survival results (data not shown).

Discussion

Our population-based analysis provides insights into contemporary patterns in incidence and survival of young women with stage I–III breast cancer in the United States. Incidence is increasing among women aged 20–49 years, driven by marked increases in HR+ cancer. Among women aged 30–49 years, increases in HR+ cancer were counterbalanced by decreases in HR− cancer. Although women in each age decade were observed to have increases in both HR+ low- and high-grade cancer, AAPCs for HR+ low-grade cancer were greater than those for HR+ high-grade cancer among women aged 20–29 and 40–49 years. We also observed consistent increases in HR+ cancer across racial and ethnic groups. Examining 10-year survival revealed that survival for women with HR+ cancer decreased with decreasing age, being lowest among women aged 20–29 years, among whom survival was lowest for those with HR+ high-grade cancer. Deaths after 5 years were observed disproportionately for women with HR+ cancer, particularly among those aged 20–29 years. Ten-year survival among women aged 20–29 years with stage I cancer was lower for HR+ high-grade than HR− cancer.

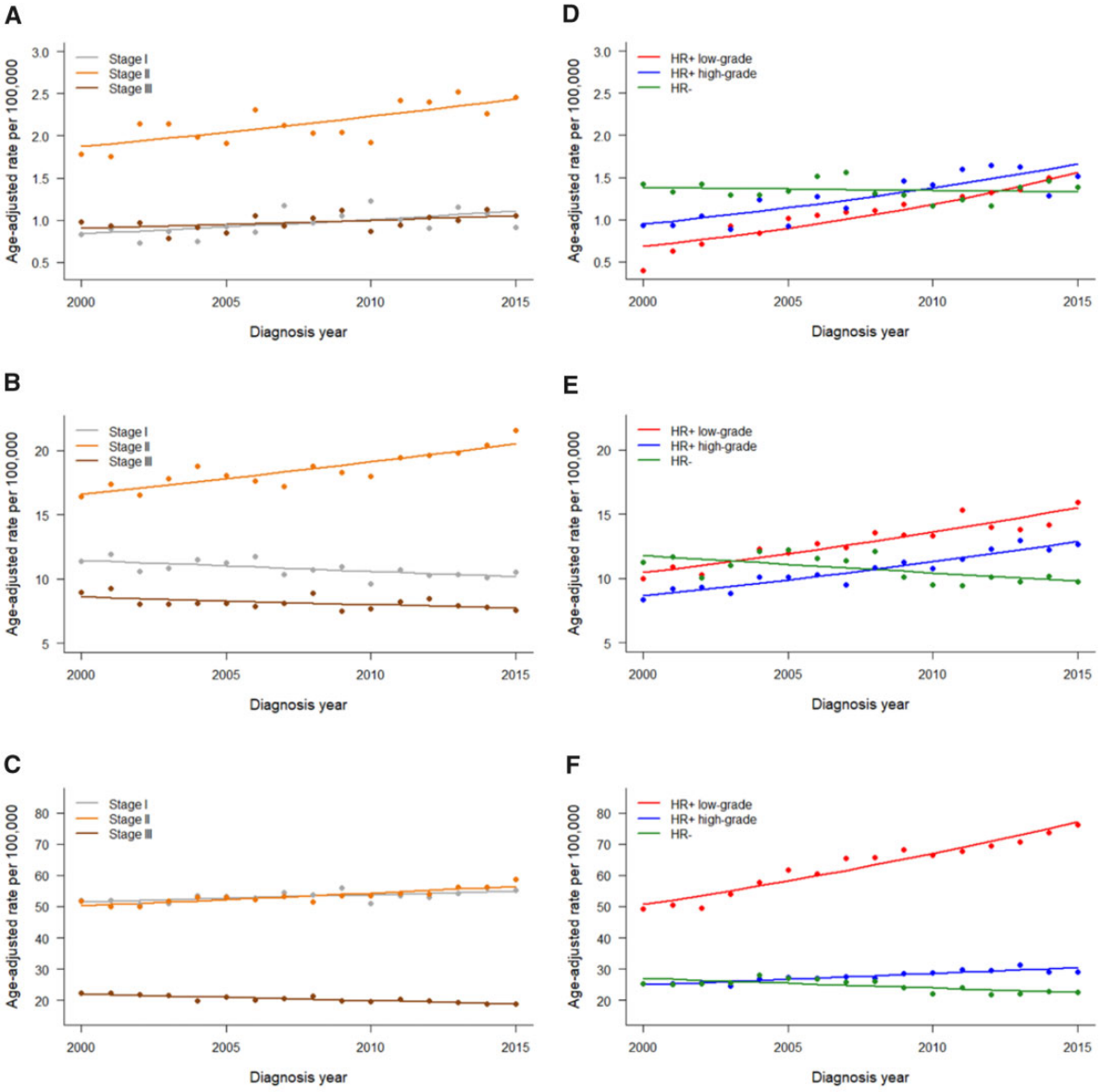

Figure 2. Breast cancer incidence rate by stage and HR status and grade for women aged 20–49 years diagnosed with stage I–III breast cancer, 2000–2015, SEER 18 registries. **A)** Women ages 20–29 years. **B)** Women ages 30–39 years. **C)** Women ages 40–49 years. **D)** Women ages 20–29 years. **E)** Women ages 30–39 years. **F)** Women ages 40–49 years. Rates for **(A, B, and C)** were calculated using the analytic sample; rates for **(D, E, and F)** were calculated using the analytic subsample. HR = hormone receptor; SEER = Surveillance, Epidemiology, and End Results.

