Comorbidities and Cardiovascular Disease Risk in Older Breast Cancer Survivors

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Objective: To evaluate cardiovascular disease (CVD) risk factors in older breast cancer survivors compared with a group of women without breast cancer.

Study Design: The retrospective study included (1) women aged 65 or more years who were initially diagnosed with stage I or II breast cancer from 1990 to 1994 in 6 US health plans and who survived at least 5 years postdiagnosis (cases) and (2) a matched comparison group. They were followed for a maximum of 15 years.

Methods: Data sources included medical charts and electronic health records. Cases (n = 1361) were matched on age, health plan site, and enrollment year to women in the comparison group (n = 1361). Subjects were followed to the first CVD outcome, health plan disenrollment, death, or study end. We compared rates of CVD in these 2 groups and used Cox proportional hazard models to estimate the hazard ratio (HR), considering body mass index, smoking history, diabetes, and hypertension.

Results: The strongest predictors of CVD were smoking history (HR = 1.29; 95% confidence interval [CI], 1.15-1.46), diabetes (HR = 1.72; 95% CI, 1.48-1.99), and hypertension (HR = 1.48; 95% CI, 1.31-1.67) rather than breast cancer case-comparison status (HR = 0.97; 95% CI, 0.87-1.09).

Conclusion: Results suggest that long-term prognosis in breast cancer patients is affected by management of preexisting conditions. Assessment of comorbid conditions and effective management of diabetes and hypertension in older breast cancer survivors may lead to longer overall survival.

Am J Manag Care. 2014;20(1):86-92

For author information and disclosures, see end of text.

More than half of the 2.6 million breast cancer survivors living in the United States are over age 65 years,[1,2] and the fraction of older people with cancer is growing, partly attributable to the success of cancer screening and treatment. Consequently, the number of older cancer survivors at risk of developing other age-related conditions such as cardiovascular disease (CVD) is increasing. Many of these older breast cancer patients also have comorbid conditions or other CVD risk factors.[3] Moreover, CVD is the leading cause of death in breast cancer survivors.[4] As comorbidities impact prognosis and cardiovascular outcomes in breast cancer patients, the role of primary care physicians in the care of survivors is expanding to manage these preexisting conditions.

Despite CVD being the leading cause of morbidity in older breast cancer survivors, very few studies have examined CVD risk factors in such women, whether these factors differ from those in women in the general population, and the long-term impact of these risk factors on CVD outcomes.[4] For example, prior studies on CVD risk in older cancer survivors were limited by cross-sectional designs; few included information on health status prior to cancer diagnosis; and even fewer included data from comparison subjects without a cancer history.[5-20] Given these limitations, it is unclear whether there is excess risk of CVD among breast cancer survivors.

Examining CVD risk poses a challenge, as long-term observation periods are required. Further, CVD is more common in older adults in general and especially in those who have established risk factors other than cancer treatments. Because few older breast cancer survivors are treated with chemotherapy,[21] particularly those agents known to be cardiotoxic, examining the impact of comorbidities on CVD risk is crucial. Therefore, a well-characterized comparison group with long follow-up is essential to determine whether there truly is excess morbidity in older women treated for breast cancer.

The purpose of this investigation was to determine whether incident CVD was greater in a group of older breast cancer survivors versus a cancer-free comparison group, and if the excess risk could be attributed to differences in comorbid conditions. To this end, we compared incident CVD in the 2 groups over a 15-year follow-up period, incorporating baseline risk factors such as race/ethnicity, body mass index (BMI), smoking history, diabetes, and hypertension.

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Take-Away Points

Our results suggest that older long-term breast cancer survivors (initially diagnosed with early-stage disease) have a cardiovascular disease (CVD) risk similar to that of otherwise healthy women of comparable ages.

- The established risk factors (very old age, smoking history, diabetes, and hypertension) were more predictive of CVD risk than breast cancer history status.
- Long-term prognosis in older breast cancer patients is affected by management of preexisting conditions, and these may be best managed by primary care providers.
- Management of comorbidities in survivors should not be different from that in the general population of older patients.

