

Short Communication

Breast Cancer Recurrence in Older Women Five to Ten Years after Diagnosis

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Abstract

Little is known about the risk of recurrence >5 years after diagnosis among older breast cancer survivors. A community-based population of women ≥ 65 years diagnosed with early-stage breast cancer who survived disease free for 5 years was followed for 5 additional years or until a diagnosis of breast cancer recurrence, second primary, death, or loss to follow-up. These 5-year disease-free survivors ($N = 1,277$) had primary breast cancers that were node negative (77%) and estrogen receptor positive or unknown (86%). Five percent ($n = 61$) developed a recurrence between 5 and 10 years after diagnosis: 25% local, 9.8% regional, and 66% distant. Women who were node positive [hazard ratio (HR), 3.9; 95% confidence interval (95% CI), 1.5-10], had poorly differentiated tumors (HR, 2.5; 95% CI, 0.9-6.6), or who re-

ceived breast conserving surgery without radiation therapy (HR, 2.4; 95% CI, 1.0-5.8) had higher recurrence rates compared with node negative, well differentiated, and receipt of mastectomy, respectively. Not receiving adjuvant tamoxifen, compared with receiving adjuvant tamoxifen, was also positively associated with late recurrence among women with estrogen receptor-positive/unknown tumors. Although relatively few women experience a late recurrence, most recurrences present as advanced disease, which is difficult to treat in older women. This study of late recurrence emphasizes that the risk, although small, is not negligible even in this group at high risk of death due to competing causes. (Cancer Epidemiol Biomarkers Prev 2009;18(11):2979-83)

Introduction

Survivorship is defined as the time between cancer diagnosis and death (1). Currently, there are >2.6 million breast cancer survivors in the United States and 1.6 million of them are ≥ 65 years old.⁷ As the number of breast cancer survivors increases due to improvements in screening, primary treatment, and adjuvant therapy (1), identifying factors associated with survival after 5 years becomes more important. Older women have the highest incidence and prevalence of breast cancer (2), yet little is known about factors affecting the risk of recurrence among women who remain disease-free 5 years after diagnosis. Recently, Brewster et al. observed that higher stage (stage II versus stage I) and hormone receptor-positive tumors (versus hormone receptor-negative tumors) without hormonal therapy were associated with risk of recurrence after 5 years (3). However, the majority of the population (78%) was <60 years old and from one

tertiary care cancer center (3), leaving an important gap regarding late recurrence risk in older women, who are the majority of breast cancer survivors. The objective of this study is to describe the risk and identify the predictors of breast cancer recurrence beyond 5 years in the community-based population of breast cancer survivors ≥ 65 years old who were included in the Breast Cancer Treatment Effectiveness in Older Women (BOW) cohort (4).

Materials and Methods

The BOW cohort (4, 5) includes women ≥ 65 years old at diagnosis with stage I or II breast cancer from 1990 to 1994 in six geographically diverse Cancer Research Network (6) healthcare systems: Group Health, Seattle, Washington; Fallon Clinic, Worcester, Massachusetts; Kaiser Permanente Southern California, Pasadena, California; Lovelace Health System, New Mexico; HealthPartners, Minneapolis, Minnesota; and Henry Ford Health System, Detroit, Michigan. Through collaborative

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⁷ Cancer Survivorship Research [Internet]. Rockville: National Cancer Institute, Division of Cancer Control and Population Sciences [updated 2006 Nov 6; cited 2009 Jun 11]. Available from: <http://cancercontrol.cancer.gov/ocs/definitions.html>.

research, the Cancer Research Network aims to increase effective preventive, curative, and supportive interventions for major cancers among diverse populations and health systems. Women who had any cancer diagnosed within 5 years before their incident breast cancer diagnosis were excluded. We chose 5 years for this boundary because cancers diagnosed more than 5 years earlier would be rare and would not affect breast cancer treatments or outcomes. The institutional review boards of the six participating healthcare systems and the Boston University Medical Center approved this study.

Demographic characteristics, breast cancer tumor characteristics and treatments, comorbid conditions, and breast cancer recurrence were collected from tumor registries, administrative data, and medical record review (7). The interrater reliability of medical record abstraction was $\geq 90\%$ overall (8), with 90% sensitivity and 96% specificity for breast cancer recurrence classification.

The survivor population for the reported study included women from the BOW cohort who survived disease-free for 5 years after initial breast cancer diagnosis (Fig. 1). Follow-up began 5 years after diagnosis and accrued until the diagnosis of first recurrence, second primary, death from any cause, disenrollment from the healthcare system, or survival for an additional 5 years (10 years disease free from diagnosis), whichever came first.