The increased incidence in breast cancer that we observed among women aged 20–39 years is consistent with findings from population-based analyses from the United States, Europe, and Asia (17–20, 30–32); however, these studies included diagnoses that spanned 1975–2015 and did not assess incidence for stage I–III breast cancer by HR status and grade. Our analyses of women diagnosed from 2000 to 2015 suggest an increased incidence among women aged 20–29 years, largely driven by HR+ cancer, and stable incidence among those aged 30–39 years. A study that analyzed SEER data among women aged 25–39 years diagnosed with breast cancer from 1976–2009 reported increased incidence over the study period for women with distant metastases, particularly for ER+ cancer, but no change to overall incidence of localized and regionalized cancer (20). Important distinctions between our study and the previous one that used SEER data are that we included women younger than age 25 years, our study period was more recent, and we observed differing incidence patterns for HR+ and HR− cancer for localized and regionalized cancer.

Our finding that young women, particularly those aged 20–29 years, have poor survival and that, over time, survival was lower for those with HR+ than HR− cancer was suggested in other recent smaller series. A prospective, observational study of nearly 3000 women aged 18–40 years diagnosed with breast cancer during 2000–2008 reported that risk of death continued to increase over time for women with ER+ cancer, but risk of death peaked at 2 years for women with ER− cancer (33). A study of 2125 Chinese women diagnosed with breast cancer during 2004–2011 observed lower 5-year survival among women no more than 40 years old with luminal A and luminal B cancers

