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The impact of young age at diagnosis (age <40 years) on prognosis varies by breast cancer subtype: A U.S. SEER database analysis

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ABSTRACT

Purpose: Women under 40 years old are at increased risk for developing human epidermal growth factor receptor 2 (HER2) positive or triple negative subtype and more advanced breast cancer, yet young age itself has also historically been an independent prognostic factor.
Methods: Using the Surveillance, Epidemiology, and End Results (SEER) Program, we examined data for 271,173 women with stage I-III breast cancer between 2010 and 2015. Using Fine and Gray regression models to account for competing risks, we examined the risk of breast cancer-specific death by age and clinical subtypes, considering grade, hormone receptor (HR) and HER2 status, adjusting for demographic, clinical and treatment variables.
Results: Of 271,173 women eligible for analysis, 14,109 were <40 years of age. Women under 40 years old were more likely to be non-white, uninsured, and to have higher stage, higher grade, HER2-positive and triple-negative subtype disease (all, $p < 0.001$). Compared to women ages 40–60, women ages <40 had higher breast cancer mortality (hazard ratio, 1.8; 95% confidence interval (CI) 1.6–1.9) in unadjusted analysis. In models controlling for demographic, clinical and treatment factors, young age was significantly associated with an increased risk of breast cancer mortality among women with HR-positive, lower grade disease (hazard ratio 1.7; 95% CI 1.4–2.1) but not for women with high grade/HR-positive, HER2-positive, or triple-negative disease. Women age >75 had increased breast cancer mortality in all subtypes.
Conclusion: With modern clinical subtyping, age under 40 remains independently associated with worse outcomes in 30 months follow-up only in HR-positive, lower grade disease.

1. Introduction

While 5-year breast cancer specific survival increased 74% from 1975 to 1979, and 88.5% from 2010 to 2015 in the United States using the Surveillance, Epidemiology, and End Results (SEER) database [1], a less favorable outcome has been demonstrated in younger women with breast cancer [2]. Adami et al. found that women under age 45 years had worse survival and higher annual hazard of recurrence compared with women diagnosed ages 45–49 [3]. Since that time, hormonal, cytotoxic and targeted therapies [4,5] have improved survival for women with breast cancer [1]. However, more recent data suggest patients aged <40 years continue to have significantly inferior overall and breast cancer-specific survival (BCSS) compared to middle-aged women [6].

Breast cancer is a heterogenous disease that can be divided into several intrinsic molecular subtypes with different clinical and prognostic characteristics. Sorlie and Perou classified breast cancer carcinomas based on variations in gene expression patterns in 2001 [7], allowing breast cancer to be classified into intrinsic subtypes including luminal A, luminal B, normal breast like, human epidermal growth factor receptor 2 (HER2) positive and basal like [8]. Clinical subtypes are defined by immunohistochemistry results of estrogen receptor (ER), progesterone receptor (PR) and HER2 status, with or without additional markers. These clinical subtypes have different targeted therapies and different risks of disease recurrence and survival [9–11].

Improved understanding of disparities in breast cancer

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outcomes are critical to their mitigation. Young women are more likely to present with advanced stage breast cancer, in part because of a lack of effective screening strategies for average risk young women [12]. Breast cancer arising in younger women is also more likely to have an aggressive phenotype such as hormone receptor (HR)-negative, HER2-positive and/or high grade disease [13]. In this analysis, we examined breast cancer-specific mortality by age and subtype, with a focus on the previously documented young age-related poor survival.

2. Materials and methods

2.1. Data source and patient population

We used SEER cancer registry data to identify a cohort of patients with a first diagnosis of stage I-III unilateral breast cancer. Stage IV disease is heterogeneous, and has different entities, and we purposely excluded them given that they are treated differently from diagnosis, due to their incurable status [14]. The 18 population-based SEER cancer registries cover areas that uniformly collect information on patient demographics, tumor characteristics, initial treatment utilization, and mortality for all incident cancers. Because this study used previously collected, de-identified data, it was deemed exempt for review by the Office for Human Research Studies at the Dana-Farber Cancer Institute. Data-Use Agreement for the SEER research file was completed.

We used SEER stat (version 8.3.5) to download data from the SEER 18 registries research database, which contains data from the SEER 13 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, rural Georgia, and the Alaska Native Tumor Registry) and the registries of greater California, Kentucky, Louisiana, New Jersey, and greater Georgia. Radiation and chemotherapy treatment variables were requested in an additional data agreement.

