Breast Cancer Res Treat (2006) 100:121–126
DOI 10.1007/s10549-006-9231-y

ORIGINAL REPORT

Effects of estrogen receptor expression and histopathology on annual hazard rates of death from breast cancer

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Received: 11 March 2006 / Accepted: 14 March 2006 / Published online: 10 May 2006

Abstract
Background Breast cancer incidence rates vary according to estrogen receptor expression (ER) and histopathology. We hypothesized that annual mortality rates from breast cancer after initial diagnosis (hazard rates) might also vary by ER and histopathology.
Methods We accessioned the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER, 1992–2002) program to estimate hazard rates according to ER (positive and negative) and histopathology (duct, tubular, lobular, medullary, inflammatory, papillary, and mucinous types). We used spline functions to model hazard rates free of strongly parametric assumptions for ER negative and positive cases overall and by histopathology.
Results Hazard rates for ER negative and ER positive cases were distinct and non-proportional. At 17 months, ER negative hazard rates peaked at 7.5% per year (95% CI, 7.3–7.8% per year) then declined, whereas ER positive hazard rates lacked a sharp early peak and were comparatively constant at 1.5–2% per year. Falling ER negative and constant ER positive hazard rates crossed at 7 years; after which, prognosis was better for ER negative cases. Among ER positive and negative cases, there were proportional and non-proportional hazards according to histopathologic type, but the two basic ER-associated patterns were maintained.
Conclusions Hazard rates differed quantitatively and qualitatively according to ER and histopathology. These large-scale population-based results seem consistent with genomic studies, demonstrating two main classes of breast cancers with distinct prognoses according to ER expression.

Keywords Hazard function · Hazard regression · Survival analysis · Non-proportional hazards · Risk factors

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Introduction

Breast cancer prognosis is notably heterogeneous. A fraction of women are cured after initial diagnosis and treatment, but breast cancer death may occur months, years, or decades later [1]. Given this clinical uncertainty, the outcome of patients with breast cancer may best be characterized by the absolute cause-specific hazard function, which describes the instantaneous rate or ''force'' of breast cancer mortality over the years following initial diagnosis and treatment [2–4].

Previous studies have estimated this hazard function using long-term follow-up of women treated in various calendar time periods [2–13]. These studies have consistently found that prognostic factors such as estrogen receptor expression (ER) and tumor size do not have a proportional (or time-invariant) effect. Instead, the effect of these tumor characteristics is non-proportional (or varies) over time. Therefore, it remains a challenge to accurately describe both the shape and the magnitude of the hazard function, when prognostic factors may affect both.

In this study, we applied non-parametric hazard function estimators, which can model differences in both shape and magnitude free of ad hoc mathematical assumptions. We modeled the joint effects of ER and histopathology on the hazard using data on female breast cancer cases in the SEER database. Using this approach, we found a very significant and dominating ER-associated pattern as well as a significant interaction between ER and histopathology.

Materials and methods

We utilized the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 13-Registry Databases for breast cancer cases diagnosed during the years 1992–2001 and followed through 2002. The 13-Registry Database collected data from registries in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, rural Georgia, and Alaskan Native Tumor Registries [14].

Incident patient and tumor characteristics included age at diagnosis, tumor size, ER expression, and histopathology. Because no centralized laboratory was used to determine hormone receptor status, each SEER registry recorded hormone receptors as positive, negative, missing, borderline, or unknown. We combined missing, borderline, and unknown data into one group, designated as other or unknown. Unknown data were excluded from these analyses.

Histopathologic types were identified with ICD-O codes from the International Classification of Diseases for Oncology—3rd edition (ICD-O-3) [15, 16]: duct carcinoma of no special type (duct NST, ICD-O-3 code 8500), tubular carcinoma (ICD-O-3 codes 8211), lobular carcinoma (ICD-O-3 codes 8520–8521), medullary carcinoma (ICD-O-3 codes 8510–8512), inflammatory carcinoma (ICD-O-3 code 8530), papillary carcinoma (ICD-O-3 codes 8050, 8260, 8503), mucinous carcinoma (ICD-O-3 codes 8480–8481), other or unknown included all other ICD-O-3 codes.

Hazard functions

The annual hazard for breast cancer death describes the instantaneous rate of breast cancer death in a specified time interval following primary diagnosis in women who are alive at the beginning of that time interval. We used spline functions to estimate the hazard rate curve [17]. Join-points of a piece-wise cubic spline model were selected using Akaike's Information Criteria (AIC) [18]. We constructed 95% confidence intervals (95% CI) using bootstrap resampling [19].

