Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Hazard of Recurrence among Women after Primary Breast Cancer Treatment—A 10-Year Follow-up Using Data from SEER-Medicare

Lee Cheng[1], Michael D. Swartz[3], Hui Zhao[3], Asha S. Kapadia[3], Dejian Lai[3], Paul J. Rowan[4], Thomas A. Buchholz[5], and Sharon H. Giordano[2]

Abstract

Background: Few studies have used SEER-Medicare data to describe recurrence of breast cancer after primary treatment for U.S. women.

Methods: We used SEER-Medicare data to estimate the annual hazard rate (HR) of recurrence for women with breast cancer between 1991 and 1997 with 10 years of follow-up. The Kaplan–Meier method was used to derive the HR. Multivariate Cox proportional hazards model was used to estimate the relative hazard of the recurrence-associated prognostic factors.

Results: Of 20,027 women, 36.8% had recurrence within 10 years, with most of these recurrences (81.9%) occurring within 5 years after diagnosis. Women with stage III cancer showed the highest HR peak and largest magnitude than women with stage I or II disease (both $P < 0.01$) within the first 5 years. Women with negative tumor hormone receptor status had a higher peak hazard of developing recurrence within the first 5 years ($P < 0.01$), but the hazards were remarkably lower beyond 5 years of follow-up than in women with positive or unknown hormone receptor status ($P > 0.05$). Women with poorly differentiated histologic grade tumors showed higher HR in the first 5 years than women with other grades after primary treatment (both $P < 0.01$). The increased risk of recurrence of breast cancer was associated with advanced stage, moderate and poorly differently grades, and negative hormone receptor status (all $P < 0.01$).

Conclusion: The HRs of the recurrence are dynamic over 10 years and are markedly determined by prognostic factors at diagnosis.

Impact: Our study suggests that the optimal follow-up may differ among women. *Cancer Epidemiol Biomarkers Prev; 21(5); 800–9. ©2012 AACR.*

Introduction

Breast cancer has one of the highest incidences among all cancers in women. For example, in 2010, an estimated 207,090 new cases of invasive breast cancer were expected to be diagnosed and about 39,840 women were expected to die of the disease (1). Because more breast cancers are being detected at earlier stages and are being treated more frequently with adjuvant chemotherapy, patients are surviving longer (2). The most recent data indicate that the relative survival rates for women diagnosed with breast cancer are 82% at 10 years after diagnosis and 75% after 15 years (1).

Authors' Affiliations: Departments of [1]Clinical Effectiveness and [2]Breast Medical Oncology, Divisions of [3]Biostatistics, [4]Management, Policy, and Community Health, and [5]Radiation Oncology, The University of Texas School of Public Health at Houston, Houston, Texas

Corresponding Author: Lee Cheng, Department of Clinical Effectiveness, Unit 1425, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Phone: 713-794-3223; Fax: 713-792-8427; E-mail: lcheng@mdanderson.org

doi: 10.1158/1055-9965.EPI-11-1089

Surveillance care after primary cancer treatment is a new area of research for the care of cancer survivors in recent years (3–7). Several organizations have provided guidelines for clinical surveillance or follow-up of women after breast cancer treatment (4, 5, 8), including the American Society of Clinical Oncology (ASCO), which recommends periodic outpatient clinic visits for the patient to be examined for a possible recurrence or a second primary breast tumor and also to receive information and psychosocial support. The recommended schedules involve clinic visits every 3 to 6 months for the first 3 years, visits every 6 to 12 months for years 4 and 5, and annual visits after 5 years (9).

The hazard function is a sensitive tool for describing the patterns of event occurrence. Examining the hazard function itself in detail can reveal important properties of the disease (10). By examining the variation over time in the magnitude of the hazard function of breast cancer recurrence, we can identify when breast cancer recurrence is most likely or less likely to occur and can develop a general profile of risk over time.

Early studies have explored the distribution of the recurrence pattern in women with breast cancer from

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

different patient populations (11–19). However, few studies have used the extensive SEER-Medicare data to describe the changes of hazard on recurrence timing for women with breast cancer in the U.S. population. In the current study, we used SEER-Medicare data to identify recurrences over a 10-year period for women diagnosed with breast cancer between 1991 and 1997. We included only those women with American Joint Committee on Cancer (AJCC) stage I, II, or III invasive breast cancer identified in SEER data, and we then generated a hazard function of incidence of the first recurrence events considering the major prognostic factors over 10 years.

Materials and Methods

Patients

We used the SEER-Medicare linked database for this study. The SEER program, supported by the U. S. National Cancer Institute (NCI), collects data from tumor registries; during the years included in this study, the database covered 14% to 25% of the U.S. population. The Medicare program is administered by the Centers for Medicare and Medicaid Services and covers 97% of the U.S. population ages 65 years and older. The SEER participants are matched with their Medicare records under an agreement between the National Cancer Institute and the Centers for Medicare and Medicaid Services. Of SEER participants who were diagnosed with cancer at age 65 years or above, 94% are matched with their Medicare enrollment records.

Women between 65 and 80 years of age at the diagnosis of breast cancer [cancer site labeled "breast" by ICD-O-3 codes (C50.0–C50.9)] between 1991 and 1997 were included in this study. We included only those women with AJCC stage I, II, or III invasive breast cancer in the SEER data. Patients with breast cancer diagnosed between 1991 and 1997 were then linked to their Medicare claims from years 1991 through 2007. Patient demographics and tumor characteristics at the time of diagnosis were extracted from the SEER-Medicare Patient Entitlement and Diagnosis Summary File (PEDSF). Patient treatment information about surgery, radiation, and chemotherapy were extracted from Medicare claims files for durable medical equipment (DME), physician (NCH), inpatient service (MEDPAR), and outpatient service files (OUTPAT). The study was reviewed and approved by the Institutional Review Board.

