Hazard of Breast Cancer-Specific Mortality among Women with Estrogen Receptor-Positive Breast Cancer after Five Years from Diagnosis: Implication for Extended Endocrine Therapy

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Purpose: More than half of the patients with estrogen receptor (ER)-positive breast cancers will relapse and die from breast cancer at 5–10 yr after diagnosis despite 5-yr endocrine therapy. Subpopulations of ER-positive patients at high risk of breast cancer-specific mortality (BCSM) at 5–10 yr are undetermined.

Methods: Using the Surveillance, Epidemiology, and End-Results program (1990–2003), we analyzed the relative hazard ratio (HR) and absolute HR of BCSM and the cumulative 10-yr breast cancer-specific survival (BCSS) in 111,993 breast cancer patients, stratified by ER, age, and lymph node (LN), and adjusted for other prognostic factors.

Results: At 5–10 yr after diagnosis, ER-positive patients had increased risk of BCSM [HR, 0.71; 95% confidence interval (CI), 0.66–0.76; ER-positive as reference] compared with ER-negative patients. Specifically, younger ER-positive patients (<40 yr) had a constant plateau of annual hazard rate, a higher hazard of BCSM (HR, 0.43; 95% CI, 0.35–0.52; ER-positive as reference), and poor 10-yr BCSS, despite LN status. Among ER-positive patients aged 40–60 yr having no obvious plateau of hazard rate, only those with LN-positive disease had a significantly increased hazard of BCSM and poor 10-yr BCSS. Elderly ER-positive patients aged 60–74 yr had a hazard of BCSM, similar to that of ER-negative patients, and those with LN-positive disease had poor 10-yr BCSS.

Conclusion: Our findings help to define the ER-positive subpopulations at higher risk of BCSM at 5–10 yr after diagnosis and are useful in choosing candidates for clinical trials of extended endocrine therapy after 5-yr treatment and in guiding individualized treatment. (***J Clin Endocrinol Metab* 97: E2201–E2209, 2012**)

Breast cancer is a heterogeneous disease that may recur at any time after initial diagnosis and treatment. For women with estrogen receptor (ER)-negative breast cancer, 5 yr is an important milestone because the majority of patients with these tumors will develop metastases within this time frame. However, more than half of women with ER-positive tumors will relapse and die from breast cancer after 5 yr (1, 2). The annual hazard rate plot shows no plateau for both the recurrence and overall survival of ER-positive patients, indicating a low but continuous risk of relapse and death even after 10 yr (2). Ironically, 5-yr adjuvant endocrine therapy [up-front tamoxifen in premenopausal women, up-front aromatase inhibitor (AI) in postmenopausal women, or 2- to 3-yr tamoxifen followed by 3- to 2-yr AI] is currently considered the standard of care for patients with ER-positive, early-stage breast cancer (3).

To reduce the risk of recurrence and death at 5–10 yr after diagnosis, more than four trials (4–7) in extended tamoxifen and three trials (8–12) in extension of AI after

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Abbreviations: AI, Aromatase inhibitor; BCSM, breast cancer-specific mortality; BCSS, breast cancer-specific survival; CI, confidence interval; *df*, degrees of freedom; ER, estrogen receptor; OM, overall mortality.

5-yr tamoxifen have been reported thus far. Accordingly, continuing tamoxifen for an additional 5 yr is not recommended (2, 13), whereas extended AI is only recommended to the postmenopausal patients who had completed 5-yr tamoxifen, and the AI treatment duration should not exceed 5 yr (3). There is a dilemma that, for a proportion of ER-positive patients who are at high risk of death resulting from breast cancer at 5–10 yr after diagnosis, only a minority of patients (postmenopausal and having completed 3–5 yr tamoxifen) had a chance to receive the extended AI therapy; many younger premenopausal women taking tamoxifen and almost all the postmenopausal women taking an up-front AI, however, had to stop the drugs at the sixth year despite constantly existing risk of relapse and death.

Because the optimal timing and duration of endocrine treatment remain unresolved, we believe further trials would be launched evaluating durations of endocrine therapy longer than 5 or even 10 yr. Learning from results of previous trials and the discrepancies among them, we believe that there is an urgent need to identify the subpopulations that are likely to benefit from an extended strategy and those that are not likely to benefit. Because recurrence might be an unreliable surrogate for mortality in ER-positive patients (14), we prefer to choose breast cancer-specific mortality (BCSM) as the primary outcome in the present study. In analysis, we considered the time-dependent effect of ER and investigated the interaction between ER status, age at diagnosis, and lymph node (LN) involvement to see which subpopulation of breast cancer patients is indeed at a relatively higher risk of BCSM at 5–10 yr after diagnosis.