We used Poisson regression [20] to test for interactions between hazard rates and calendar time, for cases diagnosed during the years 1992–2001 and followed through the year 2002. Using a series of likelihood ratio tests for distinct hazard functions between successive years, we identified ''benchmark'' time periods that included only years with similar hazard rates. Annual hazard rates in women with ER negative tumors did not change among breast cancer cases diagnosed between the years 1992–2001, yielding an ER negative benchmark period that extended from 1992 to 2001 with up to 11 years of follow-up (1992–2002). In contrast, annual hazard rates in women with ER positive tumors improved for breast cancer cases diagnosed during the early 1990s, and then the rate stabilized in 1995, producing an ER positive benchmark period that extended from 1995 to 2001 with up to 8 years of follow-up (1995–2002).

We also applied Poisson regression models with interactions between baseline hazard function and histopathology or ER status to test the proportionality of the hazard in subgroups of breast cancer cases with different combinations of ER and histopathology. *P*-values for pair-wise comparisons were reported and the overall significances accounting for multiple comparisons were obtained by applying a False Discovery Rates (FDR) procedure [21]. Proportional hazard differences were assessed with Cox analyses and expressed as relative risks [22]. Non-proportional differences are summarized by plots of the hazard rates over time.

Due to small sample sizes, we did not estimate hazard rates for comparatively rare combinations of ER and histopathology of suspect biological significance. Specifically, we excluded ER negative tubular (n = 165), ER positive medullary (n = 425), ER negative papillary (n = 148), and ER negative mucinous (n = 248) breast carcinomas.

Results

Descriptive data (Table 1)

The SEER 13-Registry database collected data for 243,808 invasive female breast carcinoma cases, diagnosed during the years 1992–2001 and followed for 11 years (1992–2002). Duct NST and lobular tumors were the most common histopathologic types, i.e., 69% and 8%, respectively. Median ages at diagnosis ranged from a low of 51 years for medullary to a high of 71 years for mucinous breast carcinomas. Percent distribution of ER negative and positive tumors varied by histopathologic type, as previously described [23](See Table 1).

Hazard rates for all breast cancer cases combined (Fig. 1)

The hazard function for breast cancer death was calculated for all breast cancer cases combined during the benchmark

years, as described in the Materials and methods (1992–2001 for ER negative tumors and 1995–2001 for ER positive breast cancers). We observed non-proportional hazard patterns according to ER expression. ER negative hazard rates dipped initially, peaked at 17 months with a hazard of breast cancer death at 7.5% per year (95% CI, 7.3–7.8% per year), and then declined. ER positive hazard rates also fell transiently, lacked a prominent early peak, and then rose to a constant long-term rate of approximately 1.5–2% per year. Falling ER negative and stable ER positive hazard functions eventually crossed 7–8 years following breast cancer diagnosis, after which prognosis was better for ER negative than ER positive long-term survivors (see Fig. 1).

Hazard rates for inflammatory breast cancer (IBC, Fig. 2)

IBC was the most aggressive breast cancer type. The shapes of the ER negative and positive hazard functions for IBC were similar to all breast cancer cases combined, but the magnitudes were greatly amplified for IBC. Hazard rates in IBC with ER negative expression declined transiently then rose rapidly to a peak at 13 months with a hazard of breast cancer death at 46.8% per year (95% CI, 40.4–51.8%), followed by a declining trend. In contrast, hazard rates in IBC with ER positive tumors declined transiently then rose to a nearly constant long-term rate of more than 10% per year. Falling ER negative and constant ER positive hazard function crossed approximately 6 years after breast cancer diagnosis, after which the prognosis was better for ER negative than ER positive cancers (see Fig. 2).

Hazard rates by ER and histopathology (Fig. 3)

Within each histopathologic type considered (panel A compared to panel B), tests for non-proportional hazards confirmed that ER negative tumors were qualitatively different than ER positive tumors (all unadjusted and adjusted P-values < 0.01). Of note, ER negative cancers among the various histopathologic types demonstrated non-proportional as well as proportional differences for all pairwise comparisons. On the other hand, ER positive breast cancers among the different histopathologic types showed only proportional differences. For example, relative hazard rate ratios for ER positive breast cancers ranged from 0.13 for ER positive tubular carcinomas vs. ER positive duct NST to 8.29 for ER positive inflammatory breast cancers vs. ER positive duct NST (see Figs. 2 and 3).