Late breast cancer recurrence was defined as a tumor that was pathologically or clinically diagnosed between 5 and 10 years after diagnosis in the same breast as the original tumor or in any regional or distant site (Fig. 1). A tumor that occurred in the contralateral breast (second primary) was not considered a late recurrence because primary tumor therapy is aimed at reducing the risk of recurrence, not occurrence of disease in the contralateral breast. Therefore, women were censored at the date of diagnosis of second primary breast cancer.

We included age at diagnosis (65-69, 70-79, ≥ 80 y), race/ethnicity (non-Hispanic white, Hispanic and/or other race), Charlson comorbidity index (9) in the year before diagnosis (0, 1, ≥ 2), tumor size (<1 , $1-2$, $2-3$, ≥ 4 cm), nodal involvement (0, 1-3, ≥ 4), histologic grade (well differentiated, intermediate/moderate differentiated, poorly differentiated/undifferentiated/anaplastic), primary therapy (mastectomy, breast conserving surgery plus radiation therapy, breast conserving surgery only),

progesterone receptor expression (positive or unknown, negative), estrogen receptor expression (positive or unknown, negative), receipt of adjuvant tamoxifen (yes, no), and receipt of adjuvant chemotherapy (yes, no) as potential predictors of late recurrence.

The roles of estrogen and progesterone receptors in recurrence risk, and how they impact the effectiveness of tamoxifen, presented an analytic challenge. Progesterone receptor expression has little impact on the protective effect of tamoxifen after accounting for estrogen receptor expression, whereas the protective effect of tamoxifen in women with unknown estrogen receptor expression is similar, although weaker in magnitude, to its effect in women with estrogen receptor-positive tumors (10). Our results for all combinations of tamoxifen use (yes, no) cross-tabulated by estrogen and progesterone receptor expression together and separately, including and excluding women with unknown hormone expression, were all similar. We report the results of the model adjusting for a four-category variable created by cross-tabulating estrogen receptor-positive/unknown expression by receipt of adjuvant tamoxifen.

We described tumor and treatment characteristics using univariate statistics. Using the survivor cohort, all of the predictors of recurrence after 5 years were included in a Cox proportional hazards regression model using SAS version 9.1. Because breast cancer-specific mortality is often used as a surrogate outcome for recurrence, we also evaluated predictors of breast cancer-specific mortality among the 5-year disease-free survivors, following methods described earlier to identify deaths from breast cancer (11).

Results

In Table 1, we provide the characteristics of women who had definitive surgery from the BOW cohort at its inception ($n = 1837$) to put the characteristics of women who survived disease free for 5 years ($n = 1277$) in context. We also show descriptive characteristics for the women who experienced a late recurrence ($n = 61$). Similar to the BOW inception cohort, most of the 5-year disease-free survivors were between 65 and 74 years old at diagnosis (67%), non-Hispanic white (81%), had no nodal involvement (77%), and had tumors with estrogen receptor-positive (or unknown) expression (86%). Among survivors with estrogen receptor-positive (or unknown) expression, 32% were not prescribed, 39% received <5 years, and 29% received ≥ 5 years of adjuvant tamoxifen. Women with estrogen receptor-positive (or unknown) tumors who did not receive tamoxifen had less aggressive tumor characteristics than women with estrogen receptor-positive (or unknown) expression who received tamoxifen: for tumors ≤ 2 cm, 85% versus 45%, respectively; with no nodal involvement, 98% versus 68%, respectively; and for well/moderately differentiated tumors, 64% versus 38%, respectively (data not shown).

The rate of recurrence was higher in the first 5 years (40/100 woman-years) than the second 5 years (26/100 woman-years). Five percent ($n = 61$) of women disease free at 5 years had a recurrence between 5 and 10 years after diagnosis (late recurrences). Of the women with late recurrence, 25% presented with local disease, 9.8% with regional disease, and 66% with distant metastases. The

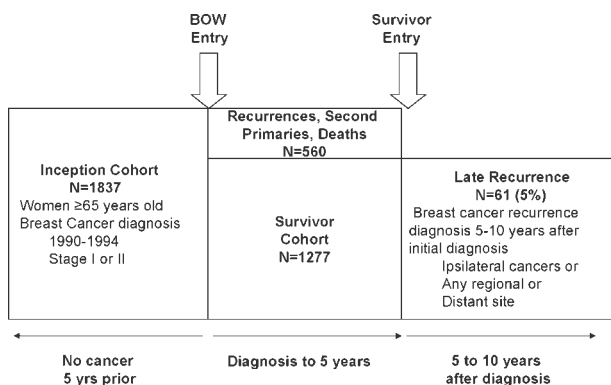


Figure 1. Inclusion criteria for the BOW inception cohort, 5-y disease-free survivor cohort, and women diagnosed with a late recurrence in a population of older breast cancer survivors.