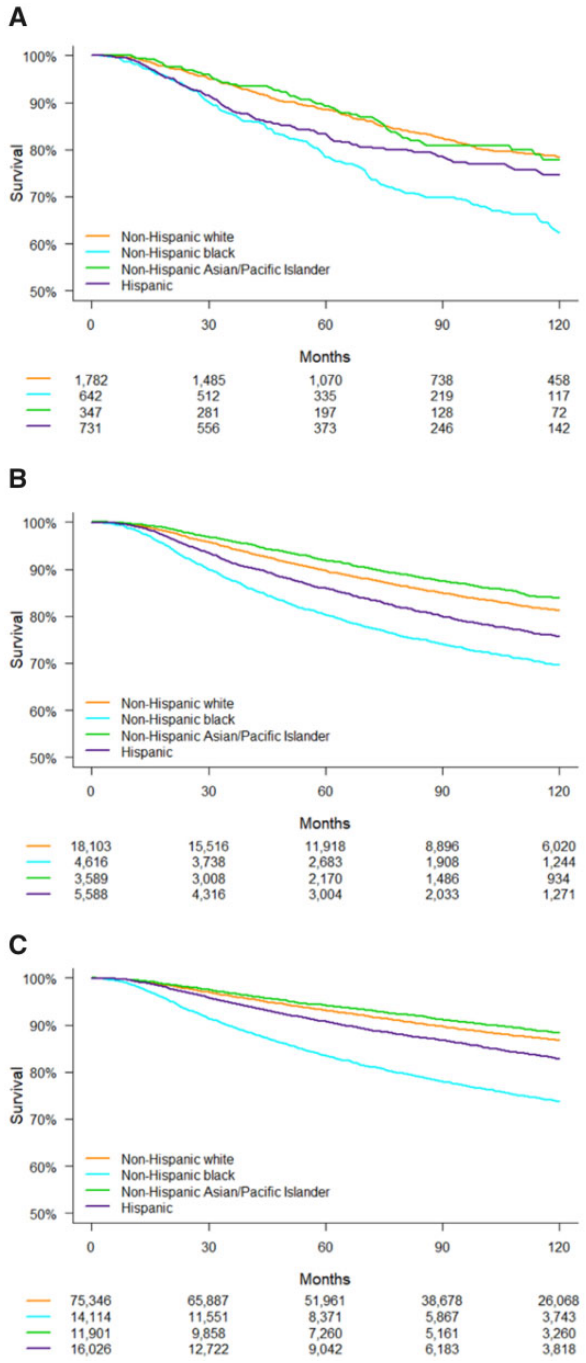

Figure 3. Ten-year survival by race and ethnicity for women aged 20–49 years diagnosed with stage I–III breast cancer, 2000–2014, SEER 18 registries. **A)** Women ages 20–29 years. **B)** Women ages 30–39 years. **C)** Women ages 40–49 years. Survival was calculated using the analytic sample. Numbers of patients at risk are given below the *x*-axis. SEER = Surveillance, Epidemiology, and End Results.

compared to those aged 41–50 years, but not among those with HER2+ cancer or HER2− and HR− cancer (34). A recent study of 17 575 women diagnosed with stage I–III breast cancer and enrolled in the National Comprehensive Cancer Network Outcomes Database Project reported that women younger than 40 years of age had poorer clinical outcomes compared to older women, particularly those with luminal breast cancers; however, the women studied received treatment from 2000–2007, a period during which the use of adjuvant taxanes as HER2-directed therapy and dose-dense approaches were emerging (1). Our findings suggest that differences in survival for HR+ and HR− cancer persist despite therapeutic advances. A recent study using SEER 9 data examined breast cancer survival for women diagnosed at aged 20–39 years from 1975 to 2015 and reported improvements in 5-year survival over the study period (32). Important distinctions between the previous study and our study include our use of SEER 18 data, examination of 10-year survival, and estimation of survival patterns by disease HR status and grade as well as patient race and ethnicity.

With regard to both incidence and survival, our observation of increasing incidence of breast cancer in non-Hispanic white women aged 20–49 years is a rare report of inferior cancer findings in this racial and ethnic group. The lower survival that we observed among non-Hispanic blacks and Hispanics has been reported previously in recent work that suggested intentional care delivery may overcome this (35). Taken together, our incidence and survival findings suggest that there will be a continuing and growing increase in the number of deaths for women aged 20–29 years diagnosed with HR+ cancer.

Undertreatment and disparities in care also may contribute to the inferior survival that we observed for the youngest women with HR+ breast cancer. Only late in our study period did data emerge on the recurrence-free survival benefit from near-complete estrogen deprivation with ovarian function suppression and an aromatase inhibitor for women under age 35 years (36–38), with guidelines recommending this therapy being published in 2016 (39). Young age has been associated with lower likelihood of both treatment-related amenorrhea and the corresponding improved disease outcomes in HR+ breast cancer (40–42). Young age also has been associated with lower adherence to anti-estrogen therapies (43), which itself has been associated with increased mortality (44). Additionally, issues of fertility and pregnancy are salient for these women of reproductive age and may influence treatment decisions (45, 46). Disparities in care delivery, particularly aspects of care that can be finance- and time-intensive and impact cosmesis, may impact breast cancer survival in younger women. In a report using the National Cancer Database, women aged 40 years and younger were less likely to receive radiation therapy if they underwent breast-conserving therapy (47). A report from the US Department of Defense database on outcomes in a single-payer system identified equivalent rates of 10-year overall survival between women younger than 50 years and those 50 years and older, even though the younger cohort received significantly more chemotherapy than the older cohort (48). This finding suggests that therapy and better access to care could mitigate disease outcomes.