Patients and Methods

Patient selection

To collect sufficient cases, we used the National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) cancer database (15). The current SEER database consists of 17 population-based cancer registries. We selected female patients with invasive breast cancer between January 1, 1990, and December 31, 2003. Patients diagnosed before 1990 were excluded because of unavailable hormone receptor data; patients diagnosed after 2003 were excluded to ensure an adequate follow-up time.

We identified 111,993 patients in the SEER database according to the following inclusion criteria: female, age at diagnosis between 18 and 74 yr, surgical treatment with either mastectomy or breast-conserving surgery, American Joint Committee on Cancer (AJCC) stages I to III, pathologically confirmed invasive ductal carcinoma, at least four axillary LNs dissected, unilateral breast cancer, known ER status, known time of diagnosis, and breast cancer as the first and only cancer diagnosis. Information on the following variables was obtained if available: tumor size, histological grade, race, and using or not using radiotherapy. Because SEER does not provide information on chemotherapy and endocrine therapy, we cannot incorporate and adjust them. This research was submitted to the Ethical Committee and Institutional Review Board in the Shanghai Cancer Center of Fudan University and determined to be qualified for institutional review board exemption. Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) gives basic characteristics of the study patients according to ER status.

Outcomes

The primary study outcome was BCSM, and the secondary outcome was overall mortality (OM). Vital status (alive or dead) was obtained. The cause of death was categorized as breast cancer-specific or non-breast cancer-related. BCSM and OM were calculated from the date of diagnosis to the date of breast cancer death and to the date of any death, respectively. In BCSM analysis, patients who died from other causes were censored at the date of death.

Statistical analysis

Based on a median follow-up of 8.2 yr and with 75% of patients followed up within 11.7 yr since diagnosis, we restricted our analysis in the time frame within 10 yr to guarantee the validity and reliability of our results.

When we calculated an overall effect of variables on mortality assuming a proportional model, the classic Cox regression model, which estimates a constant hazard ratio (HR) throughout follow-up, was employed. When we calculated a time-dependent effect, the outcomes (*e.g.* hazard rate, HR, and difference in survival) were modeled through the flexible parametric survival models using a restricted cubic spline function for the baseline mortality rate (16–18). These models, similar to Cox regression models, provide HRs with 95% confidence intervals (CIs) as a measure of association between exposures and outcome. For the baseline rate, we used a spline with five degrees of freedom (*df*). By modeling the underlying rate parametrically, it was possible to estimate various fitted curves from the model.

We first modeled the overall effect of each variable (time of diagnosis, age at diagnosis, race, grade, ER status, tumor size, LN status, and radiotherapy) using Cox proportional hazards models. Then, we modeled the piecewise effect of each variable by dividing follow-up time into three frames: 0–2, 2–5, and 5–10 yr. Choice of these particular time intervals was based on the facts that, generally, 2 yr is the time of recurrence peak in breast cancer (19) and 5 yr is the milestone of breast cancer survival (13). Within each time frame, we still assumed the hazard of mortality was proportional. A breast cancer event was defined as an event that occurred within the studied time frame; early events were not counted, and later events beyond this time window were censored (20). Subsequently, we modeled the time-dependent effect of variables using the flexible parametric survival modeling framework, which allows covariates to have time-dependent effects by fitting interactions between the covariate and time using a second spline function (18). These interaction splines typically use fewer *df* [we used three *df* (18); five *df* might be overfitting (16)] and are deviation effects from the baseline spline. Differences between groups were still reported as HRs, but the HRs were time-varying rather than constant. In our analysis, each variable was modeled by adjusting for other variables as non-

TABLE 1. HRs for BCSM and OM within 10 yr of diagnosis in women with breast cancer

