

# Can We Use Survival Data from Cancer Registries to Learn about Disease Recurrence? The Case of Breast Cancer



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## Abstract

**Background:** Population-representative risks of metastatic recurrence are not generally available because cancer registries do not collect data on recurrence. This article presents a novel method that estimates the risk of recurrence using cancer registry disease-specific survival.

**Methods:** The method is based on an illness–death process coupled with a mixture cure model for net cancer survival. The risk of recurrence is inferred from the estimated survival among the noncured fraction and published data on survival after recurrence. We apply the method to disease-specific survival curves from female breast cancer cases without a prior cancer diagnosis and with complete stage and hormone receptor (HR) status in Surveillance, Epidemiology and End Results registries (1992–2013).

**Results:** The risk of recurrence is higher for women diagnosed with breast cancer at older age, earlier period, more

advanced stage, and HR-negative tumors. For women diagnosed at ages 60–74 in 2000–2013, the projected percent recurring within 5 years is 2.5%, 9.6%, and 34.5% for stages I, II, and III HR-positive, and 6.5%, 20.2%, and 48.5% for stages I, II, and III HR-negative tumors. Although HR-positive cases have lower risk of recurrence soon after diagnosis, their risk persists longer than for HR-negative cases. Results show a high degree of robustness to model assumptions.

**Conclusions:** The results show that it is possible to extract information about the risk of recurrence using disease-specific survival, and the methods can in principle be extended to other cancer sites.

**Impact:** This study provides the first population-based summaries of the risk of breast cancer recurrence in U.S. women. *Cancer Epidemiol Biomarkers Prev*; 27(11); 1332–41. ©2018 AACR.

## Introduction

Population-based cancer registries data are indispensable in tracking and reporting the evolving burden of cancer in the population. However, they capture information only about the outcomes of diagnosis and death, whether due to the disease or other causes. Given increasing cancer survivorship, there is a growing demand to understand intermediate outcomes reflecting the postdiagnosis course of the disease.

Distant metastatic recurrence is a key outcome in the management of disease at both the individual and the population levels. Recurrence is the return of cancer after primary treatment and reflects progression to a greater disease burden. For nearly all solid tumors, distant metastatic recurrence causes a

major shift in the goals of care because cure is no longer possible.

In the absence of population-based information about the risk of recurrence, information has been limited to data reported from clinical trials (1), single-institution patient cohorts (2, 3), and prospective cohorts (4). These data cannot be generalized to the whole population of patients with cancer as patients participating in trials represent 4% of the adult cancer population and tend to be younger and healthier (5). Single-institution cohorts usually represent patients with cancer being treated at cancer research centers and also do not generalize to the population of patients treated in community settings.

Algorithms utilizing health claims data to infer recurrence have been shown to capture the recurrence event with varying degrees of accuracy (6–8). However, they are less accurate in identifying the timing of recurrence, especially for subgroups of patients with cancer who are older or who may not receive treatment immediately after recurrence (9).

Collection of recurrence information is challenging because of the diverse methods and locations at which a recurrence might be diagnosed requiring intensive surveillance over time and ability to access and extract information from medical records. Researchers and the registry community are increasingly interested in identifying ways to leverage existing data, such as electronic medical records, and harnessing informatics methods to capture recurrence events (10). However, it will take years for these efforts to produce the needed information in a population-representative manner.

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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**doi:** 10.1158/1055-9965.EPI-17-1129

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In this article, we present a novel method for extracting information about the risk of recurrence using disease-specific survival curves from cancer registry data. We use the method to produce new estimates of the risk of progressing to metastatic recurrence (recurrence) after being diagnosed with nonmetastatic breast cancer. Our approach provides population-based information on the proportion that recurred and the distribution of recurrence times and holds potential for expanding cancer registry reports to provide a more complete picture of the burden of disease and progress on cancer control. Because the methods rely on net cancer survival measures (cause-specific or relative survival; ref. 11), the estimates represent summaries of the risk of metastatic recurrence in the absence of other causes of death and reflect detection and treatment patterns as observed in the population.

## Materials and Methods

### Overview

We define recurrence as progression to distant metastatic cancer after a diagnosis with cancer at earlier stage with no evidence of metastasis. This definition is broader than the common definition of distant recurrence that requires a disease-free period after initial treatment.

Our approach to estimating the risk of recurrence makes the following assumptions. First, we assume that the disease-specific survival in the study population can be written as a mixture of cured and noncured (Fig. 1) components, where the cured component reflects long-term survivors who ultimately die of another cause. We consider assumptions to estimate the recurrence-free survival from survival among the noncured. We assume that patients in the noncured fraction progress through recurrence before dying of cancer, and write their survival time as the sum of the time to recurrence ( $T_1$ ) and the time from recurrence to death ( $T_2$ ; Fig. 1). We use external data on  $T_2$  to extract the survival curve for  $T_1$  by a method known as deconvolution, which assumes that the times  $T_1$  and  $T_2$  are statistically independent. We finally calculate the probability of progressing to recurrence by combining estimates of the cure fraction and  $T_1$ . We conduct sensitivity analyses to assess the robustness of our final estimates of the probability of progres-

sion to recurrence to model assumptions. We perform simulations to assess robustness of recurrence-free survival estimation to departures in some of the assumptions.

The disease-specific survival used as input to the method can be either net relative survival or net cause-specific survival (i.e., representing survival in the absence of other-cause death). All results are similarly interpreted as being in the absence of other-cause death. In the application to breast cancer data, we use cause-specific survival.