We identified 309,599 women who were diagnosed with their first stage I-III breast cancer between January 1, 2010 and December 31, 2015 who had cancer histology likely to be treated by standard guidelines and who were not diagnosed at autopsy or death. All breast cancers included were classified according to the American Joint Committee on Cancer (AJCC) 6th edition. Women with bilateral cancers (n = 1295), unknown ER and/or unknown PR (n = 6025) and unknown HER2 status (n = 5387) were excluded.

3. Outcome measures

The primary outcome was breast cancer specific death, with death due to other causes considered a competing event. Breast cancer specific survival was defined as the date of diagnosis until the date of death from any cause, or the date of censoring at the last follow-up date available of December 31, 2015. We ascertained deaths and causes of death from National Death Index data with the SEER file.

4. Independent variables

Our independent variables of interest included age, stage and clinical subtype. We first defined cohorts by age group (<40, 40–60, 61–75, >75 years) and then sub-cohorts of women by age and clinical subtypes. Clinical subtype was categorized using HR and HER2 status and grade (high grade; G3, lower grade; G2 or G1), with HR-positive defined ER- and/or PR-positive.

ER- or PR-positive included positive and borderline on immunohistochemical stain. ER- and PR-positive was defined as having any ER- and PR-positive staining. ER- and PR-negative was defined as those having no ER or PR staining. HER2 status was categorized as positive, negative, or unknown/borderline. Triple negative disease was defined as those having ER- and PR-negative and HER2-negative disease.

5. Control variables

Control variables included race/ethnicity (non-Hispanic White, non-Hispanic.

Black, Hispanic, other/unknown), Insurance (insured, Medicaid, unknown/uninsured), SEER region (Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta/rural Georgia, California, Kentucky, Louisiana, New Jersey), tumor grade (low/intermediate, high, unknown/others), stage and treatment.

5.1. Statistical analyses

Characteristics of the cohort by age were compared by chi-square test. Inference regarding breast cancer-specific mortality was made using Fine and Gray regression models, allowing for a sub-distribution of hazards of death due to breast cancer when considering death due to other causes as a competing event. Univariate and multivariate competing regression models and wild type tests were conducted to identify independent prognostic factors and calculate the hazard ratio and 95% confidence interval (CI). All statistical analyses were conducted SAS version 9.4 (SAS Institute, Cary, NC).

6. Results

Among 271,173 women with breast cancer eligible for analysis, 14,109 were <40 years of age at diagnosis, with a mean age of 60 years old. Median follow-up time was 30 months overall. We present the cohort flow diagram in Fig. 1. Compared with older women, women age <40 years were more likely to be non-white, have Medicaid or be uninsured, with HR-negative and high-grade tumors, and to have received chemotherapy ($p < 0.001$) (Table 1). The risk of breast cancer-specific death was highest in women age >75 years and age <40 years (Fig. 2). In unadjusted analysis, compared with women age 40–60 years (reference), women <40 years (hazard ratio 1.8, 95% CI 1.6 to 1.9) and >75 years (hazard ratio 2.1, 95% CI 2.1 to 2.3) were more likely to die of breast cancer (Table 2). Stratifying by subtype, among women with HR-positive, lower grade disease, those <40 years of age were more than twice as likely to die of breast cancer compared with women ages 40–60 years (hazard ratio 2.5, 95% CI 2.0 to 3), unadjusted analysis. After controlling for sociodemographic, disease and treatment characteristics, the association was attenuated but women age <40 years were still more likely die of breast cancer than women age 40–60 years (Table 1, hazard ratio 1.7, 95% CI 1.4 to 2.1). In HER2-positive disease, young age was not significantly associated with mortality in unadjusted and adjusted analyses ($p > 0.05$, both). In triple-negative disease, age <40 years was associated with increased mortality in the unadjusted model but after controlling for tumor characteristics and treatment factors, the risk became non-significant (hazard ratio 1.1, 95% CI 1.0 to 1.2). Women age >75 years had the highest breast cancer mortality for all subtypes (Table 3).