	BCSM (yr)						OM (yr)					
	0–2		2–5		5–10		0–2		2–5		5–10	
Variables	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age at diagnosis (yr)												
<40	1.11	0.99 to 1.24	1.26	1.16 to 1.36	1.32	1.20 to 1.45	1.08	0.97 to 1.20	1.25	1.16 to 1.35	1.30	1.18 to 1.42
40–49	1		1		1		1		1		1	
50–59	1.12	1.02 to 1.23	1.10	1.03 to 1.18	1.00	0.92 to 1.08	1.18	1.08 to 1.29	1.17	1.10 to 1.25	1.12	1.04 to 1.20
60–69	1.24	1.12 to 1.38	1.27	1.19 to 1.37	1.09	1.00 to 1.19	1.67	1.53 to 1.82	1.63	1.53 to 1.73	1.85	1.73 to 1.98
70–74	1.76	1.55 to 2.00	1.39	1.26 to 1.52	1.14	1.01 to 1.27	2.65	2.40 to 2.93	2.37	2.20 to 2.54	3.16	2.94 to 3.40
ER												
Positive	1		1		1		1		1		1	
Negative	3.97	3.66 to 4.30	1.94	1.85 to 2.05	0.71	0.66 to 0.76	2.94	2.75 to 3.14	1.74	1.66 to 1.82	0.78	0.74 to 0.83
Tumor size (mm)												
1–20	1		1		1		1		1		1	
>20	2.71	2.49 to 2.95	2.18	2.07 to 2.31	1.89	1.77 to 2.02	2.28	2.13 to 2.44	1.90	1.81 to 1.98	1.59	1.51 to 1.67
LN status												
Negative	1		1		1		1		1		1	
Positive	3.69	3.38 to 4.02	2.88	2.73 to 3.05	2.67	2.50 to 2.85	2.68	2.51 to 2.87	2.31	2.21 to 2.42	1.88	1.79 to 1.97

All HRs were adjusted for time since diagnosis (1990–1994 *vs.* 1995–1999 *vs.* 2000–2003), race (white *vs.* black *vs.* others), tumor grade (I *vs.* II *vs.* III or undifferentiated), radiotherapy (no *vs.* yes), and all variables listed in column.

time-dependent covariates. The flexible parametric survival model has been implemented in Stata (command: stpm2).

To determine whether there was significant interaction between ER and other factors in predicting BCSM, we defined an interaction term, *i.e.* ER*factor, as a study variable (21). We were particularly interested in the interaction between ER and age or LN status because age is associated with endocrine therapeutic strategy, whereas LN status is the most robust prognostic factor of mortality in early-stage breast cancer. Interactions between ER and factors were tested using likelihood ratio tests.

Comparisons of patient and tumor characteristics by ER status were performed using χ^2 tests. Survival curves were constructed using the Kaplan-Meier method, and survival difference was determined by log-rank test. Time point survival was estimated using the life-table method. All tests were two-sided, with a significance level of 0.05. Data were analyzed using Stata version 10.0 (StataCorp, College Station, TX).

Results

General results of prognostic factors

In univariate and multivariate analyses (Supplemental Table 2), year of diagnosis, age at diagnosis, race, tumor size, LN status, tumor grade, ER status, and radiotherapy were all significantly associated with breast cancer-specific survival (BCSS) and overall survival. Hazard of BCSM and OM increased in the younger age group and the older age group compared with women aged 40–49 yr. As expected, the hazard of BCSM or OM was significantly higher in women with more severe disease and significantly lower in patients undergoing radiotherapy. HR of ER status for BCSM was 1.72 (95% CI, 1.66 to 1.78; ER-positive as reference) for the whole study period, with ER-positive patients as reference.

Performance of prognostic factors over time

Because numerous studies had consistently showed a time-dependent effect of ER on either recurrence or survival (14, 18, 20, 22–25), we then tried to validate this ER effect as well as to test the time-varying effect of other characteristics on BCSM and OM (Table 1). The results indicated that positive LN status conferred an increased hazard of BCSM and OM throughout the 10-yr follow-up, although the absolute HR values decreased over time. A similar pattern was observed in tumor size. Interestingly, younger patients (age < 40 yr) had increasing risk of dying from breast cancer by time, whereas this pattern was reversed in older women. Of note, in OM, older breast cancer survivors would be more likely to die from causes unrelated to breast cancer. This observation is consistent with previous reports (18). There was a significant time-dependent effect of ER status on BCSM and OM. The hazard of BCSM was higher among patients with ER-negative tumors either in the period of 0–2 yr (HR, 3.97; 95% CI, 3.66 to 4.30) or 2–5 yr after diagnosis (HR, 1.94; 95% CI, 1.85 to 2.05), keeping ER-positive as reference. However, as follow-up time increases, patients with ER-positive disease would have higher risk of BCSM compared with those having ER-negative tumors at 5–10 yr after diagnosis (HR, 0.71; 95% CI, 0.66 to 0.76). The pattern of ER in OM was similar.