### Mixture cure survival modeling

We use mixture cure survival models (12–17) specified as

$$S(t; z) = c(z) + [1 - c(z)] S^*(t; z) \tag{A}$$

to estimate the cure fraction  $c$  and the survival time  $S^*$  for the noncured fraction  $1 - c$ , where both  $c$  and  $S^*$  can depend on covariates  $z$ . In the application, we consider  $S^*$  following a Weibull and log-logistic parametric survival function; however, the method could be generalized to other distributions. For simplicity, we will drop the covariates  $z$  from the notation.

### Analytical deconvolution method: estimating the time from diagnosis to recurrence

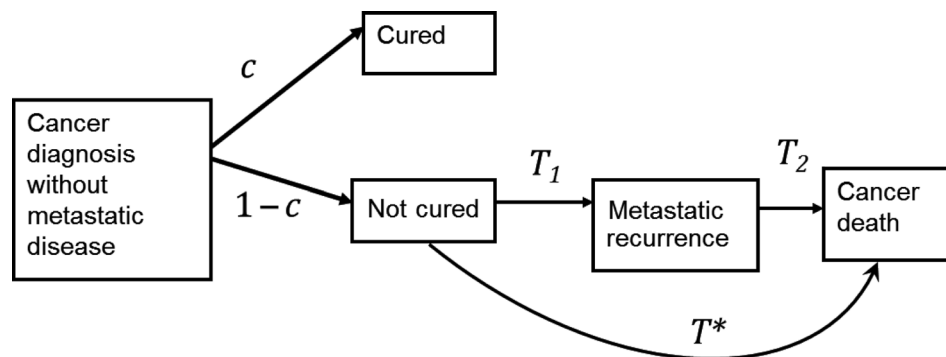
Assuming that a recurrence precedes a cancer death, we can write the survival time for the noncured fraction estimated previously from the cure model,  $T^*$ , as the sum of the time from diagnosis to recurrence  $T_1$  and from recurrence to death  $T_2$  (Fig. 1). Assuming independence between  $T_1$  and  $T_2$ , we can write the density function of  $T^*$  as

$$f^*(t) = \int_0^t f_1(u) f_2(t - u) du. \tag{B}$$

In the case that  $T_2$  is exponential  $f_2(t) = \theta e^{-\theta t}$ , an analytical estimate of  $f_1$  exists (18) and we show in the Supplementary Methods and Materials that the survival function of  $T_1$  is as follows:

$$S_1(t) = S^*(t) - \frac{1}{\theta} f^*(t). \tag{C}$$

In the case that  $T_2$  is not exponential, we provide in the Supplementary Methods and Materials a numerical solution to Eq. (B).



**Figure 1.**

Conceptual model of the diagnosis–recurrence–death pathway showing the key quantities calculated to produce the projections of the risk of recurrence based on cause-specific survival. After cancer diagnosis, a proportion  $c$  of patients are not at risk of dying of their cancer (cured) and a proportion  $1 - c$  is at risk of dying of their cancer (not cured). Those not cured will have a survival time to cancer death given by  $T^*$ , which can be written as the sum of  $T_1$ , the time from diagnosis to recurrence and  $T_2$ , the time from recurrence to cancer death.

### Estimation of survival from recurrence $T_2$

Solution of Eq. (B) requires an available estimate of the survival from recurrence to death. In the application to breast cancer, survival from recurrence to death is estimated as  $S_2 = (S_2^D)^r$ , where  $S_2^D$  is *de novo* metastatic breast cancer available from registry data and  $r$  is a cause-specific mortality rate ratio, i.e. a mortality hazard ratio. In our analysis, we use a value for  $r = 1.35$  from a study comparing *de novo* versus recurrence metastatic breast cancer survival (2) among women treated at a single institution.

### Estimating the risk of recurrence

Once we know  $S_1$ , we can calculate the recurrence-free survival probability at time  $t$ , as the probability of being cured or of being in the noncured group, but still being recurrence free as,

$$G(t) = c + (1 - c)S_1(t) \quad (D)$$

and the corresponding probability of progressing to recurrence as,

$$1 - G(t) = 1 - \{c + (1 - c)S_1(t)\} \quad (E)$$

The probability of being recurrence free at time  $t_2$  given recurrence free at time  $t_1$  is  $(1 - G(t_2))/(1 - G(t_1))$ .

### Application to breast cancer: SEER registry breast cancer cases

The Surveillance Epidemiology and End Results (SEER) Program collects clinical, demographic, and vital status information on all cancer cases diagnosed in defined geographic areas. Data included in this report are from female breast cancer cases diagnosed in SEER-13 registries (1992–2013; November 2016 submission), covering approximately 13% of the U.S. population.

Stage at diagnosis (I–IV) is defined using adjusted American Joint Committee on Cancer 6th edition staging classification (19). We further classify cases by the presence of estrogen receptor (ER) and progesterone receptor (PR). Hormone receptor status positive (HR<sup>+</sup>) is defined as ER-positive or borderline and/or PR-positive or borderline. HR<sup>-</sup> is defined as both ER negative and PR negative. We also present results for local and regional stage at diagnosis using the SEER historic stage.

Disease-specific survival is assessed via net cause-specific survival using the SEER\*Stat software (<https://seer.cancer.gov/seerstat/>). We chose cause-specific survival because early breast cancer relative survival is overestimated due to life tables not representing a healthy screening effect. Because cause of death based on death certificates may have misattribution biases, we use a modified cause-specific death assignment algorithm (20). This algorithm classifies as cancer specific any deaths that are likely to be related to the cancer and accommodates inconsistencies depending on whether the individual has one or multiple cancers (<https://seer.cancer.gov/causespecific/>).