7. Discussion

In this modern dataset representative of the U.S. population, young women with breast cancer presented with more advanced and aggressive types of breast cancer and had higher breast cancer-specific mortality compared with women ages 40–60 years,

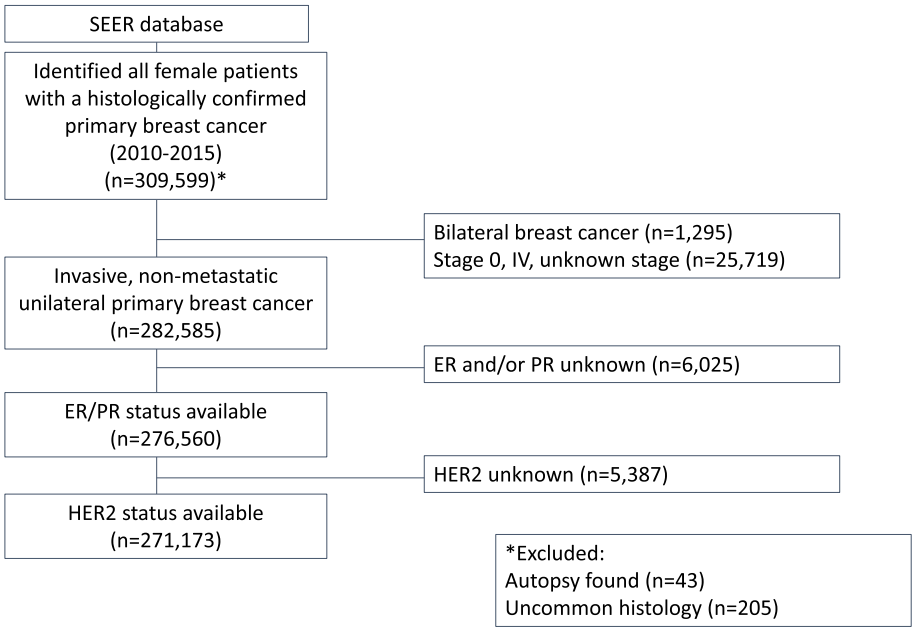

Fig. 1. Flow scheme of the Study.

particularly in HR-positive, low grade breast cancer. Importantly, young age was not independently associated with lower survival in other tumor subtypes.

This analysis also provides additional evidence that among women with triple-negative disease or HER2-positive disease, regardless of HR status, there is no increased risk of mortality among women <40 years of age, which confirms and expands on prior research in this area [2,10]. Prior analysis in the setting of HER2-positive disease demonstrated that young age was neither prognostic nor predictive among women treated with chemotherapy, whether followed by trastuzumab or not [2]. Partridge et al. [10] also published similar data in 2016 using the National Comprehensive Cancer Network (NCCN) database, concluding that age does not seem to be an independent predictor of outcome in HER2-positive breast cancer. Modern systemic therapy with targeted treatment in patients with HER2 disease improves survival in young women, and treatment principles should be similar, regardless of age, in women with HER2-positive disease.

In the setting of triple-negative disease, the risk of recurrence also seems to be worse in younger women compared with other age groups, but when controlling for tumor factors and treatment factors, breast cancer mortality seems to be similar with middle-aged women. In this report, we confirmed that in women with HER2 or triple-negative breast cancer, there was no clear increased risk of breast cancer mortality among women <40 years of age compared with middle-aged women. The study using a Korean national database showed that even women in their 20s with breast cancer have worse survival in luminal subtype, but no survival differences were observed in HER2 and triple negative subtype compared with women in their 30s and 40s [15].

Different tumor or host biology [16–18], lower hormonal therapy effectiveness [19], early restoration of ovarian function after chemotherapy [20,21], and decreased adherence to hormonal therapy [22], likely contribute to this disparity and further research to address differences is warranted. Even in patients untreated with adjuvant therapy [16] or treated with more aggressive adjuvant therapy [23], survival in young women was worse only in patients with luminal subtypes and not in those with other subtypes. Breast cancer arising at a young age seems to be biologically distinct beyond subtype distribution [24]. Azim and colleagues showed that independent of subtype, grade and stage, younger patients have higher expression of RANK-ligand, c-kit, mammary stem cell and luminal progenitors and BRCA 1 mutation signatures [24]. In addition, several recent studies have reported somatic mutations in breast cancer using next generation sequencing, including point mutations in TP53 and PIK3CA genes [25–27]. Accumulating evidence also suggests differences in breast stroma in younger patients, and changes that occur with pregnancy and breastfeeding likely contribute to the different biology of tumors arising thereafter. However, data are still insufficient to conclude that such effects play a fundamental role in carcinogenesis and tumor biology [16]. Somatic gene alteration of young tumors versus older may be different, and especially somatic mutation of TP53 [28] and GATA3 [29] have been associated with an early age at presentation of breast cancer. GATA3 directly upregulates proto-oncogenes and ER, suggesting that it may promote tumorigenesis in luminal subtypes of cancer [30]. Mutations in GATA3 affect ER binding to DNA and modulate the response of tumor cells to estrogen signaling, which might be associated with endocrine resistance and tumor growth [31,32]. These results may have clinical relevance, since the adverse prognosis associated with younger age at diagnosis has been observed mainly in patients with ER-positive breast cancer [10,33].