Our finding that young women with stage I HR+ breast cancer had disproportionally lower 10-year survival may suggest opportunities to improve survival through more intentional care delivery. For example, near-complete estrogen deprivation has demonstrated outcome benefit for premenopausal women with HR+ breast cancer (36–38), albeit with likely compromise to bone, cardiac, and reproductive health. Areas for study may include applying this treatment regimen to young women with high-risk stage I cancer, implementing a longer duration of anti-estrogen therapy, and conducting more intentional follow-up after diagnosis for these women who might otherwise be perceived by providers and patients alike to be at lower risk.

Important aspects of our work include use of a large, population-based and racially and ethnically diverse sample. By using the SEER 18 registries database, we were able to study breast cancer occurrence for more than one-quarter of the US

Table 3. Five- and ten-year survival by patient and tumor characteristics among women aged 20–49 years diagnosed with stage I–III breast cancer, 2000–2014, SEER 18 registries

Characteristic	Years	20–29 years		30–39 years		40–49 years	
		No.*	Survival (95% CI)	No.*	Survival (95% CI)	No.*	Survival (95% CI)
Analytic sample	5	3544	85.6 (84.2 to 86.8)	32 277	87.9 (87.5 to 88.3)	118 606	91.8 (91.6 to 91.9)
	10	3544	74.6 (72.6 to 76.4)	32 277	78.9 (78.4 to 79.5)	118 606	84.9 (84.6 to 85.2)
Race and ethnicity							
Non-Hispanic white	5	1782	88.6 (86.9 to 90.1)	18 103	89.7 (89.2 to 90.1)	75 346	93.1 (92.9 to 93.3)
	10	1782	78.4 (75.9 to 80.7)	18 103	81.2 (80.5 to 81.9)	75 346	86.8 (86.5 to 87.1)
Non-Hispanic black	5	642	78.4 (74.6 to 81.7)	4616	80.3 (79.1 to 81.5)	14 114	83.5 (82.8 to 84.2)
	10	642	62.4 (57.1 to 67.2)	4616	69.6 (67.9 to 71.1)	14 114	73.7 (72.8 to 74.6)
Non-Hispanic Asian/Pacific Islander	5	347	89.2 (84.9 to 92.4)	3589	91.9 (90.8 to 92.8)	11 901	94.2 (93.7 to 94.6)
	10	347	77.9 (71.3 to 83.2)	3589	83.9 (82.2 to 85.4)	11 901	88.3 (87.5 to 89.1)
Hispanic (all races)	5	731	83.3 (80.1 to 86.1)	5588	86.0 (84.9 to 87.0)	16 026	90.8 (90.3 to 91.3)
	10	731	74.7 (70.3 to 78.5)	5588	75.6 (74.1 to 77.1)	16 026	82.9 (82.1 to 83.7)
Stage							
I	5	843	95.6 (93.8 to 96.9)	9351	96.6 (96.2 to 97.0)	49 875	97.5 (97.3 to 97.6)
	10	843	89.1 (85.8 to 91.7)	9351	91.9 (91.2 to 92.6)	49 875	93.9 (93.6 to 94.2)
II	5	1855	89.5 (87.8 to 90.9)	15 807	90.4 (89.9 to 90.9)	49 529	92.2 (92.0 to 92.5)
	10	1855	80.0 (77.5 to 82.3)	15 807	81.7 (80.9 to 82.4)	49 529	84.9 (84.5 to 85.3)
III	5	846	66.9 (63.2 to 70.3)	7119	71.0 (69.8 to 72.1)	19 202	75.9 (75.3 to 76.6)
	10	846	48.1 (43.6 to 52.4)	7119	55.5 (54.0 to 56.9)	19 202	61.8 (61.0 to 62.7)
Analytic subsample	5	3186	85.0 (83.6 to 86.4)	29 336	87.9 (87.5 to 88.3)	107 161	91.8 (91.6 to 92.0)
	10	3186	74.2 (72.1 to 76.1)	29 336	78.8 (78.3 to 79.4)	107 161	85.0 (84.7 to 85.2)
HR status and grade							
HR+ low grade	5	914	94.1 (92.1 to 95.7)	10 842	95.0 (94.5 to 95.4)	58 277	96.9 (96.7 to 97.1)
	10	914	81.2 (77.1 to 84.6)	10 842	85.4 (84.5 to 86.3)	58 277	91.1 (90.8 to 91.4)
HR+ high grade	5	1097	83.5 (80.8 to 85.8)	9082	88.0 (87.2 to 88.7)	25 717	90.0 (89.6 to 90.4)
	10	1097	67.7 (63.6 to 71.4)	9082	75.3 (74.2 to 76.5)	25 717	80.2 (79.6 to 80.8)
HR−	5	1175	79.6 (76.9 to 81.9)	9412	79.8 (78.9 to 80.7)	23 167	81.4 (80.8 to 81.9)
	10	1175	73.8 (70.8 to 76.6)	9412	74.3 (73.3 to 75.3)	23 167	75.1 (74.5 to 75.8)