The study population included women diagnosed with invasive breast cancer between ages 15 and 84 and years 1992–2013 in SEER-13 ( $N = 546,415$ ). We excluded women diagnosed through death certificate or autopsy ( $N = 1,375$ ), those with zero months of survival ( $N = 409$ ), those with

another primary cancer prior to the breast cancer ( $N = 90,121$ ), and those with missing or unknown stage, ER, or PR status ( $N = 70,127$ ). Women diagnosed with another cancer prior to the breast cancer are excluded because of difficulties in ascertaining their cause of death. The final study cohort included 381,430 women. We estimate cause-specific survival for each combination of stage, HR status, period (1992–1999 and 2000–2013) and grouped age (15–59, 60–74, and 75–84) all measured at diagnosis. The number of women included in each group is displayed in Table 1. We use the CanSurv software (<https://surveillance.cancer.gov/cansurv/>; ref. 12) to fit the log-logistic and Weibull mixture cure survival models to the survival data for breast cancer cases stratified by stage and HR status (I/HR<sup>+</sup>, I/HR<sup>-</sup>, II/HR<sup>+</sup>, II/HR<sup>-</sup>, III/HR<sup>+</sup>, and III/HR<sup>-</sup>) and age group. Period of diagnosis is entered as a predictor for the cure fraction and survival for those not cured.

To estimate the survival from recurrence,  $T_2$ , we used as the base survival  $S_2^D$ , the cause-specific survival for women diagnosed with *de novo* stage IV breast cancer in the SEER-13 areas, stratified by grouped calendar year at diagnosis (1992–1999 and 2000–2013), age at diagnosis (15–59, 60–74, and 75–84), and HR status. We estimate  $r = 1.35$  using published results from a study comparing *de novo* versus recurrence metastatic breast cancer survival from an institutional cohort of patients with breast cancer (2).

### Sensitivity analyses and simulation studies to interrogate robustness of results to key model assumptions

Sensitivity analyses addressed the assumption of cure, distributional assumptions within the cure model, and the assumed value of the hazard ratio  $r$ . We considered two different distributions for survival of the noncured fraction, namely Weibull and log-logistic. To assess the assumption of cure, we fitted a log-logistic survival without cure to stage III breast cancer cause-specific survival and applied the deconvolution method to the fitted survival. To evaluate the impact of the adjustment factor,  $r$  we provide results for a range of  $r$  values from 1.0 to 1.7. We developed a nonparametric deconvolution method that did not assume an exponential distribution for  $T_2$  and used simulations to explore the impact of the assumption of independence between  $T_1$  and  $T_2$ . We also used simulation to explore the impact of misspecifications of the survival distribution for  $T_2$ . Simulations and their results are fully described in the Supplementary Methods and Materials. Simulations parameters are displayed in Supplementary Table 1.

## Results

### Breast cancer survival and fit to the mixture cure models

The observed 5- and 10-year breast cancer survival is higher for women diagnosed in the most recent period, at younger ages, less advanced stage, and HR<sup>+</sup> tumors (Table 1). Observed *de novo* stage IV breast cancer survival is higher in the most recent period, younger ages, and ER<sup>+</sup>. The mixture log-logistic cure models fit well the observed data (Fig. 2) especially for younger women diagnosed at ages 15–59 and 60–74. For the older age group and stages II and III, in which there are a small number of cases and more variability in observed breast cancer survival, the model fit well up to 15 years.

**Table 1.** Number of cases for the different groupings and breast cancer cause-specific survival (CS) and respective SE by stage, age, period, and HR status at diagnosis in percent

Stage/ age	Time from diagnosis, years	Number of cases at beginning of interval (N) breast cancer survival in percent											
		HR-positive						HR-negative					
		1992-1999			2000-2013			1992-1999			2000-2013		
		N	CS (%)	SE (%)	N	CS (%)	SE (%)	N	CS (%)	SE (%)	N	CS (%)	SE (%)
I/15-59	5	19,616	98.3	0.1	37,281	99.1	0.0	4,894	93.2	0.4	7,348	95.0	0.2
	10		95.3	0.2		97.2	0.1		89.0	0.5		91.9	0.3
I/60-74	5	18,313	98.0	0.1	29,399	98.7	0.1	2,701	93.5	0.5	3,932	95.4	0.3
	10		94.5	0.2		96.5	0.1		88.9	0.6		92.1	0.5
I/75-84	5	7,748	96.4	0.2	11,650	97.2	0.1	895	92.0	0.9	1,220	90.7	0.8
	10		91.1	0.4		92.8	0.3		85.7	1.3		82.6	1.3
II/15-59	5	14,993	93.2	0.2	29,057	95.8	0.1	6,208	81.4	0.5	9,254	86.0	0.3
	10		85.3	0.3		89.6	0.2		75.8	0.5		81.5	0.4
II/60-74	5	9,220	92.5	0.3	15,145	95.0	0.2	2,137	79.8	0.9	3,171	84.0	0.6
	10		83.8	0.4		88.0	0.3		72.4	1.0		77.9	0.7
II/75-84	5	4,318	90.1	0.5	5,669	90.3	0.4	781	71.7	1.7	933	74.8	1.1
	10		79.4	0.7		80.4	0.6		64.3	1.9		66.7	1.5
III/15-59	5	6,930	76.7	0.5	10,051	83.6	0.3	3,054	51.6	0.9	2,919	59.4	0.7
	10		59.6	0.6		67.6	0.5		44.3	0.9		51.7	0.8
III/60-74	5	3,741	72.4	0.8	4,127	80.5	0.5	1,116	48.8	1.5	996	59.5	1.1
	10		53.7	0.9		65.1	0.8		39.2	1.5		50.5	1.3
III/75-84	5	1,657	67.7	1.2	1,372	69.2	1.0	420	39.2	2.5	285	45.6	1.9
	10		49.0	1.5		51.4	1.4		26.7	2.4		35.1	2.2
IV/15-59	5	1,245	29.9	1.3	1,277	36.6	0.8	494	13.8	1.6	241	19.2	1.1
	10		13.3	1.0		16.1	0.9		10.1	1.4		13.1	1.1
IV/60-74	5	1,127	23.3	1.3	714	30.1	1.0	327	7.2	1.5	98	13.7	1.3
	10		10.7	1.0		12.6	0.9		4.4	1.2		9.7	1.4
IV/75-84	5	550	21.8	1.9	234	21.7	1.4	149	8.3	2.4	23	8.7	1.8
	10		11.1	1.7		7.9	1.3		5.3	2.1		5.4	1.8