Neugut et al. found that patients with breast cancer who were younger than 45 years of age had an odds ratio of 2.0 of non-adherence to oral endocrine therapy compared with women 55–64 years of age in a large medical and pharmacy insurance claims database [34]. Several observational studies reported that younger age is associated with lower rates of treatment compliance with endocrine therapy, possibly suggesting the level of toxicity, especially sexual toxicity, is less acceptable to women younger than 35 years of age [35–38]. Rosenberg and colleagues reported that the experience of side effects, feeling less informed, and negative emotions about endocrine therapy are the main reasons for non-adherence [39], and attention to symptom management on endocrine therapy may reduce symptom burden and improve quality of life, potentially improving endocrine therapy adherence [40]. Hopefully, increased use of ovarian function suppression among young women with higher risk disease will further improve

Table 1
Descriptive characteristics of 271,173 patients with stage I to III breast cancer according to age at diagnosis from SEER data.

	Age at diagnosis								
	<40 years N = 14,109		40–60 years N = 122,188		60–75 years N = 96,837		>75 years N = 38,039		
	No.	%	No.	%	No.	%	No.	%	p value
Race/Ethnicity									
White/non-Hispanic	7304	51.8	77100	63.1	70433	72.7	29739	78.2	<0.001
Hispanic	2798	32.8	16536	13.5	8572	8.9	2618	6.9	
Black/non-Hispanic	2086	24.5	14596	11.9	9449	9.8	3165	8.3	
Asian, PI/non-Hispanic	1726	20.2	12564	10.3	7363	7.6	2234	5.9	
Others/unknown	195	2.3	1392	1.1	1020	1.1	283	0.7	
Insurance									
Insured	11169	79.2	102651	84.0	87602	90.5	35084	92.2	<0.001
Medicaid	2440	17.3	16723	13.7	8312	8.6	2831	7.4	
Uninsured/unknown	500	3.5	2814	2.3	923	1.0	124	0.3	
SEER registry									
California	5840	41.4	49705	40.7	39004	40.3	15141	39.8	<0.001
Connecticut	643	4.6	6368	5.2	4659	4.8	2064	5.4	
Detroit	651	4.6	6346	5.2	4939	5.1	2094	5.5	
Georgia	1830	13.0	13933	11.4	10855	11.2	3765	9.9	
Iowa	458	3.2	4212	3.4	3752	3.9	1850	4.9	
Kentucky	668	4.7	6345	5.2	5534	5.7	2006	5.3	
Louisiana	717	5.1	6199	5.1	5295	5.5	2051	5.4	
New Jersey	1518	10.8	13921	11.4	10057	10.4	4346	11.4	
New Mexico	238	1.7	2265	1.9	2180	2.3	842	2.2	
Others (Hawaii, Alaska)	272	1.9	2426	2.0	1905	2.0	706	1.9	
Seattle	843	6.0	7665	6.3	6363	6.6	2213	5.8	
Utah	431	3.1	2803	2.3	2294	2.4	961	2.5	
Stage									
I	3701	26.2	56408	46.2	54925	56.7	19902	52.3	<0.001
II	7384	52.3	49022	40.1	32492	33.6	13880	36.5	
III	3024	21.4	16758	13.7	9420	9.7	4257	11.2	
Histologic grade									
High, G3	7743	54.9	42543	34.8	24718	25.5	9228	24.3	<0.001
Low,intermediate (G1, G2)	5757	40.8	75099	61.5	68884	71.1	27305	71.8	
Other (G4)/unknown	609	4.3	4546	3.7	3235	3.3	1506	4.0	
ER status									
Positive*	4049	28.7	99373	81.3	83281	86.0	33071	86.9	<0.001
Negative	10060	71.3	22815	18.7	13556	14.0	4968	13.1	
PR status									
positive*	5315	37.7	88155	72.1	72651	75.0	28689	75.4	<0.001
negative	8794	62.3	34033	27.9	24186	25.0	9350	24.6	
HER2 status									
positive	3540	25.1	21072	17.2	11580	12.0	3852	10.1	<0.001
borderline[a]	269	1.9	2594	2.1	2069	2.1	956	2.5	
negative	10300	73.0	98522	80.6	83188	85.9	33231	87.4	
Molecular subtype									
HR+, lower grade (HR+, HER2- and G1/2)	4483	31.8	65949	54.0	62554	64.6	25267	66.4	<0.001
HR+, high grade/HR + HER2+	5724	40.6	33323	27.3	20195	20.9	7488	19.7	
HER2 (HR- and HER2+)	976	6.9	6427	5.3	3437	3.5	1134	3.0	
TN (HR- and HER2-)	2757	19.5	14599	11.9	9105	9.4	3432	9.0	
Unknown	169	1.2	1890	1.5	1546	1.6	718	1.9	
Chemotherapy									
Yes	11252	79.8	65411	53.5	31884	32.9	3717	9.8	<0.001
No	2857	20.2	56777	46.5	64953	67.1	34322	90.2	
Radiotherapy									
Yes	6553	46.4	65333	53.5	55515	57.3	14036	36.9	<0.001
No	7556	53.6	56855	46.5	41322	42.7	24003	63.1	
Surgery									
Yes	13326	94.5	117738	96.4	93804	96.9	34689	91.2	<0.001
No	783	5.5	4450	3.6	3033	3.1	3350	8.8	