Discussion

The Cox hazard model assumes that the effect of a prognostic factor is proportional over time [22]. However, non-proportional hazard for recurrence and death have been described among women diagnosed with breast cancer since the 1950s according to standard tumor characteristics such as race, tumor size, nodal status, histopathology, grade,

Table 1 Descriptive statistics for selected tumour characteristics in SEER's 13 Registry Database among invasive female breast cancer cases collected during the years 1992–2002

	All breast cases				**Duct NST**				**Tubular**				**Lobular**			
Sample size	243,808				167,892				3,937				19,801			
Median age	62.0				61.0				62.3				66.0			
Median tumor size	1.6				1.6				0.8				2.0			
Rate (SE)	132.7 (*0.3*)				91.6 (*0.22*)				2.17 (*0.04*)				10.7 (*0.08*)			
Variable	***N***	***Rate***	***SE***	***RR***	***N***	***Rate***	***SE***	***RR***	***N***	***Rate***	***SE***	***RR***	***N***	***Rate***	***SE***	***RR***
ER																
ER positive	146,929	80.1	0.2	1.0	103,394	56.4	0.2	1.0	2,825	1.6	0.0	1.0	14,649	8.0	0.1	1.0
ER negative	44,218	24.2	0.1	0.3	34,000	18.7	0.1	0.3	165	0.1	0.0	0.1	1,394	0.8	0.0	0.1
Other or Unknown	52,661	~	~	~	30,498	~	~	~	947	~	~	~	3,758	~	~	~
	Medullary				**Inflammatory**				**Papillary**				**Mucinous carcinoma**			
Sample size	2,455				2,741				1,560				6,189			
Median age	51.0				56.0				70.0				71.0			
Median tumor size	2.0				5.3				1.5				1.5			
Rate (*SE*)	1.34 (*0.03*)				1.5 (*0.03*)				0.83 (*0.02*)				3.33 (*0.04*)			
Variable	***N***	***Rate***	***SE***	***RR***	***N***	***Rate***	***SE***	***RR***	***N***	***Rate***	***SE***	***RR***	***N***	***Rate***	***SE***	***RR***
ER																
ER positive	425	0.2	0.0	1.0	982	0.5	0.0	1.0	922	0.5	0.0	1.0	4,570	2.4	0.0	1.0
ER negative	1,572	0.9	0.0	3.7	907	0.5	0.0	0.9	148	0.1	0.0	0.2	248	0.1	0.0	0.1
Other or unknown	458	~	~	~	852	~	~	~	490	~	~	~	1,371	~	~	~

Key: Rate, incidence rate per 100,000 woman-years (age-adjusted to the 2000 US standard population); SE: standard error; RR: rate ratio where a given characteristic is compared to a referent characteristic with an assigned RR of 1.0; ER: estrogen receptor

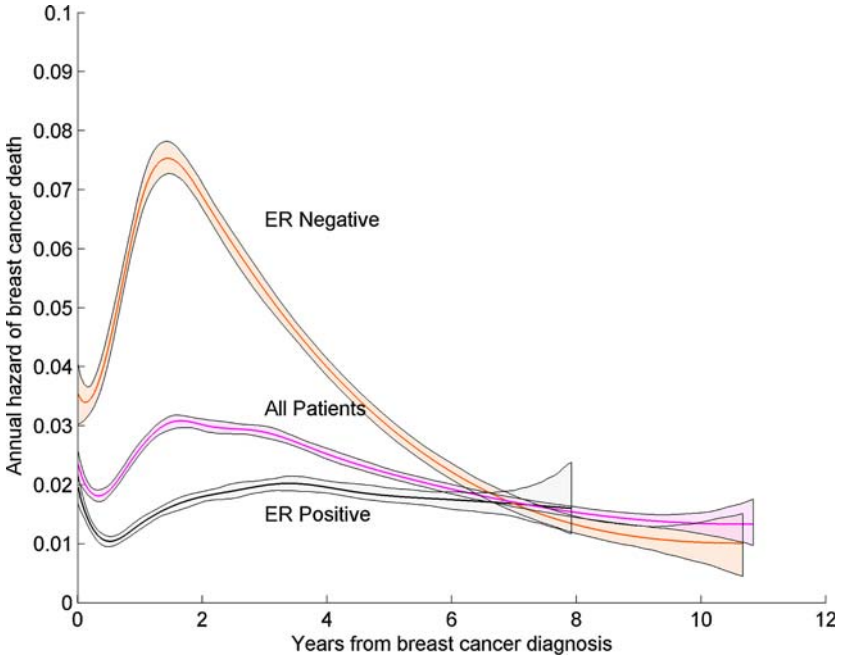

Fig. 1 Annual hazard rates of death from breast cancer after primary diagnosis, with 95% confidence bands, among all breast cancer cases (n = 243,808), according to ER negative and positive expression