Identifying first recurrence events of breast cancer

To define recurrence, we modified the method by Earle and colleagues (20). We excluded women with a second primary cancer, including breast cancer, within 10 years after primary breast cancer diagnosis. We also excluded those women who died within 6 months after the primary diagnosis. In most circumstances, women with recurrent breast cancer receive treatment without delay, suggesting that initiation of new treatment likely corresponds to the time of recurrence. We defined a woman who had received chemotherapy, radiation, or surgery according to Medicare claim whenever there was a claim for chemotherapy administration, radiation, or surgery conducted in any of 3 Medicare claims categories from outpatient setting, inpatient setting, or physician file. Surgical treatments for breast cancer were defined as patients who received breast-conserving surgery or mastectomy. If a woman initially received breast-conserving surgery, but involved mastectomy within time frame, the woman was classified in the mastectomy group. The initial primary treatment was defined as having selected claim codes 1 month before or within 4 months after the date of diagnosis in SEER. Treatment for the first recurrence was defined as a claim for chemotherapy administration, radiation, or surgery 3 months or more after the end of initial primary treatment without encountering therapeutic chemotherapy, radiotherapy, or surgery. We were not able to evaluate treatment with hormonal therapy, as oral treatments were not included in the Medicare database over this time period, or patients who did not undergo treatment for metastases. All claim codes for defining treatment regimens are available within the attached appendix. Disease-free time interval between primary treatment and recurrent treatment was defined as after the end of the original treatment episode, identified as a 3-month period with no documented delivery of therapeutic chemotherapy, radiotherapy, or surgery. We included only those women who were fully covered by Medicare Parts A and B during the follow-up periods and excluded those covered by HMO as their claims would not be complete.

The AJCC stages in the SEER data were used to categorize tumor stages in this study. The hormone receptor–positive status was considered as mixed estrogen receptor–positive (ER^+) and/or progesterone receptor–positive (PR^+), that is, ER^+/no PR data, ER^+/PR^+, ER^+/PR^-, or ER^-/PR^+, or no ER data/PR^+. The percentages of available ER, PR, and hormone receptor status among the women were 80.8%, 78.3%, and 81.4%, respectively. Tumor histologic grades were classified as well-differentiated (low-grade), moderately differentiated (intermediate-grade), poorly differentiated (high-grade), and unknown status of grade.

Data analysis

We used the hazard rate (HR) to characterize the first recurrence dynamics (21). The annual HR of the first recurrence was defined as the conditional probability of recurrence in a time interval given that the women were free of recurrence at the beginning of the interval.

We estimated the HR by using Proc Lifetest in SAS through the Kaplan–Meier method, a nonparametric method that efficiently describes the data when no suitable theoretical distributions are known. For the graphical display of recurrence events, annual HRs were estimated using an Epanechnikov Kernel–like smoothing procedure for the purposes of better graphical display (22). We also compared HRs stratified by such potential prognostic factors as disease stage at diagnosis, tumor histologic grade, and hormone receptor status. Those women who did not have a recurrence event when the 10-year follow-

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

up ended and women who died before the end of follow-up were considered censored in Kaplan–Meier analysis.

Log-rank tests were used to compare each possible pair of HRs of subgroups overall or within time intervals, and then P values were adjusted for multiple comparisons using the Bonferroni adjustments (23).

The Charlson comorbidity index was calculated by using the Klabunde adaptation of the Charlson comorbidity index (24–26). Comorbid conditions from 12 to 3 months before diagnosis of breast cancer were searched from Medicare inpatient, outpatient, and physician claim data by using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes.

We assessed the multivariate effects of covariates with Cox proportional hazards model to estimate the relative hazards of the recurrence adjusted by the following baseline variables: age group (in 5 years), tumor stage, tumor grade, hormone receptor status, and Charlson comorbidity index. Two Cox regression models were conducted to estimate the relative hazards of the event. In the first model, the first breast cancer recurrence was used as the event of interest (failure event); in the second model, the recurrent event and breast cancer–specific death before evidence of recurrence were added together and treated as overall event of interest, whichever occurred first. Hazard ratios and corresponding 95% confidence interval (CI) were estimated by the proportional hazards regression model.

To assess the extent to which each component contributes to overall failure, we conducted the cumulative incidence analyses to assess the extent to which each component contributes to overall failure. Probabilities of first recurrence and death without recurrence from breast cancer were estimated using the cumulative incidence method for competing risks (27, 28). The competing event for these endpoints is breast cancer–specific death before clinical evidence of recurrence, that is, a patient who died before breast cancer recurrence was counted as failing from a competing cause at the time of death.

All statistical analyses were conducted using SAS software (version 9.2, SAS).

Table 1. Summary of major patient characteristics at baseline

Characteristic	All (N = 20,027), *n* (%)
Age, mean, y	72.2
Age group, y	
65–69	6,781 (33.9)
70–74	7,125 (33.6)
75–79	6,121 (30.6)
AJCC stage	
I	11,506 (57.5)
II	7,203 (36.0)
III	1,318 (6.6)
ER/PR status	
Positive[a]	13,798 (68.9)
Negative	2,502 (12.5)
Both ER and PR unknown	3,727 (18.6)
Histologic grade	
Poor	5,018 (25.1)
Moderate	6,894 (34.4)
Well	2,827 (14.1)
Unknown	5,288 (26.4)
First recurrence, y	
0–5	6,041 (30.2)
0–10	7,372 (36.8)
Charlson index score	
0	17,179 (85.8)
1	1,099 (5.5)
2+	636 (3.2)
Unknown	1,113 (5.5)
Surgery	
Breast conservation surgery	7.707 (38.5)
Mastectomy	10,551 (52.7)
None	1,769 (8.8)
Radiotherapy	
Yes	7,396 (36.9)
No	12,631 (63.1)
Chemotherapy	
Yes	2,799 (14.0)
No	17,228 (86.0)

[a]ER^+/no PR data, ER^+/PR^+, ER^+/PR^-, or ER^-/PR^+, or no ER data/PR^+.