Abbreviation: HER2, human epidermal growth factor receptor 2.
HR+, low grade: ER positive and/or PR positive, HER2 negative/low grade HR+, high grade/HR+, HER2+: ER positive and/or PR positive, HER2 negative/high grade, or ER positive and/or PR positive, HER2 positive.
HER2: ER negative, PR negative, and HER2 positive.
*TN(Triple negative): ER negative, PR negative, and HER2 negative.
*Borderline was included as positive.
[a] The result of IHC, FISH, SISH etc.

survival in HR-positive disease. Continued research efforts are focused on making anti-hormonal treatment more effective and tolerable, although the present analysis is limited by a lack of information regarding the use of this strategy in the population [41,42].

Interestingly, while women <40 and those >75 years of age received less radiotherapy, there was no information regarding types of surgery. Gu et al. reported that young and old age were

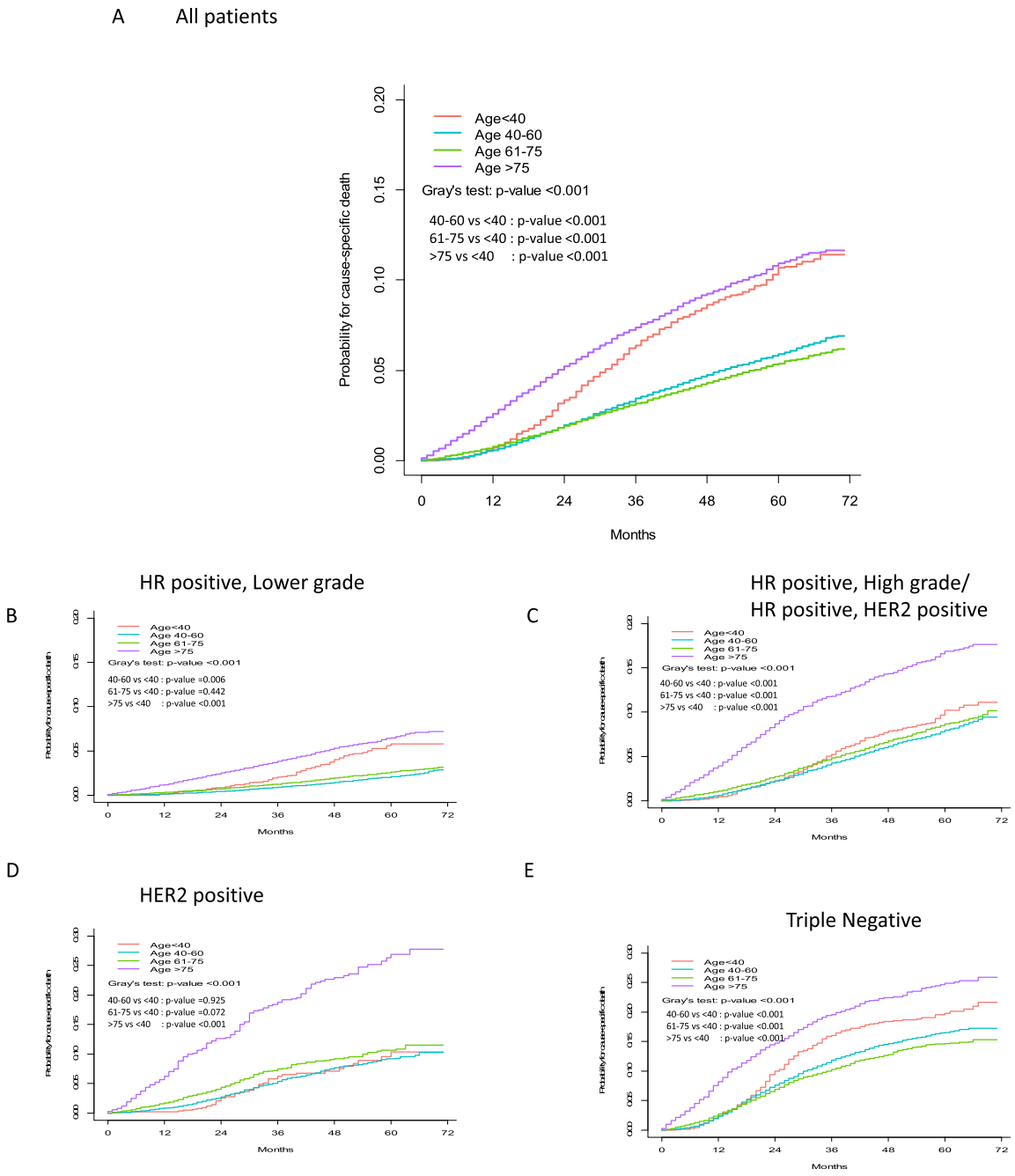