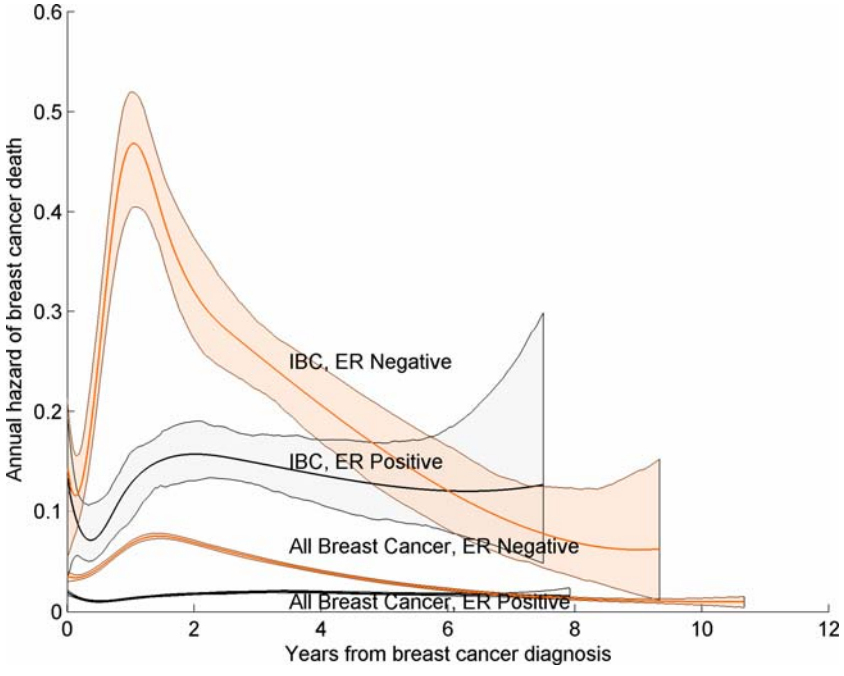

Fig. 2 Annual hazard rates of death from breast cancer after primary diagnosis, with 95% confidence bands, among inflammatory breast cancers (IBC) according to ER negative and positive expression. Corresponding hazard rates for all histopathology types combined are shown for reference

S-phase fraction, ER, and PR [2–13]. Although these time-varying prognostic effects have been characterized for breast cancer overall, a systematic examination of breast cancer hazard has not been reported for different histopathologic types.

Early detection and treatment appear to have reduced breast cancer mortality during the last decade [24–26], and this secular trend could confound the breast cancer hazard function during our study period. Screening patterns and treatment modalities are not reliably recorded in SEER. So, we used benchmark calendar years with similar hazard rates as a surrogate measure for early detection and/or improved therapy, as described in the Materials and methods.

During the benchmark time periods, we observed striking time-varying (or non-proportional) shape differences with crossing hazard patterns according to ER expression (Fig. 1). The annual risk for breast cancer death among ER negative cases rose rapidly to an early 17-month peak then fell continuously. In contrast, the risk for breast cancer death among ER positive tumors was more nearly constant at an annual hazard rate of 1.5–2% per year.