**Projected percent recurring within specified intervals from diagnosis**

Table 2 reports risk of recurrence estimates together with 95% confidence intervals (CIs) by stage, HR status, age, and calendar year at diagnosis. Risks of recurrence within 5, 10, or 15 years are lower in more recent diagnosis years and for cases with less advanced disease, HR<sup>+</sup> tumors, and younger age at diagnosis. For women diagnosed at ages 60-74 in 2000-2013, the percent recurring within 5 years is 2.5%, 9.6%, and 34.5% for stages I, II, and III HR<sup>+</sup> tumors and 6.5%, 20.2%, and 48.5% for stages I, II, and III HR<sup>-</sup> tumors, respectively. Aggregating the data for all stages and all HR status, our most contemporary estimates suggest that 19 percent of women diagnosed with stage I-III breast cancer will progress to MBC within 20 years of diagnosis (Supplementary Table 3).

Table 3 shows the percent recurring within the next 5 years conditional on being alive and recurrence free at 0, 5, and 10 years from diagnosis. In general, the risk is higher in the first 5 years after diagnosis and lower among women who are recurrence free at 5 and 10 years after diagnosis. In later intervals, the risk declines most for HR<sup>-</sup> tumors stages II and III. For example, for women diagnosed in (2000-2013) at ages 60-74 with stage II HR<sup>-</sup> breast cancer, the fraction recurring in the next 5 years given recurrence free at 0, 5, and 10 years from diagnosis are, respectively, 20.2%, 4.1%, and 1.2%. The clear exception is stage I HR<sup>+</sup>, for which conditional probabilities of recurring do not change, and even slightly increase, with survival time.

**Sensitivity analyses**

The estimated risk of recurrence is robust to the adjustment factor *r* used to estimate the survival from recurrence (Table 4A). The greatest sensitivity to this factor was observed for stage III/HR<sup>+</sup> tumors. Smaller differences for different

adjustment factors were observed for HR<sup>-</sup> tumors and longer intervals after diagnosis.

Even although the cure fraction differed between the log-logistic and Weibull models, the risk of progressing to recurrence was very similar irrespective of the cure model used (Table 4B). For example, the cure fraction estimates were 64% versus 74% for stage II ER<sup>+</sup> breast cancer in 2000-2013 using log-logistic and Weibull, respectively, and the estimated recurrence probabilities were 16.6% in both cases. The table also shows that the analytical deconvolution method that assumed an exponential distribution *T*<sub>2</sub> produced similar results to the numerical deconvolution method. Estimates varied more in the initial years (up to 5 years) after diagnosis.

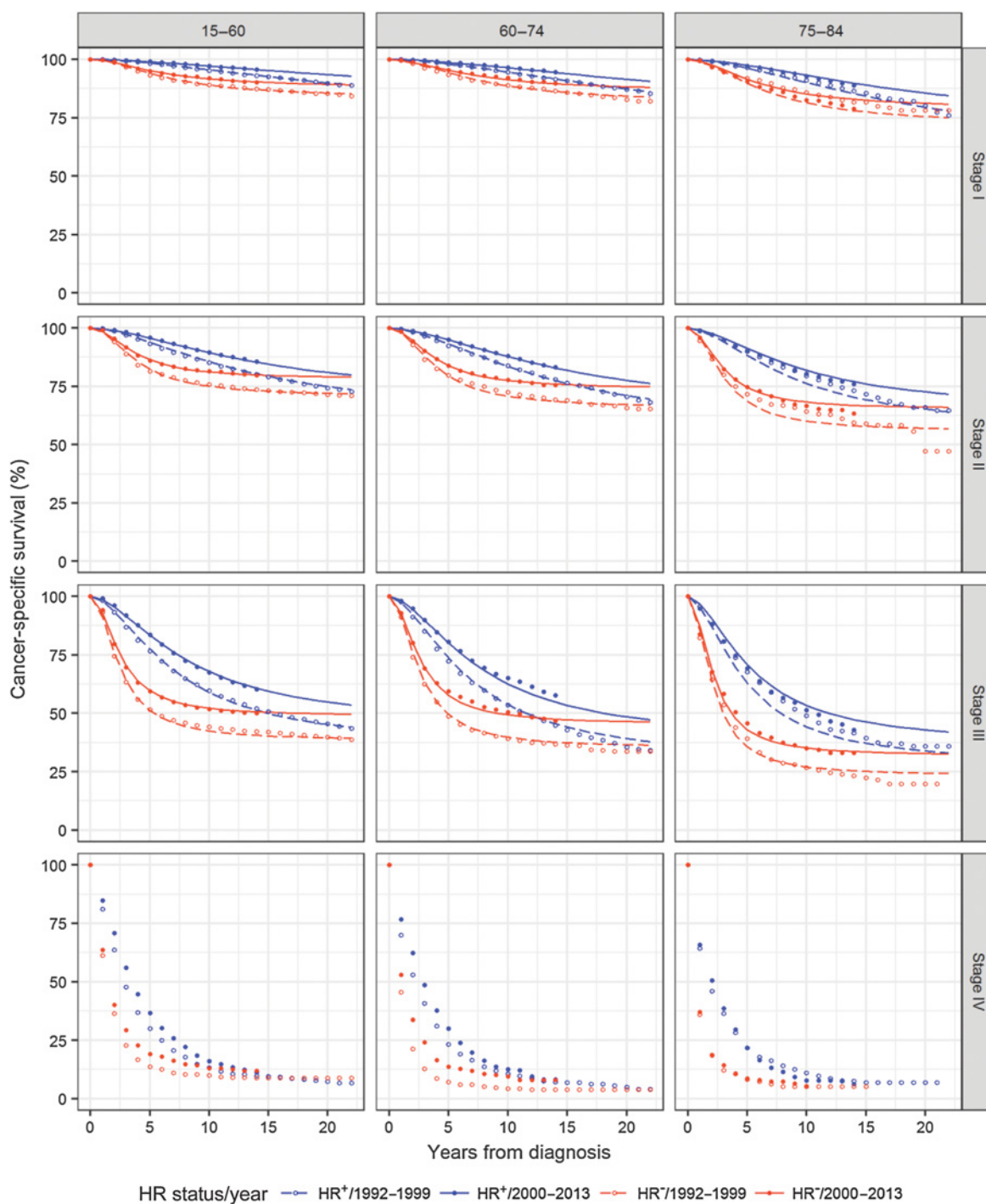
When we did not specify a cure model and applied the deconvolution method directly to a log-logistic survival without cure, fitted to the net cause-specific survival, we found modest absolute differences (still smaller than 6.5%) in the percent recurring at 10 years (Table 4C). The largest differences were for women diagnosed with stage III ER<sup>-</sup> tumors in 2000-2013, where 51.9% progressed to recurrence after 10 years under the cure model versus 59.3% assuming no cure. For ER<sup>+</sup> tumors, the differences were smaller (less than 4%) when we assumed no cure.

