Favorable Cardiac Risk among Elderly Breast Carcinoma Survivors

Elizabeth B. Lamont, M.D., M.S.[1–3]
Nicholas A. Christakis, M.D., Ph.D., M.P.H.[4]
Diane S. Lauderdale, Ph.D.[5]

[1] Section of General Internal Medicine, Department of Medicine, The University of Chicago, Chicago, Illinois.

[2] Section of Hematology-Oncology, Department of Medicine, The University of Chicago, Chicago, Illinois.

[3] Cancer Research Center, The University of Chicago, Chicago, Illinois.

[4] Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts.

[5] Department of Health Studies, The University of Chicago, Chicago, Illinois.

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Address for reprints: Elizabeth B. Lamont, M.D., University of Chicago Medical Center, 5841 S. Maryland Ave., MC 2007, Chicago, IL 60637; Fax: (773) 834-2238; E-mail: elamont@medicine.bsd.uchicago.edu

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BACKGROUND. There are two reasons why women who survive breast carcinoma may be at a lower risk of developing coronary heart disease (CHD) compared with women without a history of breast carcinoma. First, estrogens may be etiologic in the development of breast carcinoma and protective of CHD. Second, a common therapy for breast carcinoma (tamoxifen) may be associated with cardiac protection.

METHODS. In this population-level cohort study, the authors analyzed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)-Medicare program to study the cardiac risk of elderly female Medicare beneficiaries with and without a history of breast carcinoma. Using the SEER file, the authors identified elderly women survivors of Stage 0, I, or II breast carcinoma (n = 5980) diagnosed between the ages of 55 and 64. Using the Medicare 5% noncancer file, the authors also identified elderly women without a history of cancer (n = 23,165). They followed women from age 67 for up to 5 years for hospitalization for acute myocardial infarction (AMI) through a review of Medicare claims. The authors controlled the analyses for race, socioeconomic status, geographic location, cohort entry year, and medical comorbidity.

RESULTS. The hazard of hospitalization for AMI for breast carcinoma survivors relative to comparison patients was 0.66 (95% confidence interval, 0.49–0.88). This apparent cardioprotective effect of breast carcinoma survivorship was stronger in breast carcinoma survivors with documented cardiac risk factors.

CONCLUSIONS. Survivors of early-stage postmenopausal breast carcinoma are at a significantly lower risk of hospitalization for AMI than women who do not have a history of breast carcinoma. That survivors' risk varies with previous cardiac risk factors may be consistent with effects of selective estrogen receptor modulators. This phenomenon should be evaluated further with individual-level data containing information on patient cardiac risk factors and tamoxifen use to help clarify the mechanism behind the risk reduction. ***Cancer*** **2003;98:2–10.**

KEYWORDS: estrogen, coronary heart disease (CHD), elderly women, acute myocardial infarction (AMI); survivorship; breast cancer.

The hormone, estrogen, is associated strongly with both health and disease in women. Its effects are mediated through the estrogen receptor in cells, which is relevant to many organ systems including the reproductive, bone, and cardiovascular systems.[1] Comparatively high estrogen exposure (endogenous and/or exogenous) is protective against some diseases (e.g., coronary heart disease [CHD], osteoporosis), but contributory to others (e.g., breast and endometrial carcinoma).[2–9] Consistent with estrogen's role in the genesis of these conditions, an inverse relationship between osteoporosis and breast carcinoma in women has been explored and established by epidemi-

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ologic and clinical research.[10–16] Through different methodologies and in different samples of women, investigators consistently find that the women who develop osteoporosis generally do not develop breast carcinoma. Although there is reason to believe that a similar inverse relationship may also exist between the conditions of CHD and breast carcinoma in women, there is little research on this issue.[17,18]