*Number of patients at risk at start of follow-up. CI = confidence interval; HR = hormone receptor; SEER = Surveillance, Epidemiology, and End Results.

population. Limitations of our study include that this work is retrospective, and neoadjuvant or adjuvant treatment information was unavailable. Improved reporting of HR status and grade throughout the study period may have positively biased AAPC estimates in our analytic subsample; however, distributions of age, race and ethnicity, and stage were similar between women with known and unknown HR status and grade, and effects on the AAPCs were observed to be modest. Further, younger women with breast cancer have disproportionately more germline mutations than women diagnosed at older aged (12–14) and could be vulnerable to second cancers that may impact their survival. For example, the rate of germline BRCA mutations in the Prospective Outcomes in Sporadic versus Hereditary Breast Cancer study was 12% (49). After a median of 8.2 years of follow-up, these women had comparable outcomes to women without these mutations. Excluding women in our analyses who developed second cancers during the study period did not alter our findings for survival. Lastly, we did not have information on reproductive health; thus, we were unable to study the influence of parity or peripartum status on incidence and survival estimates.

Among women aged 20–39 years, breast cancer has the highest incidence and mortality of any cancer across less-developed to highly developed nations (50), underscoring the need to decrease the burden of this malignancy. Importantly, these women are younger than the age cutoffs used for initiation of radiographic screening, and further, the dense breast of younger women may limit the utility of imaging in this population (51). Although questions regarding accuracy and age cutoffs would need to be addressed, perhaps this could ultimately offer an opportunity to study novel approaches to diagnosis, such as circulating free DNA (52–54).

In summary, we characterized incidence and survival by age decade for a large, population-based retrospective cohort of premenopausal women diagnosed with stage I–III breast cancer. We observed that HR+ cancer increased in each age decade and tended to account for the highest death rate beyond 5 years, particularly among women aged 20–29 years. Our findings suggest that with longer-term follow-up, this disparity in survival will become more apparent, prompting the need for further evaluation of preventive, diagnostic, and therapeutic strategies for these women.