Results

Patient characteristics

The study included 24,815 women, age 65 through 80 years old and diagnosed with primary breast cancer (AJCC stage I, II, or III) between 1991 and 1997. All their records were linked with Medicare enrollment records, and patients were fully covered by Medicare Plan A and B during the follow-up. We excluded women if they had developed a second primary breast cancer ($n = 1,853$) or other second primary cancers ($n = 2,679$) within 10 years after primary breast cancer diagnosis. We also excluded women who survived less than 6 months after primary breast cancer diagnosis ($n = 256$). The final number of women included in the analysis was 20,027, and Table 1 briefly summarizes their major characteristics. The mean and median ages of women at diagnosis were both equal to 72.2 years. The numbers of women with recurrences during the first 5 years and 10 years of follow-up are also shown in Table 1. Of the final total of 20,027 women, 7,372 (36.8%) experienced a recurrence within 10 years of follow-up, and the majority of these recurrences (81.9%, 6,041 of 7,372) occurred during the first 5 years after primary diagnosis, as indicated by SEER-Medicare records. Most women received breast surgery after diagnosis, of the 18,258 (91.2%) women who underwent breast surgery, 57.8% received a mastectomy. Most women (85.8%) had

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

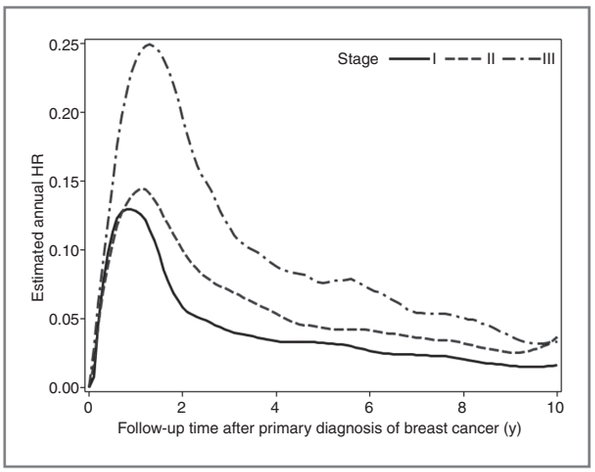

Figure 1. Smoothed hazard functions by tumor stage for first recurrence among women after primary breast cancer treatment. The HRs describe showed hazard of recurrence for each 1-year interval.

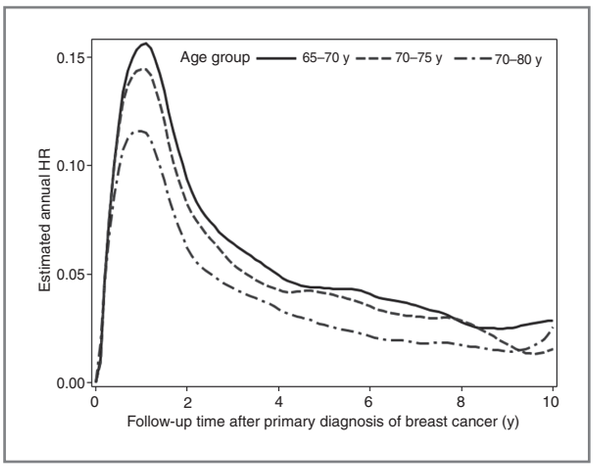

Figure 2. Smoothed hazard functions by age group for first recurrence among women after primary breast cancer treatment. The HRs describe showed hazard of recurrence for each 1-year interval.

a comorbidity score of 0, indicating a lower likelihood of comorbidity conditions contributing to mortality.

HR of the AJCC tumor stage

From the 10 years of follow-up data, the hazard curves for annual HRs for the recurrence of breast cancer stratified by AJCC stage are shown in Fig. 1. The shape of the annual recurrence hazard curve over time reveals the dynamics of recurrence. Upon visual inspection, the HR showed a similar timing of peaks between 1 and 2 years of follow-up, with long-lasting tails manifesting for all stages in the observed women. All peaks started steep and decreased slowly. Women with initially diagnosed stage III disease showed evidence of the highest hazard and largest magnitude during the first 5 years of follow-up than women diagnosed with stage I ($P < 0.01$) or stage II ($P < 0.01$). Beyond approximately 5 years, the hazard for all stages gradually decreased until the end of the 10 years of follow-up but never reached zero.

HR by age group

We categorized age at diagnosis as 65–69, 70–74, and 75–79 years old and analyzed the HR by stratifying age groups (Fig. 2). Although the results suggested that younger women had a greater hazard of recurrence ($P < 0.01$), these findings did not show an obvious effect on the HR on curves compared with the effect of tumor stages and therefore were not included in the further stratified analysis.

HR by hormone receptor status and disease stage

Patients were subdivided by hormone receptor status (positive, negative, and unknown) and by AJCC stage. The tumor hormone receptor status had a substantial effect on the hazard of the first recurrence and varied with stage (Fig. 3). Women with stage I disease showed a relatively small disparity of hazard risk of the first recurrence between the hormone receptor status category (Fig. 3, stage I; $P < 0.01$), whereas women with stage II (Fig. 3, stage II) or stage III (Fig. 3, stage III) disease showed significant disparities in patterns for recurrence risk (both $P < 0.01$). Women with hormone receptor–negative tumors had a higher peak hazard of developing recurrence in the first 5 years across all 3 AJCC stages (all $P < 0.01$), but this hazard was remarkably lower after 5 years of follow-up and showed no statistical significance when compared with women with positive or unknown hormone receptor status (Fig. 3; both $P > 0.05$). With the continuing follow-up time after 5 years, the curves showed that relative risk of the first recurrence pattern changed to the lower levels and women with different hormone receptor status having similar recurrence risk (all $P > 0.05$).

In addition, the peak annual HR for women with hormone receptor–negative status increased with increasing AJCC stage (trend test, $P < 0.01$). For example, women with stage III disease had an annual HR around 0.40, whereas women with stage I disease had a peak annual HR of 0.15, suggesting that women with negative hormone receptor status had greater risk of recurrence in the early years after initial diagnosis and treatment.