Interaction between ER status and age at diagnosis in predicting BCSM

We further investigated whether age at diagnosis modified the effect of ER on the hazard of BCSM (Table 2). There was a significant interaction between ER and age at diagnosis (adjusted P for likelihood ratio test = 0.0007),

TABLE 2. Time effect of ER status on breast cancer-specific death by age at diagnosis

Age at diagnosis (yr)	ER	BCSM (yr)								BCSS			
		0–2		2–5		5–10		Overall, 0–10		At 5 yr (%)		At 10 yr (%)	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	Rate	95% CI	Rate	95% CI
<40	Positive	1.00		1.00		1.00		1.00		89.7	88.9 to 90.4	77.4	76.2 to 78.5
	Negative	4.75	3.76 to 5.98	1.52	1.33 to 1.73	0.43	0.35 to 0.52	1.37	1.25 to 1.50	77.9	76.6 to 79.1	72.2	70.8 to 73.6
40–49	Positive	1.00		1.00		1.00		1.00		94.4	94.1 to 94.7	87.4	86.9 to 87.9
	Negative	4.56	3.87 to 5.38	2.07	1.87 to 2.28	0.71	0.62 to 0.81	1.73	1.62 to 1.86	81.3	80.4 to 82.1	75.5	74.5 to 76.4
50–59	Positive	1.00		1.00		1.00		1.00		94.7	94.4 to 95.0	88.5	88.1 to 89.0
	Negative	3.89	3.33 to 4.53	1.98	1.80 to 2.19	0.71	0.62 to 0.82	1.72	1.60 to 1.84	81.4	80.6 to 82.2	76.2	75.3 to 77.2
60–69	Positive	1.00		1.00		1.00		1.00		94.6	94.3 to 94.9	88.8	88.3 to 89.2
	Negative	3.43	2.90 to 4.07	2.35	2.11 to 2.63	0.97	0.83 to 1.13	1.98	1.83 to 2.14	80.5	79.5 to 81.5	74.1	72.9 to 75.3
70–74	Positive	1.00		1.00		1.00		1.00		93.9	93.4 to 94.3	87.8	87.0 to 88.5
	Negative	4.17	3.32 to 5.24	1.71	1.43 to 2.04	0.83	0.63 to 1.08	1.85	1.65 to 2.08	80.4	78.8 to 82.0	74.9	73.0 to 76.8

All HRs were adjusted for time since diagnosis (1990–1994 *vs.* 1995–1999 *vs.* 2000–2003), race (white *vs.* black *vs.* others), tumor grade (I *vs.* II *vs.* III or undifferentiated), tumor size (1–20 mm *vs.* >20 mm), LN status (negative *vs.* positive), and radiotherapy (no *vs.* yes).

indicating the hazard curves by ER status significantly differed in different age groups. But the interaction between ER and LN status was not detected (likelihood ratio test $P = 0.11$). As Table 2 shows, women with ER-negative tumors had an increased hazard of BCSM during the first 5 yr of follow-up in all age groups. As follow-up time increased to 5–10 yr from diagnosis, the hazard of BCSM in ER-negative patients decreased compared with that in ER-positive patients. Specifically, ER-positive patients less than 40 yr of age had significantly higher hazard of BCSM in this period (HR, 0.43; 95% CI, 0.35 to 0.52; ER-positive as reference). In contrast, the hazards of BCSM in older ER-positive patients increased moderately (HRs from 0.71 to 0.97).

Separate Kaplan-Meier curves for patients stratified by ER status and age at diagnosis are provided in Fig. 1A. In patients younger than 40 yr, the survival difference between ER-negative and ER-positive patients continuously enlarged until a maximum at the 5 yr from diagnosis (Fig. 1B), after which time point the survival difference became smaller, and the two survival curves probably crossed or converged after 10 yr. In 40- to 60-yr-old patients, the survival difference became slightly smaller after 5 yr; in even older patients, the difference was stable over time, suggesting a comparable risk of BCSM in ER-negative disease compared with that in ER-positive disease during the period of 5–10 yr.

The dynamic annual hazard rates over time provided additional information (Fig. 1C). Younger patients with ER-positive tumors has approximately a 2-fold higher hazard of BCSM compared with that in older patients. Very remarkably, the annual hazard in younger patients was cumulating at the first 4 yr and reached a peak at 4–5 yr after diagnosis; then, a plateau of hazard rate emerged and remained stable for a long time.