More work has focused on the cardiovascular effects of tamoxifen, a nonsteroidal selective estrogen receptor modulator (SERM) that is used commonly in the adjuvant treatment of postmenopausal women with breast carcinoma. An estimated 68% of elderly women with lymph node-positive tumors receive adjuvant tamoxifen as do approximately 50% of those with lymph node-negative tumors.[19] Tamoxifen has antiestrogen effects against the estrogen receptors in breast tissue and breast tumors, but may have stimulatory effects on the estrogen receptors in other sites relevant to bones and the cardiovascular system. Its antiestrogen effects on breast tumors make it an attractive anticancer therapy for women with breast tumors that express the estrogen receptor, as well as a preventive treatment for women at high risk for developing breast carcinoma. Some clinical trials have raised the possibility of a cardioprotective effect of two SERMs, tamoxifen[20–23] and raloxifene.[24] Two European randomized trials of tamoxifen among women with early-stage breast disease found statistically borderline to significant reductions in the risk of hospitalization for acute myocardial infarction (AMI) in women randomized to the adjuvant tamoxifen therapy arms.[20,21] One study reported a 32% reduction in risk of hospitalization for AMI ($P = 0.03$)[20] and the second study reported a 48% reduction in the same end point ($P = 0.05$).[21]

In the U.S., results have been suggestive, but not statistically significant.[22,23] Investigators for the National Surgical Breast and Bowel Project (NSABP) have reported a 34% (95% confidence interval [CI], 0.27–1.6) nonsignificant reduction in the risk of death from AMI among women treated on the tamoxifen arm of the randomized B-14 trial of adjuvant tamoxifen in early-stage breast carcinoma.[22] The NSABP investigators also evaluated participants of a large randomized breast carcinoma prevention trial (P-01)[23] and, overall, found no difference in the rates of cardiovascular events between women randomized to tamoxifen compared with women who received a placebo. However, among women with a history of CHD, tamoxifen-treated women had a 31% (95% CI, 0.20–2.18) nonsignificant risk reduction in the end point of total AMI (including both fatal and nonfatal) relative to similar women receiving placebo.[23]

Selective estrogen receptor modulators as potential modifiers of preexisting cardiac risk in women without a diagnosis of breast carcinoma has been suggested in the Multiple Outcomes of Raloxifene Evaluation randomized trial of raloxifene in osteoporotic postmenopausal women.[24] Although women randomized to the raxolifen arms had similar rates of cardiovascular events, women with cardiac risk factors (CRF) who were randomized to treatment with raloxifene experienced a 40% (95% CI, 0.38–0.95) reduction in their risk of cardiovascular events ($P = 0.03$). Further, the investigators found that as the patients' number of cardiovascular risk factors increased, so too did the risk reduction associated with raloxifene. Possible mechanisms include the effect of SERMs on lipids, vascular endothelium, insulin-like growth factor-I, and homocysteine.[25–29]

For two reasons, women with a history of breast carcinoma may be at a lower risk of developing CHD than women without a history of breast carcinoma. First, estrogens may be etiologic in the development of breast carcinoma and protective of CHD. Second, a common therapy for breast carcinoma (tamoxifen) may be associated with cardiac protection. We tested the hypothesis that breast carcinoma survivors are at a lower risk of CHD than women without a history of breast carcinoma.

MATERIALS AND METHODS

Data Sources

We used data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER)-Medicare program to study the cardiovascular risk of elderly female Medicare beneficiaries with and without a history of breast carcinoma. The SEER-Medicare program is an NCI-sponsored link between the clinical data collected by the SEER registries and the health services billing claims collected by Medicare for administrative purposes.

The SEER program collects information regarding the diagnosis and treatment of patients with cancer from 11 geographically diverse tumor registries to monitor trends in incidence and survival. Approximately 14% of the American population with cancer is represented in these data.[30] Previous research has shown that, in the aggregate, patients in these registries are demographically representative of the general population.[31] The SEER program collects detailed information about initial diagnosis and treatment, including date of diagnosis, site, histology, stage of tumor at diagnosis, and date of death as well as demographic information. The SEER data are linked to state death certificates by the National Center for Health Statistics and both the date and cause of death

are added to SEER records. The data are also linked to Medicare claims files. To facilitate comparisons between Medicare enrollees with and without cancer, the NCI has created a data file that identifies a 5% random sample of Medicare beneficiaries who reside in SEER areas, but who do not have cancer files in SEER. Because these are Medicare records, SEER variables, such as cause of death, are not uniformly available for these patients. We used the 5% random sample of Medicare beneficiaries to identify elderly women without a history of breast carcinoma to serve as our comparison group.