Simulations results (Supplementary Table 2) showed that estimates assuming independence between the times from diagnosis to recurrence and from recurrence to death were robust to generated data that departed from these assumptions. The largest biases occurred when *S*<sub>2</sub> was misspecified with a much lower median survival compared with the true distribution of *T*<sub>2</sub>.

**Discussion**

Although U.S. cancer registries play a vital role in tracking the population incidence of cancer, they are generally limited in

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**Figure 2.** Observed cause-specific survival (points) and fitted log-logistic mixture cure survival model (lines) for women diagnosed with breast cancer in the SEER-13 areas by stage at diagnosis, HR status and period at diagnosis. The last row of figures represents the observed cause-specific survival for *de novo* stage IV breast cancer.

their ability to capture postdiagnosis events other than mortality. This article provides a blueprint for a method that uses existing data to overcome this deficiency and a demonstration of its value in estimating the risk of metastatic breast cancer recurrence.

**Model assumptions and robustness**

The key assumptions of the method are (i) a cure model is appropriate for net disease-specific survival among cases that are not metastatic at diagnosis; (ii) the time from metastatic recurrence to death is exponential if the analytical method is

**Table 2.** Estimated percent progressing to metastatic recurrence within 5, 10, or 15 years and respective 95% CIs in parentheses by stage, HR status, age, and years at diagnosis

Stage	Year at diagnosis	Years from diagnosis	Fraction recurring in percent (95% CI)					
			HR-positive			HR-negative		
			Age: 15-59	60-74	75-84	15-59	60-74	75-84
I	1992-99	5	3.4 (3.2-3.7)	3.7 (3.4-3.9)	6.8 (6.0-7.5)	8.7 (7.9-9.6)	7.3 (6.5-8.1)	12.5 (10.8-14.2)
		10	6.6 (6.3-7.0)	7.6 (7.2-8.0)	13.2 (12.4-14.0)	12.3 (11.5-13.1)	12.2 (11.2-13.2)	19.8 (17.7-21.8)
		15	9.5 (9.0-9.9)	11.3 (10.8-11.8)	18.6 (17.3-19.8)	13.9 (13.0-14.8)	14.6 (13.5-15.8)	23.1 (20.5-25.6)
I	2000-13	5	2.3 (2.1-2.4)	2.5 (2.4-2.7)	4.5 (4.2-4.8)	7.2 (6.6-7.8)	6.5 (5.9-7.2)	10.3 (9.0-11.6)
		10	4.4 (4.1-4.6)	5.2 (4.9-5.5)	9.0 (8.4-9.5)	9.4 (8.7-10.1)	9.7 (8.9-10.6)	15.6 (13.8-17.4)
		15	6.2 (5.6-6.8)	7.8 (7.2-8.4)	12.9 (11.8-13.9)	10.4 (9.6-11.2)	11.2 (10.1-12.3)	17.9 (15.6-20.1)
II	1992-99	5	12.4 (11.7-13.0)	12.6 (11.8-13.3)	19.4 (18.2-20.7)	23.0 (21.6-24.3)	24.1 (22.7-25.5)	35.0 (32.7-37.4)
		10	19.9 (19.2-20.6)	21.5 (20.6-22.3)	28.6 (27.2-30.0)	26.3 (25.3-27.4)	30.2 (28.7-31.6)	40.7 (38.1-43.2)
		15	24.6 (23.9-25.3)	27.4 (26.5-28.3)	33.5 (31.7-35.3)	27.6 (26.5-28.6)	32.1 (30.5-33.7)	42.3 (39.6-45.0)
II	2000-13	5	9.3 (8.9-9.7)	9.6 (9.2-10.1)	14.1 (13.3-14.9)	18.2 (17.2-19.1)	20.2 (19.0-21.4)	28.1 (26.1-30.1)
		10	15.1 (14.6-15.6)	16.6 (16.0-17.2)	21.8 (20.7-22.9)	19.9 (19.2-20.7)	23.5 (22.2-24.7)	32.2 (30.0-34.5)
		15	18.8 (17.9-19.7)	21.4 (20.4-22.4)	26.1 (24.4-27.7)	20.7 (19.9-21.5)	24.6 (23.3-26.0)	33.4 (31.0-35.8)
III	1992-99	5	40.7 (39.0-42.5)	42.5 (40.7-44.4)	53.3 (50.7-55.8)	56.4 (54.3-58.5)	55.2 (53.1-57.4)	68.3 (65.5-71.2)
		10	50.3 (49.0-51.5)	54.3 (52.8-55.7)	61.5 (59.2-63.7)	59.0 (57.3-60.6)	61.1 (59.0-63.3)	73.6 (70.7-76.5)
		15	54.7 (53.5-55.9)	59.8 (58.2-61.3)	65.2 (62.7-67.8)	60.1 (58.5-61.7)	62.8 (60.6-65.1)	75.1 (72.1-78.0)
III	2000-13	5	32.1 (31.1-33.2)	34.5 (33.1-35.8)	42.3 (40.3-44.4)	47.8 (46.1-49.6)	48.5 (46.4-50.7)	60.6 (57.5-63.8)
		10	41.1 (39.9-42.3)	45.5 (43.9-47.0)	51.8 (49.4-54.1)	49.2 (47.7-50.6)	51.9 (49.7-54.0)	65.4 (62.1-68.8)
		15	45.3 (43.7-46.8)	50.7 (48.7-52.8)	56.0 (53.2-58.8)	50.0 (48.5-51.5)	53.1 (50.8-55.4)	66.8 (63.3-70.3)
<b>Historical stage</b>			<b>Local</b>			<b>Regional</b>		
	2000-13	5	6.1 (5.8-6.4)	5.3 (5.0-5.5)	7.7 (7.3-8.2)	23.1 (22.2-24.1)	21.6 (20.7-22.5)	26.6 (25.4-27.9)