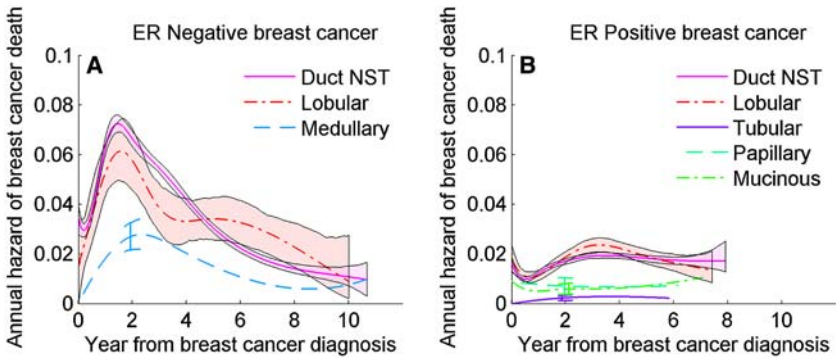

Fig. 3 Annual hazard rates of death from breast cancer after primary diagnosis, with 95% confidence bands, according to histopathology. Panel A: Hazard function for ER negative breast cancers Panel B: Hazard function for ER positive breast cancers

Eventually and perhaps somewhat paradoxically, falling ER negative rates and constant ER positive rates crossed at 7–8 years, after which prognosis was better for ER negative than ER positive tumors.

Baum et al. [12] describe double hazard peaks for breast cancer overall following initial diagnosis in Milan: (1) a sharp peak at approximately 18 months and (2) a broad peak at 5–7 years. Alternatively, our Fig. 1 demonstrates that the two peaks for all breast cases might reflect the mixing of ER negative and ER positive hazard patterns. For example, the 1st sharp peak for all patients might be due to the early ER negative hazard peak, whereas the 2nd broader peak for all patients might result from crossing ER negative and ER positive hazard patterns.

Among the different breast cancer types according to histopathology (Figs. 2, 3), ER negative cases showed proportional as well as non-proportional shape differences, whereas ER positive cases demonstrated only proportional variations. Despite significant non-proportionality, the shape of the hazard functions for the ER negative cases were qualitatively similar with a predominant early peak and declining trend. Additionally, though ER positive tumors showed only proportional differences, it must be stressed that the special histopathologic types of ER positive cases (lobular, tubular, papillary, and mucinous) were distinct in terms of the magnitude of the hazard curve if not the shape.

Hence, there appeared to be at least two distinct ER-associated hazard rate patterns. These data are consistent with the hypothesis that there are different breast cancer phenotypes according to tumor doubling time [27]. Indeed, clinicians have long suspected two main breast cancer types, with age at onset being the major determinant of breast cancer prognosis [28, 29]. The first breast cancer type is early-onset, largely ER negative and aggressive, whereas the second breast cancer type is late-onset, mostly ER positive and indolent.

The major strength of this study is that we applied hazard spline regression modeling (free of ad hoc assumptions) to the large-scale population-based SEER program. Limitations included lack of accurate screening and/or treatment records. So, we used ''benchmark'' calendar periods, which incorporated only those years with similar hazard rates as a surrogate measure for early detection or treatment. Moreover, we previously demonstrated that shape of hazard rates were coherent with incidence rate patterns [11], which should not be affected by screening or treatment. Hazard patterns were not adjusted for tumor size, nodal status, or grade; but also as previously shown [11], combining various low-risk and high-risk tumor characteristics affects the magnitude but not the shape of the hazard plot. Another potential problem is that histopathologic categorizations and ER expression data were derived from multiple institutions within SEER's standard catchment areas; and therefore, results might be affected by differential misclassification or detection rates, incomplete or non-standardized data. However, the large-scale population-based design of the SEER database should theoretically balance diagnostic and geographic variation among the SEER sites, reflecting actual practice patterns in the United States. It is also reassuring that the frequency distribution for different histopathologic types and hormone receptor expression was similar to our previous study as well as to other reported series [23, 30]. Finally, ER expression was unknown for approximately 20% of cases (Table 1; 52,661 of 243,808); but as shown in other studies [23, 31, 32], ER unknown is generally similar to ER positive tumors, which is perhaps not surprising given that 77% of known breast cancers were ER positive (Table 1; 146,929 of 146,929 + 44,218).

In summary, although breast cancers are extremely heterogeneous with respect to histopathology, clinical presentation, and molecular alterations, the hazard rates of death from breast cancer following primary diagnosis appear to be fundamentally divisible into two predominant patterns according to ER and these patterns are maintained among the various types of histopathology. These population-based observations complement emerging molecular biologic techniques, demonstrating the stratification of breast tumors into two main classes with distinct clinical outcome according to ER expression [33], and could form the basis for revised breast cancer paradigms [34]. As

additional molecular research and targeted therapies are applied in the future, data from the SEER registry and other patient cohorts will help to document the impact of these innovations in the general population.

Acknowledgments This research was supported in part by the Intramural Research Program of the NIH/National Cancer Institute.

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