HR by tumor histologic grade and disease stage

Women with different tumor grades showed even more dynamic changes in the annual HR for the first recurrence over the 10 years of follow-up (Fig. 4). Women with poorly differentiated histology had a higher annual HR of recurrence in the first 5 years than the women with other grades after primary treatment (all $P < 0.01$). The dynamic differences in hazard by histologic grade became more dynamic among women with advanced AJCC stage (Fig. 4). Unlike women with stage I disease, women with stage III disease and with a well-differentiated grade showed several peaks of hazard within the 10 years of follow-up; women with unknown grades also had a second peak around 6 years and a third sharp peak after 9 years.

However, it should be noted that the pathologic specimen may not always capture the dominant component of

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

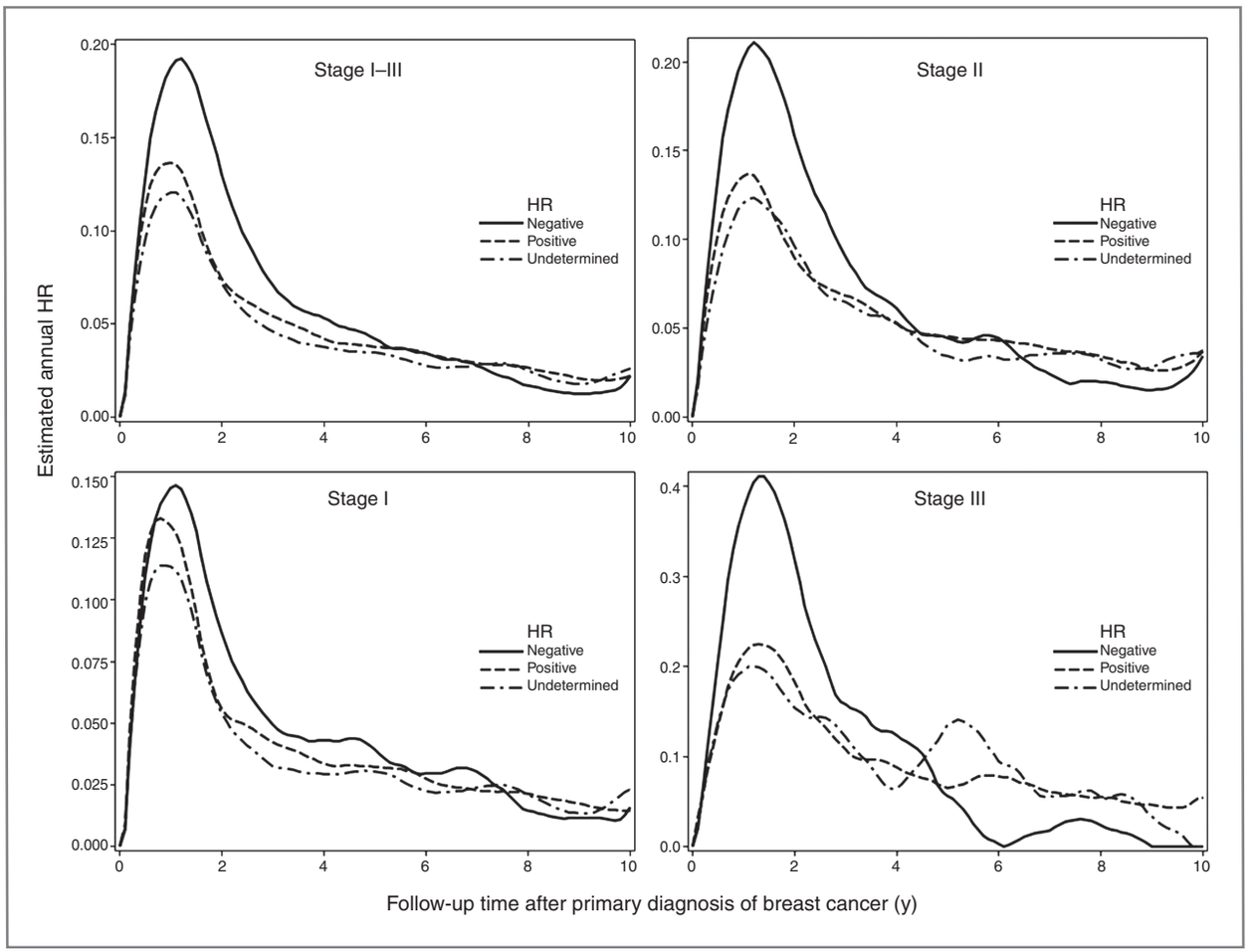

Figure 3. Smoothed hazard functions by hormone receptor (HRec) for first recurrence among women after primary breast cancer treatment. The HRs describe showed hazard of recurrence for each 1-year interval. The scale on the *y*-axis of each figure varies.

the tumor grade within entire tumor lesion. Therefore, the category of tumor with unknown grade might also consist of a mixture of grades such as well-to-moderately differentiated or poorly differentiated histopathology within the same tumor.

Cumulative incidence from competing analysis

When treating breast cancer–specific death before evidence of recurrence as a competing risk, the 10-year estimated cumulative incidence of recurrence is 35% (95% CI, 0.34–0.36), 44% (95% CI, 0.43–0.45), and 56% (95% CI, 0.54–0.59) for the stage I, II, and III, respectively. On the other hand, when treating recurrence as a competing risk, the 10-year estimated cumulative incidence of death before recurrence is 0.9% (95% CI, 0.007–0.011), 4.7% (95% CI, 0.04–0.05), and 14% (95% CI, 0.12–0.16) for the stage I, II, and III, respectively.

The results of cumulative incidence from 2 competing events, that is, recurrence and cancer-specific death before evidence of recurrence show that the hazard of competing risks of death was comparatively low, suggesting a relatively small competing risk. With a low competing risk of death, for the purpose of simplicity, the Kaplan–Meier analysis is sufficient.