METHODS

Design, Setting, and Subjects

We identified women 65 years or older who were diagnosed with early-stage breast cancer (American Joint Commission on Cancer TNM stage I, IIA, or IIB) from January 1, 1990, through December 31, 1994, who survived at least 5 years after the initial breast cancer diagnosis. We selected 5-year survivors because this time period is most often used as a benchmark to define recovery.[19] These women were participants in the BOWI study.[21] Briefly, the BOWI multisite cohort study is a 10-year longitudinal study focusing on the effectiveness of treatment for breast cancer. Women in the BOWI cohort were identified through Cancer Research Network (CRN) managed care systems: Group Health Cooperative, Seattle, Washington; Kaiser Permanente, Southern California; Lovelace Health System, New Mexico; Henry Ford Hospital and Health System, Detroit, Michigan; Health Partners, Minnesota; and Fallon Community Health Plan, Massachusetts. [21] These CRN sites were selected to achieve diversity in geography, system size, and patient populations.

The BOWII study extended data collection through 5 additional years of follow-up on the BOWI cohort and added a comparison group. The eligible BOWII case group for this analysis consisted of 1361 five-year breast cancer survivors. Comparison women were selected from the source population of each health plan. Comparisons included women who were cancer free at the time of the case's year of diagnosis, and frequency matched (1:1) on age, health plan site, and enrollment year. These potential confounders were selected as matching variables because they are strongly associated either with survival or with treatments. To be eligible, comparison women also had to survive 5 years after enrollment into the study cohort. The final cohort consisted of 2722 women (1361 matched pairs). Women were followed from 5 years after the index date (breast cancer diagnosis date or matched enrollment date) until first CVD event, disenrollment from the health plan, loss to clinical follow-up, death, or completion of 15 years of follow-up (up to December 31, 2009), whichever occurred first. The protocol for this study was reviewed and approved by the institutional review board at each participating CRN site.

Data Source

Data on CVD outcomes, demographics, comorbidities, and other covariates were ascertained primarily from the women's medical records and were supplemented with electronic health records. Standardized medical record reviews were conducted at each site by trained medical record abstractors. A detailed description of the data collection system and the training procedures implemented to standardize data collection across sites has been published elsewhere.[22] Mortality data (date of death and whether the cause was related to breast cancer) were collected using the National Death Index. We used mortality information for censoring in the analysis.

Data Elements

Cardiovascular Outcomes. Study outcomes included the following CVD events and were examined as a single binary composite outcome (presence or absence of any event): myocardial infarction, congestive heart failure, coronary artery disease, arrhythmias, and cerebrovascular disease. The CVD events were identified by the first occurrence of a diagnosis in the women's medical charts during the study follow-up period. Women with a diagnosis for multiple events on the same day were assigned a single outcome using a priority scale based on importance per the recommendation of one of the study clinicians (RAS): (1) myocardial infarction, (2) coronary artery disease, (3) cerebrovascular disease, (4) arrhythmia, and (5) congestive heart failure.[23]

Demographics and Cardiovascular Disease Risk Factors. We gathered information on date of birth, race, and ethnicity. We also collected information on diabetes, hypertension, smoking status, and BMI for both groups. Information closest to time of entry into the cohort was used in the analyses.

Statistical Analyses

Differences in demographic characteristics and CVD risk factors between case and comparison women were first examined by comparing frequency distributions (*P* values were based on χ^2 or Fisher exact tests). Cox proportional hazards models were used to estimate the hazard ratio (HR) of the association of CVD composite outcome with case-comparison status. Because we examined only the first CVD outcome (and not multiple occurrences), and as this model is the standard approach for analyzing cohort data, we used the Cox model.[24]

Table 1. Demographics and CVD Risk Factors Among Breast Cancer Cases and Comparisons at Study Entry