Fig. 2. Cumulative incidence functions for cancer specific death according to age group in: A) all patients, B) HR positive, lower grade, C) HR positive, high grade/HR positive, HER2 positive, D) HER2 positive, E) Triple negative from SEER data.

Table 2
Age and breast cancer mortality using SEER registry database.

Age	No. of breast cancers	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]	HR (95% CI)[d]
<40 years	14109	1.8 (1.6–1.9)	1.7 (1.53–1.79)	1.1 (1.04–1.22)	1.1 (1.04–1.22)
40–60 years	122188	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
60–75 years	96837	0.9 (0.9–1.0)	1 (1.0–1.1)	1.3 (1.2–1.4)	1.3 (1.2–1.3)
>75 years	38039	2.2 (2.1–2.3)	2.4 (2.3–2.5)	3.1 (3.0–3.3)	2.5 (2.4–2.7)

Abbreviations: CI, confidence interval; HR, hazard ratio; REF, reference.
[a] unadjusted.
[b] Adjusted for race/ethnicity, insurance, SEER registry.
[c] Adjusted for race/ethnicity, insurance, SEER registry, Stage at diagnosis, subtype.
[d] Adjusted for race/ethnicity, insurance, SEER registry, Stage at diagnosis, subtype, treatment.

Table 3
Univariate and Multivariate analysis of age and breast cancer mortality according to breast cancer clinical subtype from SEER data.