Table 1. Descriptive, tumor, and treatment characteristics for older women of the inception cohort who received surgery (n = 1,837), 5-y disease-free breast cancer survivors (n = 1,277), and survivors who developed a recurrence between 5 and 10 y after diagnosis (n = 61)

Characteristic	Inception cohort (n = 1,837)	5-y survivor cohort (n = 1,277)	Recurrence 5-10 y after diagnosis (n = 61)	HR* (95% CI)
	No. (%)	No. (%)	No. (%)	
Age categories, y				
65-69	626 (34)	478 (37)	24 (39)	Reference
70-74	547 (30)	388 (30)	26 (43)	1.7 (0.9-2.9)
75-79	304 (17)	201 (16)	6 (9.8)	0.8 (0.3-2.0)
≥80	360 (20)	210 (16)	5 (8.2)	0.8 (0.3-2.3)
Race/Ethnicity				
Non-Hispanic white	1,503 (82)	81 (81)	46 (75)	Reference
Hispanic and/or other race	334 (18)	241 (19)	15 (25)	1.2 (0.7-2.5) [†]
Charlson comorbidity index				
0	1,252 (68)	926 (73)	44 (72)	Reference
1	498 (27)	307 (24)	16 (26)	1.4 (0.7-2.5)
≥2	87 (4.7)	44 (3.5)	1 (1.6)	0.6 (0.1-4.4)
Tumor size (cm)				
<1	376 (20)	295 (23)	11 (18)	Reference
1- $<$ 2	759 (41)	548 (43)	23 (38)	1.1 (0.5-2.3)
2- $<$ 3	428 (23)	278 (22)	16 (26)	1.2 (0.5-2.8)
≥3	274 (15)	156 (12)	11 (18)	1.3 (0.5-3.3)
Node positivity				
0 nodes	1,371 (75)	984 (77)	30 (49)	Reference
1-3 nodes	333 (18)	236 (18)	23 (38)	2.5 (1.3-4.8)
≥4 nodes	133 (7.2)	57 (4.5)	8 (13)	3.9 (1.5-10.1)
Histologic grade				
Well differentiated	297 (16)	238 (19)	6 (9.8)	Reference
Intermediate/moderate	676 (37)	473 (37)	25 (41)	1.9 (0.8-4.7)
Poorly differentiated/ undifferentiated/anaplastic	429 (23)	266 (21)	22 (36)	2.5 (0.9-6.6)
Not determined/stated	435 (24)	300 (23)	8 (13)	1.1 (0.4-3.1)
Primary therapy				
Mastectomy	977 (53)	658 (52)	32 (52)	Reference
Breast conserving surgery (BCS) plus radiation therapy	639 (35)	499 (39)	22 (36)	1.4 (0.8-2.7)
BCS	221 (12)	120 (9.4)	7 (11)	2.4 (1.0-5.8)
Progesterone receptor expression				
Positive or unknown	1,538 (84)	1,093 (86)	52 (85)	Reference
Negative	299 (16)	184 (14)	9 (15)	0.6 (0.3-1.1)
Estrogen receptor expression				
Positive or unknown	1,538 (84)	1,093 (86)	52 (85)	Reference [‡]
Received tamoxifen	1,028 (67)	746 (68)	42 (81)	
No tamoxifen	510 (33)	347 (32)	10 (19)	2.4 (0.7-8.1)
Negative	299 (16)	184 (14)	9 (15)	
Received tamoxifen	134 (45)	75 (41)	3 (33)	0.5 (0.1-2.2)
No Tamoxifen	165 (55)	109 (59)	6 (67)	1.6 (0.5-4.4)
Chemotherapy received				
Yes	187 (10)	120 (9.4)	14 (23)	1.2 (0.5-2.7)
No	1,243 (90)	1,157 (91)	47 (77)	Reference

NOTE: The inception cohort is similar to that reported by Geiger et al. (5) The variables have been modified by collapsing categories and recategorizing race/ethnicity, tumor size, node positivity, progesterone receptor expression, estrogen receptor expression, and tamoxifen therapy. The inception cohort was not used in any analyses for late recurrence.

*Cox proportional hazards model simultaneously included all predictors and health care system.

[†]Non-Hispanic white compared with Hispanic and/or Other Race (African American or Asian).

[‡]The reference group for the comparison of positive or unknown estrogen receptor expression compared with negative estrogen receptor expression.

median time to recurrence after the first 5 disease-free years was 2.8 years.