NOTE: The results used the analytical deconvolution method and the log-logistic cure mixture model and represent probabilities in the absence of other causes of death. Survival from recurrence used an adjustment of HR  $r = 1.35$  compared with *de novo* distant-stage breast cancer. Estimates using historical stage for women diagnosed with breast cancer in 2000-2013 are also presented.

used (the numerical method does not require the assumption); (iii) the survival hazard after metastatic recurrence is a known multiple  $r$  of the survival from *de novo* metastatic diagnosis; and (iv) time from diagnosis to recurrence does not influence the time from recurrence to death.

The method uses a cure model for net cancer survival. Cure fraction estimates and their interpretation as cure are problematic when risk of cancer death (or excess mortality in the case of relative survival) persists over the long term (15, 20). In these situations, cure models may not converge, and if they do, different cure models often yield different estimates for the cure fraction. We found that the log-logistic model provided a better fit to the observed data and converged in all settings, whereas the Weibull did not converge for stage I HR<sup>+</sup> breast cancer survival. However, when both models converged and cure fraction estimates differed, the estimated recurrence probabilities were ultimately very similar. The projected probability of recurrence is robust within the observed follow-up

time, probably because it mimics the functional form of the mixture cure model  $[c + (1 - c) S^*]$  that fits the observed data. Furthermore, sensitivity analyses assuming no cure for stage III breast cancer showed that the estimates of the risk of recurrence were only modestly different from the estimates assuming a cure model. In principle, if excess mortality persists over the long term and the notion of cure is not applicable the deconvolution method can be applied to disease-specific survival without cure. However, if the cure model fits the data well at the end of follow-up and provides a nontrivial cure probability, as in our application, we would recommend it be used.

Our main results use an analytical approach to extract the recurrence-free survival from the noncured survival distribution, which assumes an exponential distribution for the time from recurrence to death. However, results are similar under a flexible, smooth distribution (numerical approach). Furthermore, simulations using data generated from a nonexponential

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**Table 3.** Conditional probabilities of progressing to metastatic recurrence (MR) in the absence of other causes of death in an interval given being alive and recurrence free at the beginning of interval by stage, HR status, grouped age, and years at diagnosis

	Years from diagnosis	Percent progressing to MR among women recurrence free at the beginning of the interval					
		HR-positive			HR-negative		
		15-59	60-74	75-84	15-59	60-74	75-84
Stage I							
1992-1999	0-5	3.4%	3.7%	6.8%	8.7%	7.3%	12.5%
	5-10	3.3%	4.1%	6.9%	3.9%	5.3%	8.3%
	10-15	3.0%	4.1%	6.2%	1.8%	2.8%	4.1%
2000-2013	0-5	2.3%	2.5%	4.5%	7.2%	6.5%	10.3%
	5-10	2.1%	2.7%	4.7%	2.4%	3.4%	5.9%
	10-15	1.9%	2.7%	4.3%	1.1%	1.6%	2.7%
Stage II							
1992-1999	0-5	12.4%	12.6%	19.4%	23.0%	24.1%	35.0%
	5-10	8.6%	10.2%	11.4%	4.4%	8.0%	8.7%
	10-15	5.9%	7.6%	6.9%	1.7%	2.8%	2.8%
2000-2013	0-5	9.3%	9.6%	14.1%	18.2%	20.2%	28.1%
	5-10	6.4%	7.7%	8.9%	2.2%	4.1%	5.7%
	10-15	4.4%	5.7%	5.5%	0.9%	1.5%	1.7%
Stage III							
1992-1999	0-5	40.7%	42.5%	53.3%	56.4%	55.2%	68.3%
	5-10	16.1%	20.4%	17.5%	5.9%	13.1%	16.6%
	10-15	8.9%	12.0%	9.8%	2.8%	4.5%	5.5%
2000-2013	0-5	32.1%	34.5%	42.3%	47.8%	48.5%	60.6%
	5-10	13.2%	16.8%	16.3%	2.6%	6.4%	12.2%
	10-15	7.1%	9.7%	8.7%	1.7%	2.5%	3.9%

NOTE: The results used the analytical deconvolution method and the log-logistic cure mixture model. Survival from recurrence used an adjustment of HR  $r = 1.35$  compared with *de novo* distant-stage breast cancer.

distribution for the time from recurrence showed the estimates of the recurrence-free survival to be robust, so long as the median time from recurrence is relatively close to the true median value.