	Cases (n = 1361)		Comparisons (n = 1361)		Total (n = 2722)		
Characteristic[a]	**No.**	**%**	**No.**	**%**	**No.**	**%**	***P***
Age category, y							
70-74	502	36.88	502	36.88	1004	36.88	
75-79	417	30.64	417	30.64	834	30.64	
≥80	442	32.48	442	32.48	884	32.48	
Race/ethnicity							.34
White non-Hispanic	1115	81.93	1147	84.28	2262	83.10	
Asian	37	2.72	27	1.98	64	2.35	
African American	137	10.07	125	9.18	262	9.63	
Hispanic	72	5.29	62	4.56	134	4.92	
BMI, kg/m²[a]							.012[b]
<20	74	5.44	104	7.64	178	6.54	
20-29	717	52.68	720	52.90	1437	52.79	
30+	291	21.38	245	18.00	536	19.69	
Missing	279	20.50	292	21.45	571	20.98	
Smoking history							.62[b]
Never	363	26.67	368	27.04	731	26.86	
Nonsmoker	513	37.69	484	35.56	997	36.63	
Current	77	5.66	89	6.54	166	6.10	
Former	336	24.69	341	25.06	677	24.87	
Missing	72	5.29	79	5.8	151	5.55	
Diabetes							.19[b]
Yes	206	15.14	182	13.37	388	14.25	
No	1155	84.86	1179	86.63	2334	85.75	
Hypertension							.0053
Yes	866	63.63	795	58.41	1661	61.02	
No	495	36.37	566	41.59	1061	38.98	

*BMI indicates body mass index; CVD, cardiovascular disease.
[a]Counts may not sum to total due to missing data.
[b]*P* values are based on known values.

We tested the proportional hazards assumption using Schoenfeld residuals.[25] The subjects' entry into the analysis corresponded to 5 years after the initial breast cancer diagnosis for the cases and matched enrollment date for the comparisons. We examined the association with 2 models: a parsimonious model adjusted for the matching factors, age, and site, and another model that included hypertension, diabetes, smoking history, BMI, and race/ethnicity. Life table analysis was used to compare CVD incidence by case-comparison status.

RESULTS

Demographic characteristics, comorbidities, and CVD risk factors for cases and comparisons are displayed in Table 1. Although the majority of women in both groups were white non-Hispanic (81.9% and 84.3% for cases and comparisons, respectively), the race/ethnicity distribution was similar in both groups (P = .34). Case patients were more likely to be obese (BMI >30 kg/m^2, P = .01) and have hypertension (P = .005) than comparison women. There were no significant differences observed in smoking history and diabetes between the 2 groups.

Table 2 displays follow-up characteristics of the case and comparison groups. The mean follow-up time among cases was 5.0 years (1828 days) after entry into the cohort compared with 5.3 years (1942 days) among comparisons. Nearly 20% of women in both groups completed 15 years of follow-up (17.4% and 19.7% for cases and comparisons, respectively). Nearly half of the women in both groups experienced a CVD event during the follow-up period, with a slightly higher proportion of comparisons experiencing a CVD event (47.7%) than cases (45.3%). The fraction of deaths was nearly 2-fold

Table 2. Follow-up Among Breast Cancer Cases and Comparisons

Follow-up	Cases (n = 1361)	Comparisons (n = 1361)	Total (n = 2722)
Follow-up, y			
Mean	5.00	5.32	—
Median	4.53	5.28	—
Interquartile range (Q1, Q3)	1.58, 8.93	1.87, 9.40	—
Follow-up status, n (%)			
Incident CVD	617 (45.33)	649 (47.69)	1266 (46.51)
Completed 15-year follow-up	237 (17.41)	268 (19.69)	505 (18.55)
Disenrolled/lost to follow-up[a]	212 (15.58)	279 (20.5)	491 (18.04)
Died	295 (21.67)	165 (12.12)	460 (16.90)
Breast cancer deaths	97 (7.20)	2 (0.15)	99 (3.64)
Died due to other causes	198 (14.55)	163 (11.98)	361 (13.26)

CVD indicates cardiovascular disease.
[a]Category includes women who may still have been insured through the health maintenance organization, but who clinically were lost to follow-up (eg, receiving care at nursing home).

greater in cases (21.7%) than in comparisons (12.1%). As expected, there was a greater risk of death due to breast cancer among cases. Nearly one-third died of breast cancer in the case group (97/295) versus 1% in the comparison group (2/165).