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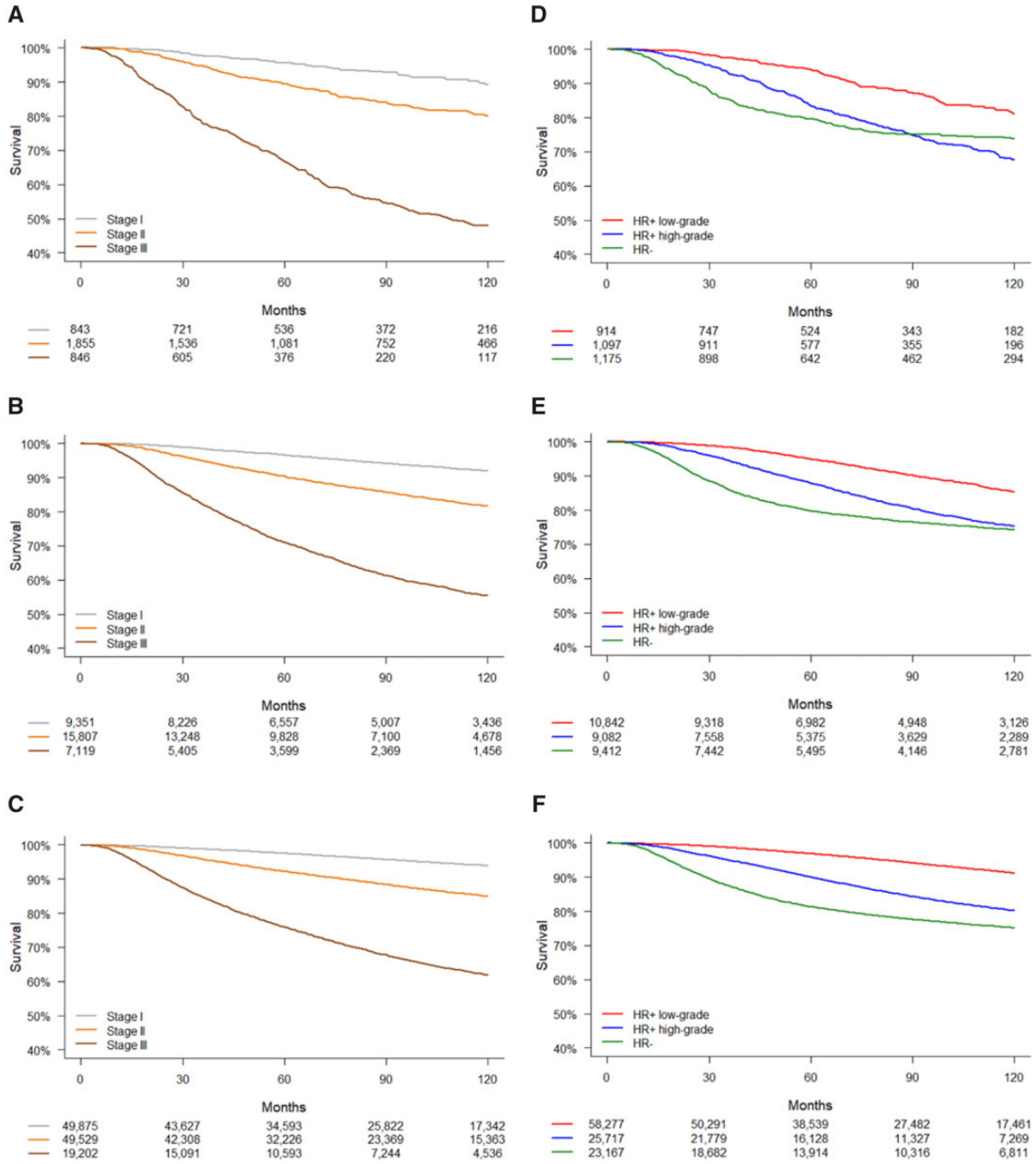

Figure 4. Ten-year survival by stage and HR status and grade for women aged 20–49 years diagnosed with stage I–III breast cancer, 2000–2014, SEER 18 registries. **A)** Women ages 20–29 years. **B)** Women ages 30–39 years. **C)** Women ages 40–49 years. **D)** Women ages 20–29 years. **E)** Women ages 30–39 years. **F)** Women ages 40–49 years. Survival for **(A, B, and C)** was calculated using the analytic sample; survival for **(D, E, and F)** was calculated using the analytic subsample. Numbers of patients at risk are given below the *x*-axis. HR = hormone receptor; SEER = Surveillance, Epidemiology, and End Results.

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References

1. Partridge AH, Hughes ME, Warner ET, et al. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. *J Clin Oncol*. 2016; 34(27):3308–3314.
2. Azim HA Jr, Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res*. 2014;16(4):427.