Multivariate analysis of prognostic factors associated with development of recurrence

In Table 2, multivariable Cox proportional hazard regression showed that the increased risk of recurrence of breast cancer was associated with advanced disease stage, moderate and poorly differently grades, and negative hormone receptor status (all $P < 0.01$). Women with stage III disease had a 2-fold greater risk than stage I women for developing recurrence (hazard ratio, 2.04; 95% CI, 1.88–2.22). Older age was associated with lower risk of recurrence (all $P < 0.01$). The baseline Charlson comorbidity index score was not associated with the risk of recurrence (all $P < 0.01$).

When both recurrent events and breast cancer–specific deaths before evidence of recurrence were treated as outcomes of interest, the results from Cox regression were nearly identical for all covariates compared with the first regression model (Table 2).

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

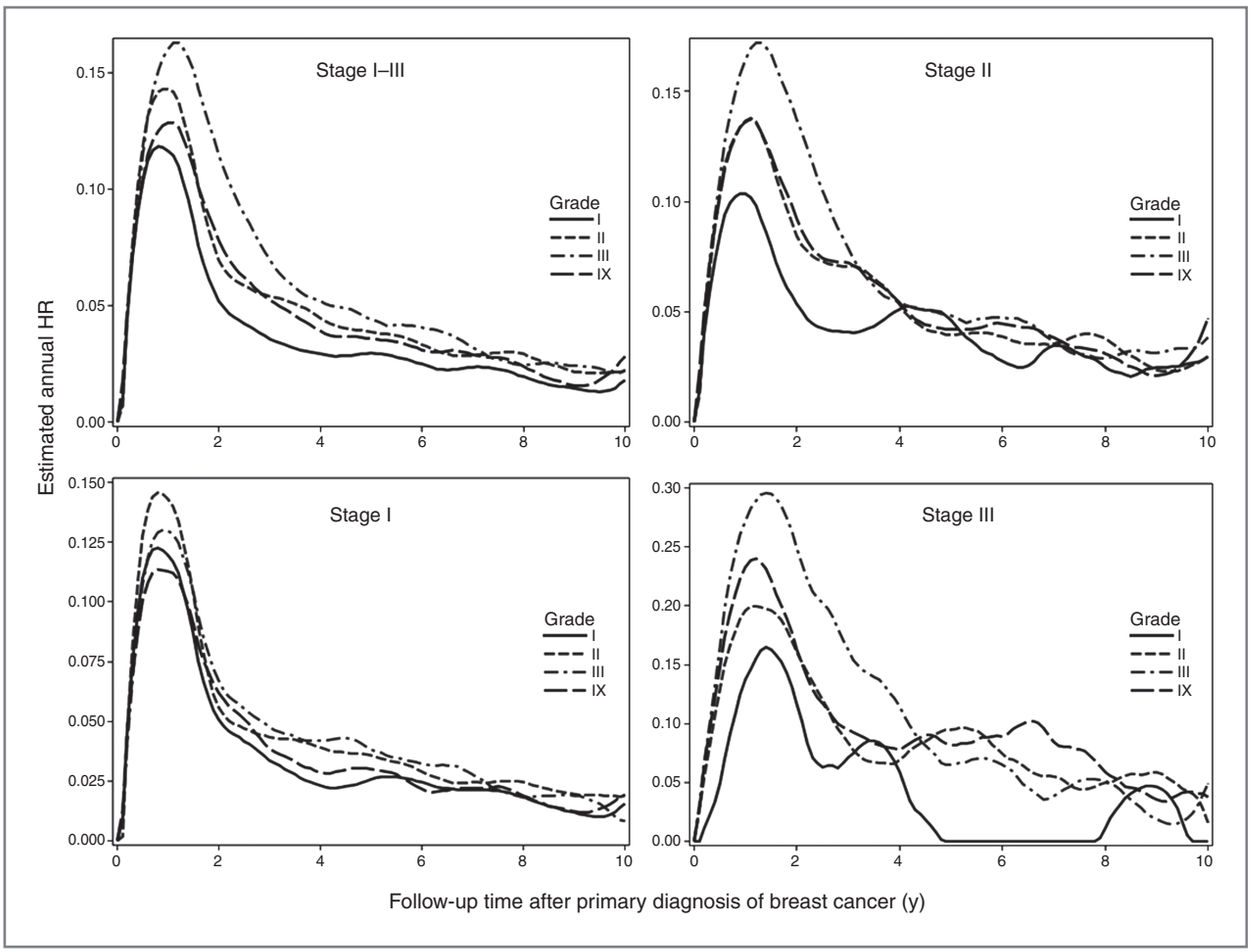

Figure 4. Smoothed hazard functions by histologic grade for first recurrence in women after primary breast cancer treatment. Tumor histologic grade I, well-differentiated (low-grade); grade II, moderately differentiated (intermediate-grade); grade III, poorly differentiated (high-grade); and IX, unknown status of grade. The HRs described showed hazard of recurrence for each 1-year interval. The scale on the *y*-axis of each figure varies.

Discussion

Our study explored the extensive SEER-Medicare data to characterize how the hazard of the first recurrence of breast cancer among women varied with prognostic factors over 10 years. The curves of hazards estimated from our study provide a rich view of the recurrence experience of women after primary treatment. Our results suggest that the greatest frequency of first recurrence occurred between 0 and 5 years of follow-up. We also found that most differences among prognostic factors for the first recurrence also occurred within this time period. Beyond 5 years, the hazards of recurrence were relatively constant within subtypes of patients. Women with poor prognostic features such as having advanced AJCC stage, hormone receptor–negative status, or poorly differentiated histologic tumor grade were more likely to have more recurrence. Our study population consists of older postmenopausal women with breast cancers, and therefore, these findings might not necessarily apply to premenopausal women with breast cancers.

The significant differences in hazard of the first recurrence occurred between 0 and 5 years after initial treatment; after year 5, the differences in hazards for all women were small. Women with younger age, advanced stages, negative hormone receptor status, and poorly differentiated tumor cells experienced the greatest hazard for recurrence, suggesting that great attention should be paid to future follow-up for patients with breast cancer with adverse prognostic factors in the first 5 years of follow-up.