Of the 2722 total women in the entire cohort, 1266 (46.5%) experienced a CVD event. Of the 1266 women, 740 experienced 1 of the 5 CVD events constituting the composite outcome and 526 experienced 2 or more CVD events during follow-up (data not shown). Table 3 shows the incidence of first CVD event during the follow-up period (maximum 10 years) for the composite outcome as well as the individual conditions. No overall differences were found with the composite CVD outcome (P = .40) nor with the individual outcomes in terms of risk. The rates of the composite CVD outcome and the individual outcomes were also similar in cases and comparisons (83.3/1000 person-years vs 82.90/1000 person-years, respectively). We also examined the risk of CVD in the 2 groups over time. The life table curves for CVD events by case-comparison status showed no difference in overall survival probabilities between the 2 groups (data not shown).

Table 4 presents the adjusted HR for the association between CVD and case-comparison status. Multivariable models were initially adjusted for matching factors (model 1 included age at diagnosis and health plan site). Cases were no more likely to experience a CVD event than comparisons (HR = 1.00; 95% confidence interval [CI], 0.90-1.12). In model 2, we further examined race/ethnicity, BMI, smoking history, diabetes, and hypertension. Interestingly, the strongest predictors of CVD were smoking history, diabetes, and hypertension rather than breast cancer case-comparison status (HR = 0.97; 95% CI, 0.87-1.09). For example, smoking history increased CVD risk by nearly 30% (HR = 1.29; 95% CI, 1.15-1.46). Women with diabetes were 72% more likely to develop CVD (HR = 1.72; 95% CI, 1.48-1.99), and those with hypertension were 48% more likely to develop CVD after accounting for case-comparison status (HR = 1.48; 95% CI, 1.31-1.67). Also, white women were 50% (HR = 1.51; 95% CI, 1.28-1.77) more likely to develop CVD than minority women. As expected, CVD risk increased with older age (P for trend <.10). We did not find a trend with BMI categories, possibly due to missing values. We repeated the Cox regression analysis excluding the 121 survivors exposed to chemotherapy (and their matched comparisons). As the subset results were similar, we reported the HRs of the full cohort.

DISCUSSION

Our goal was to determine whether older cancer survivors are at increased risk of CVD events compared with the general population. In this population-based study of more than 2700 breast cancer survivors 65 years and older and age-matched comparison women, we found that the risk of CVD was similar in the 2 groups. The incidences of the composite CVD outcome were the same, as were the incidences of the individual conditions.

Very few studies have compared CVD risk factors and outcomes of cancer survivors with those of a general population of women to determine whether there truly is an excess risk among cancer survivors. Our results were consistent with the few studies that have included a comparison group. For example, a Dutch study examined more than 4000 breast cancer survivors and compared their CVD incidence with that of a

Table 3. Distribution of CVD Incidence (First Event) by Case and Comparison Status

	Cases (7407 PYs)			Comparisons (7828 PYs)			Total	
Outcome	No.	%	Crude Rate per 1000 PYs	No.	%	Crude Rate per 1000 PYs	No.	%
Composite CVD outcome[a] (*P* = .40)	617	45.33	83.30	649	47.69	82.90	2722	100
CVD outcome[a]								
Myocardial infarction	125	9.18	16.88	145	10.65	18.52	270	9.92
Coronary artery disease	108	7.94	14.58	101	7.42	12.90	209	7.68
Cerebrovascular disease	108	7.94	14.58	132	9.70	16.86	240	8.82
Arrhythmia	176	12.93	23.76	167	12.27	21.33	343	12.60
Congestive heart failure	100	7.35	13.50	104	7.64	13.29	204	7.49

CVD indicates cardiovascular disease; PYs, person-years.
[a]Priority ranking of first CVD event for women with more than 1 event on same day: myocardial infarction, coronary artery disease, cerebrovascular disease, arrhythmia, congestive heart failure.