3. Anders CK, Fan C, Parker JS, et al. Breast carcinomas arising at a young age: unique biology or a surrogate for aggressive intrinsic subtypes? *J Clin Oncol*. 2011;29(1):e18–20.
4. Azim HA Jr, Michiels S, Bedard PL, et al. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. *Clin Cancer Res*. 2012;18(5):1341–1351.
5. Lambertini M, Pinto AC, Ameye L, et al. The prognostic performance of Adjuvant! Online and Nottingham Prognostic Index in young breast cancer patients. *Br J Cancer*. 2016;115(12):1471–1478.
6. Gnerlich JL, Deshpande AD, Jeffe DB, et al. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. *J Am Coll Surg*. 2009; 208(3):341–347.
7. Collins LC, Marotti JD, Gelber S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. *Breast Cancer Res Treat*. 2012;131(3):1061–1066.
8. Ruddy KJ, Gelber S, Tamimi RM, et al. Breast cancer presentation and diagnostic delays in young women. *Cancer*. 2014;120(1):20–25.
9. Johnson A, Shulman L, Kachajian J, et al. Access to care in Vermont: factors linked with time to chemotherapy for women with breast cancer—a retrospective cohort study. *J Oncol Pract*. 2016;12(9):e848–857.
10. Primeau SW, Freund KM, Ramachandran A, et al. Social service barriers delay care among women with abnormal cancer screening. *J Gen Intern Med*. 2014; 29(1):169–175.
11. Rosenberg SM, Ruddy KJ, Tamimi RM, et al. BRCA1 and BRCA2 mutation testing in young women with breast cancer. *JAMA Oncol*. 2016;2(6):730–736.
12. Malone KE, Daling JR, Doody DR, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women aged 35 to 64 years. *Cancer Res*. 2006;66(16): 8297–8308.
13. Valencia OM, Samuel SE, Viscusi RK, et al. The role of genetic testing in patients with breast cancer: a review. *JAMA Surg*. 2017;152(6):589–594.
14. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. *Br J Cancer*. 2000;83(10):1301–1308.
15. Nguyen B, Venet D, Azim HA Jr, et al. Breast cancer diagnosed during pregnancy is associated with enrichment of non-silent mutations, mismatch repair deficiency signature and mucin mutations. *NPJ Breast Cancer*. 2018;4:23.
16. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. *Breast Cancer Res Treat*. 2016;160(2):347–360.
17. Bouchardy C, Fioretta G, Verkooijen HM, et al. Recent increase of breast cancer incidence among women under the age of forty. *Br J Cancer*. 2007;96(11): 1743–1746.
18. Pollan M, Pastor-Barriuso R, Ardanaz E, et al. Recent changes in breast cancer incidence in Spain 1980-2004. *J Natl Cancer Inst*. 2009;101(22):1584–1591.
19. Merlo DF, Ceppi M, Filiberti R, et al. Breast cancer incidence trends in European women aged 20-39 years at diagnosis. *Breast Cancer Res Treat*. 2012; 134(1):363–370.
20. Johnson RH, Chien FL, Bleyer A. Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. *JAMA*. 2013; 309(8):800–805.
21. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 18 Regs Research Data, Nov 2017 Sub (1973-2015) <Katrina/Rita Population Adjustment>—Linked To County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.
22. Greene FL. The American Joint Committee on Cancer: updating the strategies in cancer staging. *Bull Am Coll Surg*. 2002;87(7):13–15.
23. Roberti NE. The role of histologic grading in the prognosis of patients with carcinoma of the breast: is this a neglected opportunity? *Cancer*. 1997;80(9): 1708–1716.
24. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784–2795.
25. Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.3.5. www.seer.cancer.gov/seerstat.
26. Joinpoint Regression Program, Version 4.6.0.0—April 2018; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.
27. Zhang NR, Siegmund DO. A modified Bayes information criterion with applications to the analysis of comparative genomic hybridization data. *Biometrics*. 2007;63(1):22–32.
28. R Core Team. R: a language and environment for statistical computing. Vienna, Austria; R Foundation for Statistical Computing. 2018. https://www.R-project.org/.