The observed variations in the risk of recurrence such as for timing and magnitude might differ depending on potential prognostic factors that were not included in this study. In this study, we sought to determine whether HRs of first recurrence among women with breast cancer differed and to provide evidence for developing strategies for follow-up schedules. This is the first use of the extensive SEER-Medicare data to describe the changes of hazard on recurrence timing for women with breast cancer, and the results from this study are comparable with the results of early studies from different patient populations (11–19).

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

Table 2. Multivariate Cox regression analysis of recurrence of breast cancer

	Recurrence only		Recurrence or disease-specific death before recurrence	
Variable	**Hazard ratio (95% CI)**	***P***	**Hazard ratio (95% CI)**	***P***
Age group, y				
65–69	1.00		1.00	
70–74	0.91 (0.87–0.97)	0.001	0.92 (0.88–0.97)	0.002
75–79	0.70 (0.66–0.74)	<0.001	0.75 (0.70–0.79)	<0.001
AJCC stage				
I	1.00		1.00	
II	1.27 (1.21–1.33)	<0.001	1.36 (1.30–1.43)	<0.001
III	2.04 (1.88–2.22)	<0.001	2.47 (2.29–2.67)	<0.001
ER/PR status				
Positive[a]	1.00		1.00	
Negative	1.17 (1.09–1.25)	<0.001	1.26 (1.18–1.34)	<0.001
Unknown	0.91 (0.85–0.96)	0.002	0.95 (0.89–1.00)	0.678
Histologic grade				
Well	1.00			
Moderate	1.22 (1.12–1.31)	<0.001	1.23 (1.14–1.33)	<0.001
Poor	1.30 (1.20–1.41)	<0.001	1.38 (1.27–1.50)	<0.001
Unknown	1.12 (1.03–1.21)	0.007	1.17 (1.08–1.26)	<0.001
Carlson index				
0	1.00		1.00	
1	1.01 (0.91–1.12)	0.826	1.07 (0.97–1.18)	0.209
2+	0.95 (0.82–1.10)	0.489	1.05 (0.92–1.21)	0.464
Unknown	1.01 (0.92–1.12)	0.797	1.02 (0.93–1.12)	0.666

[a]ER^+/no PR data, ER^+/PR^+, ER^+/PR^-, or ER^-/PR^+, or no ER data/PR^+.

We did not observe evidence for a secondary peak in the distribution of hazard curves in our patient population, as reported in earlier studies (14, 29). Earlier studies included women with tumor stage I through stage IV and did not stratify by stage when calculating the HR over follow-up time. Apparently, the second peak of recurrence might have reflected the treatment patterns of stage IV metastatic disease rather than new recurrences. In addition, early studies had combined recurrence or death as the endpoint, and therefore the 2 peaks presented might have been due to the different time distributions of recurrence and death. These confounding variables may have masked the time dependence of the hazard function and obscured the curve of the HR over time for women after primary treatment of breast cancer, especially for women with stage IV disease.

We observed that women with positive hormone receptor status had a lower risk of hazard of first recurrence in the first 5 years than women with negative hormone receptor status ($P < 0.01$). However, these data must be interpreted with caution, as women with hormone receptor–positive disease would have been likely to be initially treated with hormonal therapy, which would not be captured in this study. Recurrence for patients with hormone receptor–positive disease would not be captured until treated with chemotherapy, radiation therapy, or surgery was initiated, which could be some time after the initial diagnosis of recurrence or never. Women with negative hormone receptor status had an increased risk of recurrence during the first 5 years, suggesting that more frequent follow-up visits may be needed for such women.

Although our results suggest that younger women have a greater hazard of recurrence (Fig. 2, Table 2), the curves or hazard ratio also might be explained if older women were less likely to be treated with chemotherapy for a recurrence, that is, they would be more likely to get hormonal therapy and either never get chemotherapy or get it later in time.

Breast cancer can recur at any time throughout the patient's lifetime. A recently published overview by the Early Breast Cancer Trialists' Collaborative Group looked at 15-year breast cancer recurrence and survival rates, and although the hazard ratios for recurrence were highest during the first few years after diagnosis, there seemed to be a steady relapse rate through 15 years and beyond (30). They found that for women with ER-positive breast cancer treated with tamoxifen for 5 years, the 15-year probability of death from breast cancer is more than 3 times as high as the 5-year probability. Their studies suggested that the majority of breast cancer recurrences occurred more than 5 years after diagnosis when patients were observed for more than 15 years. These findings have implications for

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

long-term breast cancer surveillance (30). Our current study also showed that the annual HR of recurrence remained above zero to the end of the 10 years of study, also implying that we might boost patient benefit by continuing to monitor for recurrence beyond 5 or 10 years after breast cancer diagnosis in women.

With the consistently increasing number of new breast cancer cases each year and more women entering survivorship, it is worthwhile to reconsider the follow-up or surveillance schedules for women after primary treatment (31–33). For example, we shall plan to use the current available data and develop a practical statistical model to offer a schedule that considers known adverse prognostic factors. Creating objective decisions derived from evidence or searching for a balance to shape the current follow-up schedules will improve the early detection of recurrence and consequently lead to individualized patient care in the future.

We acknowledge several limitations in our present study. First, inaccuracies in coding the SEER and Medicare data may have varied over time. Second, pathologic reports have been read by different pathologists at different sites and there could be variations with site and time. Third, our study included only women between 65 and 80 years of age, and therefore the results derived may not represent the broader U.S. population. Fourth, the cancer recurrence information was captured by using Medicare data and therefore misreporting due to coding issues might happen. Our data also excluded 13% of women who were enrolled in HMOs or who were not fully covered by Medicare Parts A and B during the follow-up periods. Although the frequency distributions of cases between those included and excluded were very close in terms of tumor stage, grade, and hormone status, the distribution of age differed: women who were excluded from the study were younger than patients chosen for the study. Fifth, the Medicare data may not capture usage of hormone therapies and this could have led to an underestimation in the number of recurrence events or delay in the timing for those women with positive hormone receptor status. Sixth, we were unable to assess the prognostic significance of lifestyle factors such as body mass index or tobacco use because this information was not systemically reported over time in the Medicare data. Finally, recurrences among women who never received chemotherapy, radiation, and surgery would be missed. Despite these potential limitations, the SEER-Medicare is the single most nationally representative source of data. The strengths of SEER-Medicare data make it the optimal source to determine the relationship between the recurrence of breast cancer and the hazard function over time.