Hazard of BCSM in subpopulations stratified by ER status, age at diagnosis, and LN status

Moreover, we inspected whether LN status could modify the hazard of BCMS based on age and ER status (Table 3). It had been decided by consensus that the low clinical risk group is defined as patients with 10-yr overall survival probabilities of at least 88% for ER-positive tumors (26). Here, we chose a cutoff of 92% (1-[1–88%]*65%) for 10-yr BCSS because death resulting from breast cancer accounts for approximately 65% of overall death according to our SEER data or external data (18). In the LN-negative group (Table 3 and Fig. 2A), younger ER-positive patients had a relatively poor BCSS with a 2-fold (HR, 0.53; 95% CI, 0.38 to 0.72) hazard of BCSM compared with that in ER-negative patients, whereas ER-positive patients older than 40 yr had a substantially higher 10-yr BCSS around 93–95%, with comparable HRs with ER-negative patients at 5–10 yr (Table 3 and Fig. 2B). In comparison, all LN-positive patients, despite positive ER status, had a 10-yr BCSS less than 80% (Fig. 2C). The hazard of BCSM in LN-positive, ER-positive patients significantly increased over time in patients less than 60 yr old but not in elderly patients (Fig. 2D).

Discussion

In the present study, we confirmed a time-dependent effect of ER on breast cancer mortality and defined ER-positive subpopulations that are indeed at high risk of BCSM 5–10 yr after diagnosis. Our findings suggest that younger patients (<40 yr old) with ER-positive tumors had a constantly high hazard of BCSM throughout the period of 5–10 yr, whereas the older patients had moderately increased risk (in 40- to 59-yr-old patients) or fundamentally no increased risk (in 60- to 74-yr-old patients) of BCSM compared with ER-negative patients in the same