Table 4. Comparison of CVD Risk Between Breast Cancer Group and Comparison Group

CVD Risk	Adjusted HR	95% CI
Model 1[a]		
Breast cancer cases	1.00	0.90-1.12
Comparison	1.00	Reference
Model 2[b]		
Breast cancer cases	0.97	0.87-1.09
Comparison	1.00	Reference
Age category, y		
70-74	1.00	Reference
75-79	1.39	1.20-1.60
≥80	2.44	1.12-2.80
Race/ethnicity		
White non-Hispanic	1.51	1.28-1.77
All other	1.00	Reference
BMI, kg/m^2		
<20	1.00	Reference
20-29	0.87	0.76-0.99
30+	1.02	0.87-1.20
Smoking history		
Current/former	1.29	(1.15-1.46)
Never/nonsmoker/no mention	1.00	Reference
Diabetes		
Yes	1.72	(1.48-1.99)
No	1.00	Reference
Hypertension		
Yes	1.48	(1.31-1.67)
No	1.00	Reference

BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
[a]Adjusted for age and health plan site.
[b]Model included health plan site in addition to listed variables.

general female population, and determined that radiation to the breast alone did not increase CVD risk.[26] Similar to our present study, breast cancer survivors followed in Ontario, Canada, also did not have an increased risk of myocardial infarction compared with age-matched women from the general population (other CVD outcomes were not studied).[27] However, in these 2 studies, comorbid conditions were not examined. The remaining studies examined CVD outcomes *within* a group of breast cancer survivors and focused on cancer treatments, whereas our aim was to examine risk factors common to both groups. Further, few of these studies included a cancer-free comparison group and, again, did not examine the impact of comorbid conditions or lacked information on lifestyle factors (smoking history, BMI).[10,11,26,27]

Our study has a number of strengths. A major advantage of this study is that data elements were mainly obtained from medical record reviews, not solely from electronic clinical data.[20] We carefully identified a group of comparison women (without breast cancer) to determine whether there truly was excess CVD morbidity in the cancer case group. In addition, mean follow-up time was similar in both groups, thereby reducing the potential for selection bias. Importantly, the case and comparison groups were followed a maximum of 15 years; manifestation of CVD requires more than a decade of follow-up.

Certain limitations of this study must be considered. Although we captured low-density lipoprotein (LDL) cholesterol and glycated hemoglobin (A1C) levels from health plan laboratory databases, very few women had these values (overall, about 70% of women had missing LDL levels and 85% had missing A1C levels; data not shown). Therefore, we did not include these variables in the analyses. However, the percentage of missing values was nondifferential (71% of the cases had missing LDL cholesterol levels vs 67% of comparisons; 83% of cases had missing A1C levels vs 85% of comparisons), so any bias resulting from this exclusion was likely to be minimal. Similarly, many women were missing BMI, but again, the percentage of missing values was nondifferential (roughly 20% in both groups). In addition, all women in this study were selected from integrated healthcare delivery systems, so their experiences may not reflect those of others in the general population. However, we selected a nationally representative group of health plans, and the race/ethnic distribution of these subjects was similar to the source population at each health plan.