In summation, our results using 10 years of follow-up data yield pertinent information on trends for first cancer recurrence in women with breast cancer. Specifically, our results show that the annual HR of recurrence is not uniformly distributed over time but is dynamic and markedly determined by prognostic factors at diagnosis. Our results also show that recurrence was most likely to occur in the first 5 years of follow-up, which supports the current guidelines for an intensive follow-up schedule in this time period.

Our findings suggest that follow-up visits should be planned according to the times when the recurrence events are most likely to occur, as determined by known prognostic factors. Given our findings, researchers can begin to answer questions about the frequency of follow-up, the total duration of follow-up, and which tests are most appropriate for each patient during each follow-up visit.

Appendix. Codes for identifying recurrence events of breast cancer

Type of treatment	ICD-9-CM diagnosis	ICD-9-CM procedure	HCPCS codes	CPT procedure codes
Breast-conserving surgery	—	85.2, 85.20, 85.21, 85.22, 85.23, or 85.25	—	19110, 19120, 19125, 19126, 19160, or 19162, 19301, 19302
Mastectomy	—	85.4, 85.41, 85.42, 85.43, 85.44, 85.45, 85.46, 85.47, 85.48	—	19180, 19182, 19200, 19220, 19240, 19303, 19304, 19305, 19306, 19307
Chemotherapy	V58.1, V66.2, V67.2	99.25	J9000–J9999, Q0083–Q0085, J8520, J8521, J8530, J8540, J8560, J8597, J8610, J8999; Excluding all of the following codes: J9003, J9165, J9175, J9202, J9209, J9212-J9226, J9240, J9295, J9381, J9395	96401, 96402, 96405, 96406, 96409, 96411, 96413, 96415–96417, 96420, 96422, 96423, 96425, 96440, 96445, 96450, 96521–96523, 96542, 96549
Radiotherapy	V58.0, V66.1, V67.1	92.2, 92.20–92.27, 92.29, 92.3, 92.30–92.39, 92.4, 92.41	G0174, G0251, G0339, G0340	77371–77373, 77401–77499, 77750–77799

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

Disclosure of Potential Conflicts of Interest

The interpretation and reporting of these data are the sole responsibility of the authors. No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Cheng, P.J. Rowan, T.A. Buchholz, S.H. Giordano
Development of methodology: L. Cheng, A.S. Kapadia, S.H. Giordano
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.H. Giordano
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Cheng, M.D. Swartz, H. Zhao, A.S. Kapadia, D. Lai, S.H. Giordano
Writing, review, and/or revision of the manuscript: L. Cheng, M.D. Swartz, H. Zhao, D. Lai, P.J. Rowan, T.A. Buchholz, S.H. Giordano
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.H. Giordano
Study supervision: L. Cheng, D. Lai, S.H. Giordano

Acknowledgments

This study used the linked SEER-Medicare database. The authors thank the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Grant Support

S.H. Giordano is supported by ACS RSGI-09-149-01-CPHPS and CPRIT RP101207-P02.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 30, 2011; revised February 15, 2012; accepted March 2, 2012; published OnlineFirst March 16, 2012.

References

1. American Cancer Society. Cancer facts & figures 2010. Atlanta, GA: American Cancer Society.2010 [cited 2011 Jun 14]; Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-026238.pdf.
2. National Cancer Institute. Fact sheet. Adjuvant and neoadjuvant therapy for breast cancer. Bethesda, MD: National Cancer Institute. [cited 2010 Oct 28.]; Available from: http://www.cancer.gov/images/documents/922487a5-daf0-40ce-b42e-316e067195f8/Fs7_20.pdf
3. Jacobsen PB. Clinical practice guidelines for the psychosocial care of cancer survivors: current status and future prospects. Cancer 2009;115:4419–29.
4. Snyder CF, Frick KD, Kantsiper ME, Peairs KS, Herbert RJ, Blackford AL, et al. Prevention, screening, and surveillance care for breast cancer survivors compared with controls: changes from 1998 to 2002. J Clin Oncol 2009;27:1054–61.
5. Hollowell K, Olmsted CL, Richardson AS, Pittman HK, Bellin L, Tafra L, et al. American Society of Clinical Oncology-recommended surveillance and physician specialty among long-term breast cancer survivors. Cancer 2010;116:2090–8.
6. Ghafoor Q, Sanghera P, Grieve RJ. A study of medical intervention in routine breast cancer follow-up. Clin Oncol (R Coll Radiol) 2010;22:91–6.
7. Elit L, Fyles AW, Oliver TK, Devries-Aboud MC, Fung-Kee-Fung M. Follow-up for women after treatment for cervical cancer. Curr Oncol 2010;17:65–9.
8. NCCN. Breast cancer. Fort Washington, PA: NCCN. 2010 [cited 2010 Oct 10]; Available from: http://www.nccn.org/index.asp.
9. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006;24:5091–7.
10. Aalen OO, Gjessing HK. Understanding the shape of the hazard rate: a process point of view. Stat Sci 2001;16:1–22.
11. Karrison TG, Ferguson DJ, Meier P. Dormancy of mammary carcinoma after mastectomy. J Natl Cancer Inst 1999;91:80–5.
12. Demicheli R, Ardoino I, Boracchi P, Coradini D, Agresti R, Ferraris C, et al. Recurrence and mortality according to estrogen receptor status for breast cancer patients undergoing conservative surgery. Ipsilateral breast tumour recurrence dynamics provides clues for tumour biology within the residual breast. BMC Cancer 2010;10:656.
13. Demicheli R, Biganzoli E, Boracchi P, Greco M, Retsky MW. Recurrence dynamics does not depend on the recurrence site. Breast Cancer Res 2008;10:R83.
14. Demicheli R, Abbattista A, Miceli R, Valagussa P, Bonadonna G. Time distribution of the recurrence risk for breast cancer patients undergoing mastectomy: further support about the concept of tumor dormancy. Breast Cancer Res Treat 1996;41:177–85.
15. Montgomery DA, Krupa K, Jack WJ, Kerr GR, Kunkler IH, Thomas J, et al. Changing pattern of the detection of locoregional relapse in breast cancer: the Edinburgh experience. Br J Cancer 2007;96:1802–7.
16. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 1996;14:2738–46.
17. Dignam JJ, Dukic V, Anderson SJ, Mamounas EP, Wickerham DL, Wolmark N. Hazard of recurrence and adjuvant treatment effects over time in lymph node-negative breast cancer. Breast Cancer Res Treat 2009;116:595–602.
18. Jatoi I, Tsimelzon A, Weiss H, Clark GM, Hilsenbeck SG. Hazard rates of recurrence following diagnosis of primary breast cancer. Breast Cancer Res Treat 2005;89:173–8.
19. Brewster AM, Hortobagyi GN, Broglio KR, Kau SW, Santa-Maria CA, Arun B, et al. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. J Natl Cancer Inst 2008;100:1179–83.
20. Earle CC, Nattinger AB, Potosky AL, Lang K, Mallick R, Berger M, et al. Identifying cancer relapse using SEER-Medicare data. Med Care 2002;40:IV-75–81.
21. Klein J, Moeschberger M. Survival analysis: techniques for censored and truncated data. 2nd ed. New York: Springer-Verlag; 2003.
22. Epanechnikov VA. Nonparametric estimation of a multivariate probability density. Theor Probab Appl 1969;14:153–8.
23. Wright SP. Adjusted *P*-value for simultaneous inference. Biometrics 1992;48:1005–13.
24. National Cancer Institute. SEER-Medicare: calculation of comorbidity weights. Bethesda, MD: National Cancer Institute. [cited 2011 Dec 14]; Available from: http://healthservices.cancer.gov/seermedicare/program/comorbidity.html.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
26. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol 1993;46:1075–9; discussion 1081–90.
27. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer 2004;91:1229–35.
28. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics 1978;34:541–54.
29. Demicheli R, Ardoino I, Boracchi P, Coradini D, Agresti R, Ferraris C, et al. Recurrence and mortality dynamics for breast cancer patients undergoing mastectomy according to estrogen receptor status: different mortality but similar recurrence. Cancer Sci 2010;101:826–30.
30. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–717.