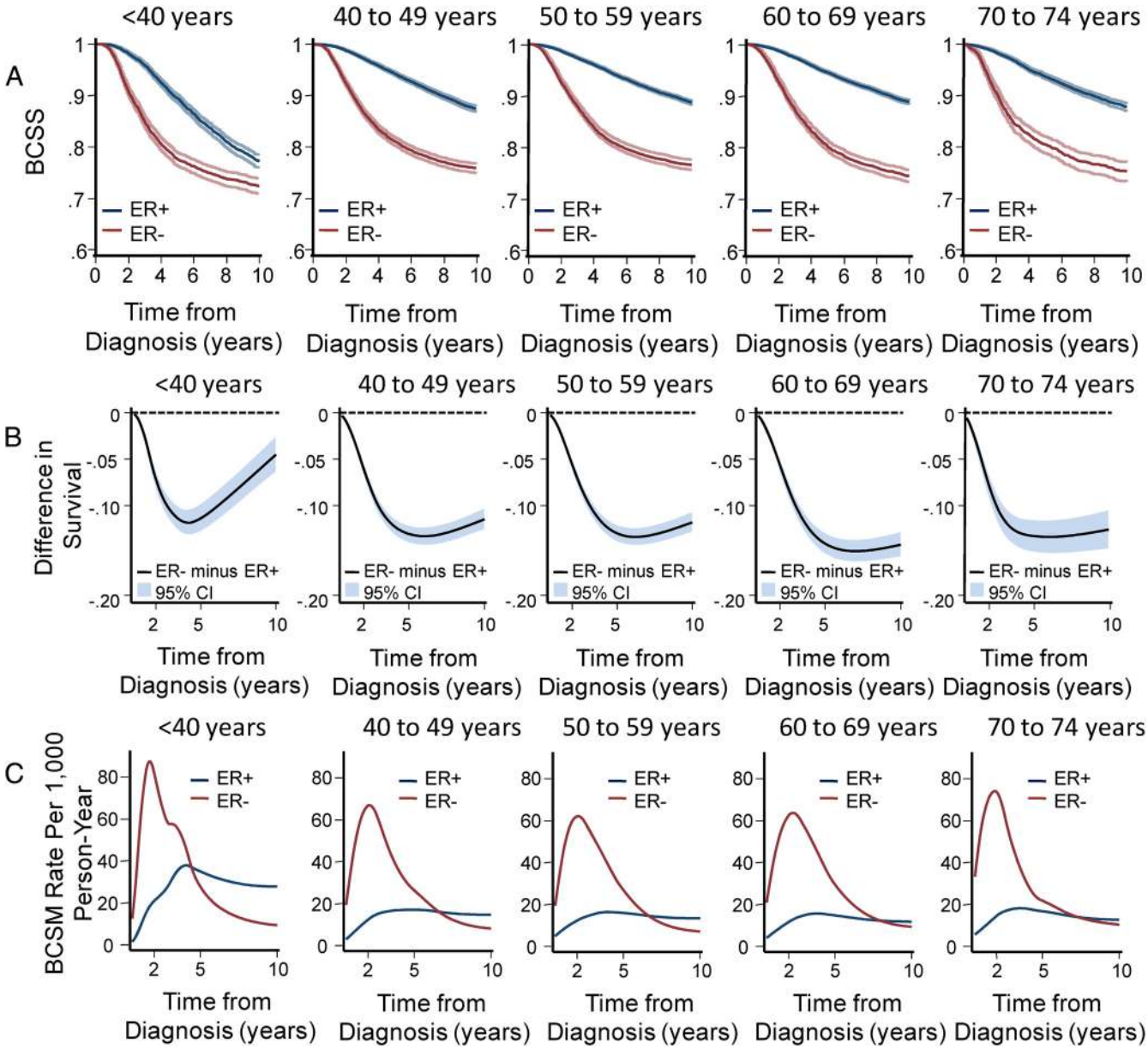

FIG. 1. Survival and annual hazard rates according to ER status and age at diagnosis within 10 yr. A, Separate Kaplan-Meier curves of BCSS for patients stratified by ER status and age at diagnosis. *Light red and light blue lines* represent 95% CI of survival. B, Survival difference between ER-positive and ER-negative breast cancer patients. *Plots from left to right* represent different age groups. C, Estimated continuous annual hazard rates of ER-positive and ER-negative breast cancer patients in each age group. Hazard rates estimated from flexible parametric survival models with age as the only covariate. Hazard rates were reported per 1000 persons per year.

observation period. In addition, older ER-positive patients concurrent with LN-negative disease had a very favorable prognosis, with a 10-yr BCSS of more than 93%. These results may help physicians determine which patients are and are not at a high risk of dying from breast cancer 5–10 yr after diagnosis. Our findings might be useful to clarify a question with clinical relevance, *i.e.* who are the candidates for extended endocrines 5–10 yr since diagnosis?

For postmenopausal patients with ER-positive breast cancer, the current "gold standard" of adjuvant endocrine therapy is 5-yr AI or 3 to 2-yr AI if 2- to 3-yr tamoxifen has been administered first (3). Thus far, three trials [MA.17 (8–10), NSABP B-33 (11), and ABCSG-6a (12)] evaluating 3- to 5-yr AI extension after completed 5-yr tamoxifen have provided encouraging results in relapse-free survival even in overall survival (9). This strategy is recommended for all the eligible patients (3), but only a proportion of pre- or perimenopausal women would have the chance to use this strategy clinically in the current era of AI. No trial of extended AI after 5-yr up-front AI has been reported, and relevant trials have been or would be designed and conducted. Our results provide some helpful information on candidate selection in trial. We propose that not all

TABLE 3. Interaction between ER, age, and LN status in predicting breast cancer-specific death at 5 to 10 yr from diagnosis

Age at diagnosis (yr)	ER	LN-negative					LN-positive				
		BCSS at 10 yr (%)		Hazard of BCSM at 5–10 yr			BCSS at 10 yr (%)		Hazard of BCSM at 5–10 yr		
		Rate	95% CI	HR	95% CI	*P*	Rate	95% CI	HR	95% CI	*P*
<40	Positive	88.7	87.3 to 89.9	1			68.0	66.2 to 69.7	1		
	Negative	84.4	82.8 to 86.0	0.53	0.38 to 0.72	<0.001	59.2	57.0 to 61.4	0.37	0.29 to 0.48	<0.001
40–49	Positive	94.3	93.8 to 94.8	1			79.2	78.2 to 80.1	1		
	Negative	85.9	84.8 to 86.9	0.81	0.65 to 1.02	0.07	62.8	61.2 to 64.4	0.66	0.55 to 0.78	<0.001
50–59	Positive	94.7	94.3 to 95.1	1			79.0	78.0 to 79.9	1		
	Negative	86.0	84.9 to 87.0	0.85	0.68 to 1.07	0.16	62.7	61.0 to 64.3	0.64	0.54 to 0.77	<0.001
60–69	Positive	94.4	94.0 to 94.8	1			77.3	76.2 to 78.3	1		
	Negative	84.9	83.6 to 86.2	1.07	0.84 to 1.36	0.59	56.8	54.6 to 59.0	0.90	0.73 to 1.11	0.31
70–74	Positive	93.8	93.1 to 94.4	1			74.2	72.3 to 75.9	1		
	Negative	85.8	83.7 to 87.6	0.89	0.61 to 1.30	0.55	55.3	51.5 to 58.9	0.76	0.52 to 1.09	0.14

All HRs were adjusted for time since diagnosis (1990–1994 *vs.* 1995–1999 *vs.* 2000–2003), race (white *vs.* black *vs.* others), tumor grade (I *vs.* II *vs.* III or undifferentiated), tumor size (1–20 mm *vs.* >20 mm), and radiotherapy (no *vs.* yes).

postmenopausal patients are at high risk of dying from breast cancer at 5–10 yr after diagnosis. Inclusion of low-risk LN-negative patients in an AI extension trial might not only cause a problem of low cost-effectiveness or a concern for low efficiency and high toxicity, but also might dilute the treatment effect and make it difficult to detect a survival difference. For instance, the MA.17 trial, which included both LN-negative and LN-positive disease, finally detected a significantly superior overall survival in the letrozole group at a median follow-up of 64 months (9); however, such an advantage in overall survival had been detected at a median follow-up of 30 months among LN-positive patients (10).