Women who had ≥ 4 positive nodes at their original diagnosis had nearly four times the rate of late recurrence compared with node-negative women. Women with poorly differentiated tumors had 2.5 times the recurrence rate as women with well-differentiated tumors. When tumor size and nodal involvement were combined to form stage categories, women with stage II tumors had 2.6 times the recurrence rate as stage I women (95% confidence interval, 1.4-5.0). Higher recurrence rates were also experienced by women who received breast conserving surgery without radiation therapy than women who re-

ceived a mastectomy. For adjuvant therapy, there seemed to be an increased rate of late recurrence among the women with estrogen receptor-positive (and unknown) tumors who did not receive adjuvant tamoxifen compared with women who received tamoxifen. However, we did not observe an association between receipt of adjuvant chemotherapy and late recurrence (Table 1).

The results for breast cancer-specific mortality parallel those for late recurrence. Women with ≥ 4 positive nodes (hazard ratio, 4.5; 95% confidence interval, 1.9-11) and who received breast conserving surgery without radiation therapy (hazard ratio, 2.1; 95% confidence interval, 1.1-4.3) were more likely to die of breast cancer 5 to

10 years after diagnosis compared with women who were node negative or received a mastectomy, respectively.

Discussion

In a large cohort study of older women with early-stage breast cancer treated in community-based settings, we found that tumor characteristics and primary tumor therapy continue to predict recurrence risk after 5 years of disease-free survival. Specifically we found that nodal involvement, poor histology, and breast conserving surgery without radiation therapy increased the rate of late recurrence. We also observed a positive association between not receiving adjuvant tamoxifen and the risk of late recurrence among estrogen receptor-positive women.

Our results are consistent with previous findings of mostly younger women (3, 11-14). Although comorbid diseases were not associated with late recurrence in our older cohort, existing comorbidities were associated with receipt of suboptimal treatment (4). More aggressive tumor characteristics and inadequate primary tumor therapy increased the risk of recurrence after 5 years (3, 12-15). The association of higher stage (stage II versus stage I) is similar to the finding of Brewster et al. (3). The positive association among estrogen receptor-positive women who did not receive adjuvant tamoxifen and late recurrence is also consistent with previous findings (12-15). However, we must be cautious in our interpretation of this finding because our data are also compatible with a 30% protective effect of adjuvant tamoxifen on late recurrence among estrogen receptor-positive women.

The risk of recurrence among estrogen receptor-positive women has been shown to vary over time with a greater risk of recurrence in the later years than in the first two years (12-15). Studies have shown that estrogen receptor-negative tumors mostly recur within the first 5 years after diagnosis, whereas estrogen receptor-positive tumors recur later (13, 14). In addition, early discontinuation of adjuvant tamoxifen before the completion of 5 years may also explain our increased risk of recurrence among our estrogen receptor-positive women (12). Approximately 70% of our older survivors with estrogen receptor-positive (and unknown) tumors received adjuvant tamoxifen. However, nearly 40% received <5 years of adjuvant tamoxifen. These women may not have had the complete benefit of tamoxifen because they were treated in the 1990s when recommendations for the duration of tamoxifen treatment were evolving, and before the advent of aromatase inhibitors (16, 17). Although there is growing support for our finding (3, 12-14), the biological mechanisms explaining the difference in risk over time by estrogen receptor expression are still unknown. At the time of diagnosis and treatment of our cohort, CYP2D6 and subtypes of estrogen receptor-positive expression (human epidermal growth factor receptor 2) were not routinely assayed. Future evaluation of late breast cancer recurrence by genetic factors and subtypes may be useful to further explain the increased risk beyond 5 years in older women with estrogen receptor-positive tumors (18, 19).

Although the treatment patterns of today differ from those of the 1990s, 10 years of follow-up required that women were diagnosed with incident breast cancer in the 1990s. An additional limitation is that the majority of our older survivor cohort were non-Hispanic white,

so our results may not apply to risk in other racial and ethnic populations. Despite these limitations, the BOW cohort is one of the largest cohorts of older women with breast cancer in the United States and has the unique feature of nearly complete follow-up through 10 years.

To our knowledge, this study is one of the first to specifically assess the risk of late recurrence in a cohort restricted to older women. Older women with breast cancer increasingly survive ≥ 5 years after initial diagnosis, despite the risk of death due to breast cancer and other competing causes. These women remain at risk for recurrence as well as coexisting morbidity and mortality 5 to 10 years after their diagnosis. Although relatively few older women recur after 5 years, those who do often have advanced cancers that are difficult to treat. To improve outcomes for older women, particularly those with a 5-year or longer life expectancy, providing guideline therapy for the primary tumor (20, 21) and surveillance for recurrence beyond 5 years (22) of survival are essential to reducing morbidity and mortality, and maintaining quality of life.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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