Published OnlineFirst March 16, 2012; DOI: 10.1158/1055-9965.EPI-11-1089

31. American Cancer Society. Breast cancer facts & figures 2009–2010. Atlanta, GA: American Cancer Society. [cited 2010 Oct 08]; Available from: http://www.cancer.org/acs/groups/content/@nho/documents/document/f861009final90809pdf.pdf
32. Wheeler T, Stenning S, Negus S, Picken S, Metcalfe S. Evidence to support a change in follow-up policy for patients with breast cancer: time to first relapse and hazard rate analysis. Clin Oncol (R Coll Radiol) 1999;11:169–73.
33. Gulliford T, Opomu M, Wilson E, Hanham I, Epstein R. Popularity of less frequent follow up for breast cancer in randomised study: initial findings from the hotline study. BMJ 1997;314:174–7.

Cancer Epidemiology, Biomarkers & Prevention

Correction: Hazard of Recurrence among Women after Primary Breast Cancer Treatment—A 10-Year Follow-Up Using Data from SEER-Medicare

In this article (Cancer Epidemiol Biomarkers Prev 2012;21:800–9), which was published in the May 2012 issue of *Cancer Epidemiology, Biomarkers & Prevention* (1), the authors regret a typographical error that appeared in Table 1. The value for "Breast conservation surgery" appeared as 7.707. The correct value is 7,707. A corrected table is shown below.

Table 1. Summary of major patient characteristics at baseline

Characteristics	All, $N = 20,027$ (%)
Age, mean (y)	72.2
Age group	
65–69 years	6,781 (33.9)
70–74 years	7,125 (33.6)
75–79 years	6,121 (30.6)
AJCC stage	
I	11,506 (57.5)
II	7,203 (36.0)
III	1,318 (6.6)
ER/PR status	
Positive*	13,798 (68.9)
Negative	2,502 (12.5)
Both ER and PR unknown	3,727 (18.6)
Histologic grade	
Poor	5,018 (25.1)
Moderate	6,894 (34.4)
Well	2,827 (14.1)
Unknown	5,288 (26.4)
First recurrence	
0–5 years	6,041 (30.2)
0–10 years	7,372 (36.8)
Charlson Index score	
0	17,179 (85.8)
1	1,099 (5.5)
2+	636 (3.2)
Unknown	1,113 (5.5)
Surgery	
Breast conservation surgery	7,707 (38.5)
Mastectomy	10,551 (52.7)
Non	1,769 (8.8)
Radiotherapy	
Yes	7,396 (36.9)
No	12,631 (63.1)
Chemotherapy	
Yes	2,799 (14.0)
No	17,228 (86.0)

NOTE: ER+/no PR data, ER+/PR+, ER+/PR−, or ER−/PR+, or no ER data/PR+

Reference

1. Cheng L, Swartz MD, Zhao H, Kapadia AS, Lai D, Rowan PJ, et al. Hazard of recurrence among women after primary breast cancer treatment—a 10-year follow-up using data from SEER-Medicare. Cancer Epidemiol Biomarkers Prev 2012;21:800–9.

Published OnlineFirst August 15, 2012.
doi: 10.1158/1055-9965.EPI-12-0818

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Hazard of Recurrence among Women after Primary Breast Cancer Treatment—A 10-Year Follow-up Using Data from SEER-Medicare

Lee Cheng, Michael D. Swartz, Hui Zhao, et al.

Cancer Epidemiol Biomarkers Prev 2012;21:800-809. Published OnlineFirst March 16, 2012.