Considering the treatment-related toxicity of AI, the relative risk of BCSM, and the absolute 10-yr survival, we suggest that the ER-positive, LN-negative, early-stage breast cancer patients might be not candidates for trials of extended AI after 5-yr endocrine therapy. Of note, extended AI therapy in elderly patients should be treated with caution, although data from MA.17 declared that such an extension is safe and effective (27). Because most elderly women might not receive standardized treatment, the observed poor survival could be a result of insufficient treatments rather than a real sign of needs for extended endocrine treatment. Moreover, aging is related to higher levels of endocrine therapeutic drug metabolites, and the toxicity might be more pronounced in elderly women (28, 29).

In premenopausal women, the present gold standard of adjuvant endocrine therapy is still the 5-yr tamoxifen. More than four trials (4–7) of extended tamoxifen after 5-yr tamoxifen (although these trials were conducted not only in premenopausal women) reported inconsistent results, which could be explained by underpowered sample size in some trials and differences in patient selection. Premenopausal patients could be divided into two groups according to age: one group is younger than 40 yr, and the other is older than 40 yr (but most patients should be less than 60 yr old because they are premenopausal). For those younger (<40) premenopausal patients, our results showed that they had significantly higher hazard of BCSM in the 5–10 yr after diagnosis; moreover, they had a relatively poor BCSS of 89% (92% is a standard of good prognosis). Therefore, the premenopausal patients younger than 40 yr are at high risk of death due to breast cancer and should be good candidates for extended tamoxifen after 5-yr treatment. For premenopausal patients older than 40 yr, our results showed that they had a substantially high 10-yr BCSS around 93–95% in LN-negative cases but low 10-yr BCSS (<80%) in LN-positive cases, indicating that only those with LN-positive disease need further treatment.

Our study had several limitations. First, the SEER data lack several important tumor characteristics (*e.g.* HER2) and cancer therapy (adjuvant systemic treatment). Thus, our analysis could not adjust for these potential confounding factors. Knowledge of HER2 status would permit further classification of ER-positive tumors as luminal-A (HER2-negative) or luminal-B (HER2-positive), which probably have different hazard rates over time (1). Of note, a published study with large sample size (10,000 cases of invasive breast cancer from 12 cohorts) shows that the HER2 distribution is not significantly different in each age group in ER-positive patients ($P = 0.21$), indicating that the effect of HER2 on survival difference in different age groups might be limited. Bias may be introduced without adjustment for systemic treatment. However, many studies have demonstrated that the time-dependent effect of ER is unchanged with or without systemic treatment (14, 18, 30). It is unlikely that the observed time-depen-