Breast cancer clinical subtype and age	No. of Breast Cancers	sHR (95% CI)[a]	sHR (95% CI)[b]	sHR (95% CI)[c]	sHR (95% CI)[d]
HR+, lower grade (HR+, HER2- and G1/2)		2.45 (1.99–3.01)	2.29 (1.86–2.82)	1.71 (1.39–2.1)	1.73 (1.4–2.13)
<40 years	4483	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
40–60 years	65949	1.34 (1.21–1.49)	1.4 (1.26–1.55)	1.68 (1.51–1.86)	1.67 (1.5–1.85)
60–75 years	45802	3.79 (3.42–4.19)	4.04 (3.65–4.47)	4.67 (4.22–5.17)	3.79 (3.37–4.26)
>75 years	42019				
HR+, high grade/HR + HER2+		1.2 (1.05–1.37)	1.16 (1.02–1.32)	1.02 (0.89–1.16)	1.03 (0.91–1.18)
<40 years	5724	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
40–60 years	33323	1.14 (1.04–1.24)	1.2 (1.1–1.31)	1.33 (1.22–1.45)	1.26 (1.16–1.38)
60–75 years	20195	2.73 (2.5–2.99)	2.97 (2.71–3.26)	3.11 (2.84–3.42)	2.3 (2.06–2.56)
>75 years	7488				
HER2 (HR- and HER2+)		0.98 (0.72–1.34)	0.97 (0.71–1.33)	0.8 (0.58–1.1)	0.84 (0.61–1.16)
<40 years	976	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
40–60 years	6427	1.32 (1.1–1.58)	1.4 (1.17–1.68)	1.52 (1.27–1.82)	1.43 (1.19–1.71)
60–75 years	3437	3.75 (3.11–4.52)	4.06 (3.35–4.91)	4.15 (3.42–5.04)	2.89 (2.35–3.55)
>75 years	1134				
TN (HR- and HER2-)		1.27 (1.13–1.43)	1.24 (1.1–1.4)	1.1 (0.98–1.24)	1.09 (0.96–1.23)
<40 years	2757	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
40–60 years	14599	0.9 (0.82–0.98)	0.95 (0.87–1.04)	1.06 (0.97–1.16)	1.03 (0.94–1.13)
60–75 years	9105	1.81 (1.64–2)	2.01 (1.82–2.22)	2.08 (1.88–2.3)	1.81 (1.61–2.03)
>75 years	3432	2.45 (1.99–3.01)	2.29 (1.86–2.82)	1.71 (1.39–2.1)	1.73 (1.4–2.13)

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; REF, reference; sHR, subdistribution hazard ratio; TN, triple-negative; +, positive; -, negative.
[a] Unadjusted.
[b] Adjusted for race/ethnicity, insurance, SEER registry.
[c] Adjusted for race/ethnicity, insurance, SEER registry, Stage at diagnosis, subtype.
[d] Adjusted for race/ethnicity, insurance, SEER registry, Stage at diagnosis, subtype, treatment.

associated with increased likelihood of mastectomy [43]. Fear of recurrence and the increasing rate of contralateral prophylactic mastectomy seems to support more mastectomy in young age groups [44,45]. Women of older age may choose mastectomy for a more expedient treatment, avoiding radiation and placing less value on cosmetic outcomes as age increases [43].

This study should be considered in the context of its limitations. First, 30-month follow up is a relatively short period to access survival differences, particularly HR-positive disease, and longer term survival outcomes are worth observing. Second, we grouped HER2+, ER + disease with high grade HER2-, ER + disease as luminal B-like, as has been done in previous studies and in light of the limitation of not having the ability to assess the use of anti-HER2 therapy in this dataset. Third, we classified grades 1 and 2 as lower grade disease. Sotiriou et al. showed that grade 2 is a heterogeneous group according to gene expression, therefore, HR-positive, lower grade disease may include genetic high risk patients [46]. Fourth, for the analysis of survival, cause-of-death information in the SEER database was used, which has limitations with regard to reliability and completeness. And finally, adherence with adjuvant therapy could not be adjusted for in the analysis and may impact outcomes.

8. Conclusions

Nevertheless, the strengths of this study include the population-based, national sample of women with breast cancer with modern clinical subtyping, including tumor HER2 status. This study supports and expands upon the growing evidence from North America [10], Europe [33], and Asia [19,47] that young age remains an independent prognostic factor in HR-positive/lower grade subtype breast cancer, and further research to understand and improve the outcomes of this vulnerable population is imperative.

Prior presentations

This study was presented in part during the AACR outstanding investigator award lecture at the 2018 San Antonio Breast Cancer Symposium.

Data availability statement

All data are available publicly through SEER.

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Author contributions

Conceptualization: HJK SK, RAF, AHP. Formal analysis: SK. Writing – original draft: HJK, SK, RAF, AHP. Writing – review & editing: HJK SK, RAF, AHP.

Declaration of competing interest

None.

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