We use a mortality hazard ratio  $r = 1.35$  (2) to relate the survival from recurrence to the survival from *de novo* metastatic diagnosis. A factor higher than 1 represents poorer survival from recurrence compared with survival from *de novo* metastatic diagnosis and accounts for greater susceptibility to the cancer as well as greater vulnerability to treatment morbidities because of the accumulation of cancer treatments. In principle, this hazard ratio may vary by patient factors such as age at diagnosis and HR status. Further studies are needed to more comprehensively establish how *de novo* metastatic survival relates to recurrent metastatic survival. We find that our results are very robust across a wide range of plausible adjustment values, from  $r = 1.35$  to  $r = 1.7$ .

Our method can account for some association between time to recurrence and time from recurrence to death by stratifying survival and analyses. We stratified by age, stage, period, and HR status in our application. Within each stratum, there may be residual association between the times from diagnosis to recurrence and from recurrence to death. Simulations incorporating this association have shown that it does not materially affect results (see Supplementary Table 2).

**Application to breast cancer**

Our results provide novel insights into how the risk of recurrence varies with breast cancer stage, HR status, age, year of diagnosis, and time since diagnosis. Because we require at least 10 years of follow-up for our analysis, we were not able to examine recurrence risk by human epidermal growth factor receptor (HER2) status, which has only been collected by SEER since

2010. In addition, adjuvant treatment information in the SEER data is incomplete and could not be incorporated in the estimates. Thus, the estimates reflect the risk of recurrence under observed patterns of care.

Some broad trends are immediately apparent. These include a decline in the risk of recurrence in the more recent time period, a trend toward a worse risk in older cases, and a higher risk of recurrence among HR<sup>-</sup> cases soon after diagnosis that rapidly declines thereafter. Furthermore, although HR<sup>+</sup> cases have lower risk of recurrence soon after diagnosis, their risk persists for longer than is the case for HR<sup>-</sup> cases. The patterns are similar to those observed in two Canadian cohorts diagnosed from 1992–2002 and 2004–2008, respectively (4).

It is likely that decreased risk for more recent diagnoses reflects the benefits of novel targeted treatments such as taxanes (21), aromatase inhibitors (22), and a dose-dense chemotherapy schedule (23), since screening and adjuvant chemotherapy had largely disseminated in the U.S. population by the end of the 1980s (24, 25). A major development in 2005 was the rapid adoption of trastuzumab for early-stage HER2-positive breast cancer (26–28). Although we could not include HER2 status as a predictor in this analysis due to lack of measurement in the registry until recently, HER2-targeted therapy likely contributed to the decline in recurrence that we observed in the later interval. We do not expect screening to have played a role in the observed trends with year of diagnosis since mammography screening had more or less fully disseminated within the U.S. population by the start of the diagnosis period considered.

Increases in the risk of recurrence among older women are consistent with reduced use of systemic chemotherapies as patients age (25). Results from an international study also show that the risk of breast cancer recurrence increases with age for

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**Table 4.** Sensitivity of estimated percent progressing to metastatic recurrence to the adjustment HR  $r$  (A), the numerical and analytical solution using log-logistic and Weibull mixture cure survival models (B), and  $r = 1.35$  and the assumption of no cure for women diagnosed with stage III breast cancer (C)

		Percent progressing to recurrence							
		A. Sensitivity to the adjustment $r$ of the <i>de novo</i> stage IV breast cancer survival							
		HR-positive				HR-negative			
Years from diagnosis		$r = 1.0$	$r = 1.35$	$r = 1.5$	$r = 1.7$	$r = 1.0$	$r = 1.35$	$r = 1.5$	$r = 1.7$
Stage I	5	3.0%	2.5%	2.4%	2.3%	7.2%	6.5%	6.3%	6.1%
	10	5.8%	5.2%	5.0%	4.9%	10.1%	9.7%	9.6%	9.5%
	15	8.3%	7.8%	7.6%	7.4%	11.4%	11.2%	11.2%	11.1%
Stage II	5	11.3%	9.6%	9.2%	8.7%	21.7%	20.2%	19.8%	19.4%
	10	18.1%	16.6%	16.2%	15.7%	23.8%	23.5%	23.4%	23.3%
	15	22.5%	21.4%	21.1%	20.7%	24.7%	24.6%	24.6%	24.5%
Stage III	5	39.6%	34.5%	33.0%	31.4%	50.8%	48.5%	47.9%	47.2%
	10	48.3%	45.5%	44.7%	43.8%	52.3%	51.9%	51.7%	51.6%
	15	52.2%	50.7%	50.3%	49.9%	53.2%	53.1%	53.0%	53.0%