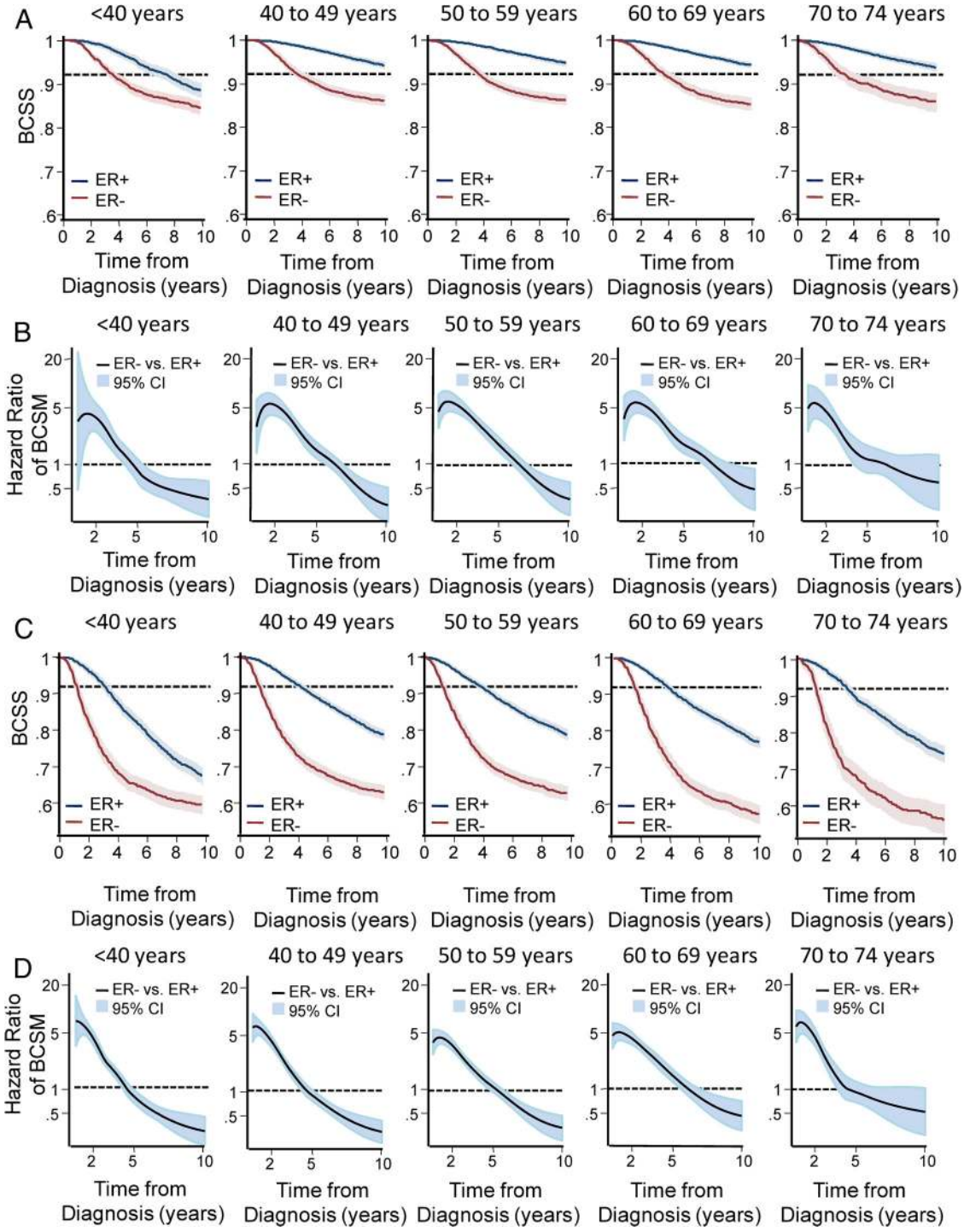

FIG. 2. Kaplan-Meier curves of BCSS by ER status and time-dependent effect of ER on HRs for BCSM within 10 yr of diagnosis. Plots are shown by LN status, LN-negative in panels A and B, and LN-positive in panels C and D. A and C, Kaplan-Meier curves of BCSS in each age group. *Dashed line* at a 92% BCSS represents a cutoff of low-clinical risk. *Light red and light blue shadows* represent 95% CI of survival. B and D, HRs with 95% CIs were estimated from the flexible parametric survival models, stratified by age at diagnosis and LN status, and adjusted for year of diagnosis, race, grade, tumor size, and radiotherapy. Curves cut off at 0.5 yr from diagnosis because of sparse data.

dent effect of ER on survival is a result of adjuvant treatment (18). Other risk factors such as young patients carrying mutated genes (*e.g.* BRCA1/2), surgical treatment, and endocrine conditions are potential interfering factors. Second, methodologically, the spline approach, although flexible, is limited by the diminishing number of breast cancer events in stratification. It is important to replicate our findings in other large databases with long-term follow-up. Third, the SEER database does not discriminate between the relapse of primary breast cancer and the occurrence of second primary tumor. However, some (31), but not all (32), studies indicate that the ER status of the

primary breast cancer is associated with that of the contralateral breast for patients not receiving tamoxifen, and adjuvant endocrine therapy effectively prevents the contralateral ER-positive breast cancer (13, 29, 33, 34). Finally, our study is based on the assumption that ER-positive, high-risk patients would continuously benefit from endocrine therapy. Our conclusion would not stand if the continued treatment with tamoxifen or AI results in treatment resistance or an unexpectable agonist effect.

In conclusion, our study indicated that the effect of ER on predicting BCSM is time-dependent. Stratification by age, ER, and LN status, and not assuming proportional hazards, allows us to reveal the subpopulations that are at relatively higher risk of BCSM 5–10 yr after diagnosis. Our findings may be helpful in choosing appropriate candidates for clinical trials of extended endocrine therapy after 5-yr treatment and in guiding individualized therapeutic strategies.

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