Because our main objective was to examine factors common to *both* cases and comparisons, and because very few breast cancer patients in our study underwent chemotherapy (121 of 1361 cases), we did not examine the impact of chemotherapy within the cancer case group. In a sensitivity analysis, when we excluded breast cancer survivors exposed to chemotherapy, the results were similar to those with the full cohort. In general, as older breast cancer survivors are less likely to receive chemotherapy, our results are still generalizable to a broader group of older breast cancer survivors.[21] However, our results may only be generalizable to breast cancer survivors cared for in other integrated healthcare delivery systems. For similar reasons, we did not examine the impact of aromatase inhibitors in the breast cancer survivor group. Few survivors used such drugs (98 of 1361 cases), as the majority were diagnosed before the availability of aromatase inhibitors in the mid 2000s. However, given the long latency of CVD (which may be 10 or more years), we were able to capitalize on the long observation period in this study (maximum of 15 years postdiagnosis).[27] Before risk-benefit ratios can be determined, data on the long-term toxicity profiles of aromatase inhibitors need to be available, and these data are still pending. In addition, while a few studies suggest that aromatase inhibitors may slightly increase cardiotoxicity,[28,29] tamoxifen may be cardioprotective.[30,31] Therefore, given that nearly 900 of the 1361 breast cancer patients used tamoxifen, it is possible that the lack of difference in CVD outcomes between cases and comparisons could be partially attributed to the cardioprotective effect of tamoxifen.

Overall, our results suggest that older long-term, early-stage breast cancer survivors have a risk of CVD similar to that of otherwise healthy women of comparable ages. The established risk factors (very old age, smoking history, diabetes, and hypertension) were more predictive of CVD risk than breast cancer history status. For long-term survivors, comorbid conditions are a greater health threat than the initial cancer.[32] This study demonstrates that long-term prognosis in older breast cancer patients is affected by management of preexisting conditions, and these may be best managed by primary care providers.[33] Our results also suggest that management of comorbidities in survivors should not be different from that in the general population of older patients. The transfer of cancer survivorship care to primary care settings is a challenge; however, careful attention to follow-up care of other chronic diseases in survivors may best be facilitated in coordinated healthcare systems.

Acknowledgments

The BOWII study is an HMO Cancer Research Network–affiliated study supported by Public Health Service grant R01CA093772-05A2 (Rebecca A. Silliman, MD) from the National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services. The goal of the HMO Cancer Research Network is to use the consortium of 14 integrated healthcare delivery systems with more 11 million enrollees nationwide to conduct research on cancer prevention, early detection, treatment, long-term care, surveillance, and cancer communication and dissemination and implementation research (NCI U19 CA079689 Ed Wagner, principal investigator).[34]

Participating institutes include the following: (1) Meyers Primary Care Institute, Fallon Community Health Plan; (2) Geisinger Center for Health Research, Geisinger Health System; (3) Group Health Research Institute, Group Health Cooperative; (4) Department of Population Medicine, Harvard Pilgrim Healthcare Institute; (5) Health Partners Research Foundation, HealthPartners; (6) Department of Research, Henry Ford Hospital and Health System; (7) Institute for Health Research, Kaiser Permanente Colorado; (8)

Center for Health Research–Southeast, Kaiser Permanente Georgia; (9) Center for Health Research–Hawaii, Kaiser Permanente Hawaii; (10) Division of Research, Kaiser Permanente Northern California; (11) Center for Health Research–Northwest, Kaiser Permanente Northwest; (12) Department of Research and Evaluation, Kaiser Permanente Southern California; (13) LCF Research, Lovelace Health System; and (14) Marshfield Clinic Research Foundation, Marshfield Clinic. Additional support for the analysis was provided by NCI R01CA136743 (RH).

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Funding Source: Research reported in this publication was supported by the National Cancer Institute, National Institutes of Health, under award numbers R01CA093772 (RAS), R01CA136743 (RH), and U19CA079689 (EW).

Author Disclosures: Dr Haque reports that she has received grants from California Breast Cancer Research Program. The other authors (MP, AMG, AK, SST, CA, RAS, VQ, MUY) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (RH, SST, RAS, MUY); acquisition of data (RH, AK, VQ, MUY); analysis and interpretation of data (RH, SST, RAS, MUY); drafting of the manuscript (RH, SST, RAS, and MUY); critical revision of the manuscript for important intellectual content (RH, SST, RAS, MUY); statistical analysis (RH, SST); provision of study materials or patients (RH, AK, VQ, MUY); obtaining funding (RAS); administrative, technical, or logistic support (RH, CA, RAS, VQ); and supervision (RH, RAS).

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