		B. Sensitivity to log-logistic vs. Weibull assumption							
		HR-positive				HR-negative			
Stage/Year at diagnosis	Years from diagnosis	Cure log-logistic		Cure Weibull		Cure log-logistic		Cure Weibull	
		Analytical	Numerical	Analytical	Numerical	Analytical	Numerical	Analytical	Numerical
Stage I/	Cure fraction	65%		n.a.		81%		83%	
1992-1999	5	3.7%	3.0%	n.a.	n.a.	7.3%	6.6%	6.5%	5.9%
	10	7.6%	6.9%	n.a.	n.a.	12.2%	12.0%	11.7%	11.4%
Stage I/	Cure fraction	75%		n.a.		86%		88%	
2000-2013	5	2.5%	2.2%	n.a.	n.a.	6.5%	5.8%	6.3%	5.6%
	10	5.2%	4.9%	n.a.	n.a.	9.7%	9.7%	9.8%	9.7%
Stage II/	Cure fraction	56%		65%		66%		67%	
1992-1999	5	12.6%	10.6%	12.0%	10.1%	24.1%	22.8%	21.4%	19.9%
	10	21.5%	20.3%	21.3%	20.0%	30.2%	30.3%	30.1%	30.0%
Stage II/	Cure fraction	64%		74%		74%		75%	
2000-2013	5	9.6%	8.6%	9.5%	8.5%	20.2%	19.3%	19.7%	18.5%
	10	16.6%	16.0%	16.6%	16.0%	23.5%	24.1%	23.8%	24.5%
Stage III/	Cure fraction	29%		37%		35%		37%	
1992-1999	5	42.5%	38.0%	39.8%	34.9%	55.2%	54.4%	52.9%	51.0%
	10	54.3%	53.6%	55.1%	53.9%	61.1%	61.7%	61.9%	62.5%
Stage III/	Cure fraction	38%		48%		45%		47%	
2000-2013	5	34.5%	32.0%	33.4%	30.9%	48.5%	48.4%	48.5%	47.5%
	10	45.5%	45.1%	45.9%	45.5%	51.9%	53.7%	52.4%	52.7%

		C. Sensitivity to the cure assumption: log-logistic with no cure (cure = 0%)			
		No cure log-logistic		No cure log-logistic	
Stage III		Analytical	Numerical	Analytical	Numerical
1992-1999	5	40.0%	35.7%	49.7%	48.0%
	10	55.5%	53.9%	63.9%	63.6%
2000-2013	5	30.8%	28.4%	45.1%	43.2%
	10	45.4%	44.5%	58.3%	58.8%

NOTE: Results are shown for women diagnosed at ages 60-74 years.

patients included in the Tamoxifen Exemestane Adjuvant Multi-national Trial (29).

Our observation that the risk of recurrence declines sharply over time from diagnosis for women with HR<sup>-</sup> tumors is consistent with results from other studies that show the hazard of breast cancer mortality is initially higher for HR<sup>-</sup> cases but drops below that of HR<sup>+</sup> cases 3 to 5 years after diagnosis (4, 30-33). Although women with stage I HR<sup>+</sup> tumors have very low risk of recurrence, their risk remains somewhat constant even after remaining recurrence free 5 or 10 years after diagnosis.

The cause of the observed differences in recurrence patterns by HR status is not fully understood. One possible explanation is a cure/no cure distribution of HR<sup>-</sup> breast tumors, with some HR<sup>-</sup> cancers being cured by adjuvant chemotherapy (and thus never recurring), whereas the remainder recur quickly due to their aggressive biology (34). The reasons for differential response

to chemotherapy are a subject of intense study, and part of the answer may lie in genetic susceptibility. Studies have reported superior response to chemotherapy among HR<sup>-</sup> cancers in *BRCA1/2* mutation carriers (35, 36) and these findings might extend to other newly recognized causes of genetic susceptibility to HR<sup>-</sup> breast cancer (37). With HR<sup>+</sup> breast cancer, the persistent risk of recurrence more than a decade after diagnosis has prompted trials of extended adjuvant endocrine therapy, with some showing modest benefits (38, 39) and others yielding less conclusive findings (40-42). A possible explanation is that endocrine therapy may act to delay recurrence in many HR<sup>+</sup> tumors, rather than achieving a cure.

Our results are quite consistent with international studies that routinely collect recurrence information for their national registries. A study in the Munich Cancer Register reported a 5-year breast cancer recurrence risk of 10% for 18,592 patients with no distant metastases at diagnosis between 1995 and 2003

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(43). Data from cancer registry of nonmetastatic breast cancer cases in Australia (44) estimated that the risk of developing a distant recurrence within 5 years was 5.3% (95% CI, 4.6%–6.0%) for women with localized node-negative disease and 18.1% (95% CI, 16.7%–19.7%) for women with regional breast cancer. Our estimates are slightly higher compared with the Australian registry results: the probabilities of progressing to recurrence within 5 years range from 6.1% to 7.7% for localized and 21.6% to 26.6% for regional breast cancer, respectively, depending on age at diagnosis (Table 2). This is consistent with the exclusion of women progressing to metastatic breast cancer within 120 days of diagnosis in the Australian study.

Our estimates use net cancer-specific survival and represent net risk of metastatic recurrence in the absence of other-cause death. Because they isolate the effect of cancer on survival by removing the effects of competing mortality, they are useful as cancer control measures for tracking progress against cancer over time or for comparisons across groups of patients. They are limited to risk groups reflected by patient and disease characteristics routinely captured by cancer registries, and reflect patterns of postdiagnosis surveillance and treatment as observed at the population level. These results are highly relevant to the great majority of U.S. cancer patients who are treated in the community setting, but they are not designed to be used for individual treatment decision making. Because our estimates do not include the chances of dying of other causes, they are less useful for individualized predictions and clinical decision making; future work will develop probabilities of recurrence under competing risks.

In conclusion, there is an urgent need for population-representative estimates of cancer recurrence risks. Our results are the first developed for the U.S. population and are likely to add materially to the information currently provided by registry

data. We anticipate that the approach will be applicable to other cancers, in particular those amenable to mixture cure modeling, enhancing our understanding of the burden of cancer in the population.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCI or the NIH.

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### Acknowledgments

This work was supported by the NCI at the NIH.

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Received December 6, 2017; revised February 27, 2018; accepted July 27, 2018; published first October 18, 2018.

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