29. Sun J, Meng H, Yao L, et al. Germline mutations in cancer susceptibility genes in a large series of unselected breast cancer patients. *Clin Cancer Res*. 2017; 23(20):6113–6119.
30. Keramatinia A, Mousavi-Jarrahi SH, Hiteh M, Mosavi-Jarrahi A. Trends in incidence of breast cancer among women under 40 in Asia. *Asian Pac J Cancer Prev*. 2014;15(3):1387–1390.
31. Leclere B, Molinie F, Tretarre B, et al. Trends in incidence of breast cancer among women under 40 in seven European countries: a GRELL cooperative study. *Cancer Epidemiol*. 2013;37(5):544–549.
32. Guo F, Kuo YF, Shih YCT, Giordano SH, Berenson AB. Trends in breast cancer mortality by stage at diagnosis among young women in the United States. *Cancer*. 2018;124(17):3500–3509.
33. Copson E, Eccles B, Maishman T, et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study. *J Natl Cancer Inst*. 2013;105(13):978–988.
34. Lian W, Fu F, Lin Y, et al. The impact of young age for prognosis by subtype in women with early breast cancer. *Sci Rep*. 2017;7(1):11625.
35. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin*. 2017;67(6): 439–448.
36. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*. 2018;379(2):122–137.
37. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372(5):436–446.
38. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;371(2): 107–118.
39. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline update on ovarian suppression. *J Clin Oncol*. 2016;34(14):1689–1701.
40. Lambertini M, Campbell C, Bines J, et al. Adjuvant anti-HER2 therapy, treatment-related amenorrhea, and survival in premenopausal HER2-positive early breast cancer patients. *J Natl Cancer Inst*. 2019;111(1):86–94.
41. Ganz PA, Land SR, Geyer CE Jr, et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. *J Clin Oncol*. 2011;29(9):1110–1116.
42. Vanhuyse M, Fournier C, Bonneterre J. Chemotherapy-induced amenorrhea: influence on disease-free survival and overall survival in receptor-positive premenopausal early breast cancer patients. *Ann Oncol*. 2005;16(8): 1283–1288.
43. Huiart L, Bouhnik AD, Rey D, et al. Early discontinuation of tamoxifen intake in younger women with breast cancer: is it time to rethink the way it is prescribed? *Eur J Cancer*. 2012;48(13):1939–1946.
44. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat*. 2011;126(2): 529–537.
45. Llarena NC, Estevez SL, Tucker SL, Jeruss JS. Impact of fertility concerns on tamoxifen initiation and persistence. *J Natl Cancer Inst*. 2015;107(10):djv202.
46. Pagani O, Ruggeri M, Manunta S, et al. Pregnancy after breast cancer: are young patients willing to participate in clinical studies? *Breast*. 2015;24(3): 201–207.
47. Freedman RA, Virgo KS, Labadie J, et al. Receipt of locoregional therapy among young women with breast cancer. *Breast Cancer Res Treat*. 2012;135(3): 893–906.
48. Zimmer AS, Zhu K, Steeg PS, et al. Analysis of breast cancer in young women in the Department of Defense (DOD) database. *Breast Cancer Res Treat*. 2018; 168(2):501–511.
49. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol*. 2018;19(2):169–180.
50. Fidler MM, Gupta S, Soerjomataram I, et al. Cancer incidence and mortality among young adults aged 20-39 years worldwide in 2012: a population-based study. *Lancet Oncol*. 2017;18(12):1579–1589.
51. Kerlikowske K, Hubbard RA, Miglioretti DL, et al. Comparative effectiveness of digital versus film-screen mammography in community practice in the United States: a cohort study. *Ann Intern Med*. 2011;155(8):493–502.
52. Madhavan D, Wallwiener M, Bents K, et al. Plasma DNA integrity as a biomarker for primary and metastatic breast cancer and potential marker for early diagnosis. *Breast Cancer Res Treat*. 2014;146(1):163–174.
53. Uehiro N, Sato F, Pu F, et al. Circulating cell-free DNA-based epigenetic assay can detect early breast cancer. *Breast Cancer Res*. 2016;18(1):129.
54. Tang Q, Cheng J, Cao X, Surowy H, Burwinkel B. Blood-based DNA methylation as biomarker for breast cancer: a systematic review. *Clin Epigenetics*. 2016;8:115.