Medicare is a federally sponsored health insurance program administered by the Centers for Medicare and Medicaid Services (CMS). Beneficiaries include greater than 96% of all U.S. citizens aged 65 years and older.[32] The CMS maintains billing records of outpatient, inpatient, home health, hospice, and other claims for all beneficiaries not enrolled in risk contract health maintenance organizations (HMOs). To determine the inpatient and outpatient medical services for the study population (both SEER and comparison patients), we used three types of Medicare files: the Medicare Provider Analysis and Review (MEDPAR) file, the Outpatient Standard Analytic File (OUTPT), and the National Claims History (NCH) file.

Cohort Development

Using Medicare claims files from 1993 to 1998, we selected a cohort of female Medicare beneficiaries who reached age 67 years during 1992 and added women annually through 1998, who had reached age 67 years in the preceding 12 months. Additional eligibility requirements included being entitled to at least Medicare Part A during the observation period and not being enrolled in an HMO whose claims were not processed by CMS during the observation period.

The cohort included all women with SEER records that documented a history of early-stage breast carcinoma (i.e., Stage 0, I, or II disease and not patients with Stage III or IV disease) and patients who did not have SEER records for cancer but whoresided in SEER areas. We term those women with a history of breast carcinoma "breast cancer survivors" and those without a history of cancer "comparison patients." The breast carcinoma survivors (n = 5980) were all female patients in the SEER file who were diagnosed between the ages 55–64 years with pathologically confirmed American Joint Commission on Cancer (AJCC) Stage 0, I, and II carcinoma (i.e., ductual, lobular, medullary, adenocarcinoma) of the breast and who did not have claims suggestive of active breast carcinoma within Medicare files from a 2-year comorbidity adjustment period directly preceding cohort entry at age 67 years. The lower limit of the diagnostic age range (age 55 years) was chosen to ensure the exposure was postmenopausal breast carcinoma and the upper limit (age 64 years) was chosen to allow a minimum breast carcinoma acute therapy washout period of 2 years before outcome ascertainment. The median time since their breast carcinoma diagnosis was 5.5 years (range, 2.0–12.7 years). The comparison patients (n = 23,165) were all female patients within the 5% random sample of Medicare beneficiaries from 1 of the 11 SEER regions who did not appear in the SEER cancer registries and did not have claims for breast carcinoma within Medicare files from a 2-year comorbidity adjustment period directly preceding cohort entry at age 67 years.

Outcome Ascertainment

For each member of the two groups forming our cohort, we evaluated the MEDPAR files from the outcome assessment period (i.e., cohort entry date [January 1st of the cohort entry year] until death or fixed right censoring on December 31, 1998) for the principal discharge diagnosis of AMI using the method described by Krumholz et al.[33] Admissions with a primary diagnosis field containing ICD-9-CM Code 410 were coded as AMI and admissions unrelated to the acute care of an AMI were not included (i.e., those for which the fifth digit of the ICD-9-CM code is "2").

Definition of Explanatory Variables

Our key explanatory variable was breast carcinoma history ascertained from the SEER file. Additional variables of patient age and race were taken from the Medicare denominator file for each member of the cohort. As individual-level indicators of socioeconomic status are not available in the Medicare files, we used median income for the zip code of residence according to U.S. census data. This information was transformed into quartiles and treated categorically.[34,35] Patients' cancer-related variables of tumor stage and date of diagnosis were ascertained from the SEER file.

For each cohort member, we derived three broad comorbidity indices using Medicare claims files for the 2-year comorbidity adjustment period that directly preceded cohort entry. Hereafter, we refer to this period as the "24 month look-back period." The comorbidity strategy we used is an application of the Charlson comorbidity score (CS). We used the diagnosis codes (ICD-9-CM) within the Medicare MEDPAR, NCH, and OUTPT files during the 24 month look-back period[36–38] and generated a separate comorbidity index from each of the three files. That is, for each of the three Medicare files, each enrollee was placed into one of the following four categories using the method de-

scribed by Zhang et al.[38]: CS = 0, CS = 1 , CS above 1, no previous claims (for patients without claims in that file in the 24-month look-back period).

Finally, we created a new CRF score variable that represented the sum of three common CRFs: 1) previous myocardial infarction, 2) diabetes, and 3) emphysema (as a proxy for tobacco history). We screened each patient's three CS diagnoses for any code indicating the three CRFs. For each patient, we added the risk factors and generated a single CRF summary score (range, 0–3 [i.e, from no risk factors present to all three risk factors present]). Our conclusions did not vary with different parameterizations of the cardiac risk score including a multiple indicator variables approach. Therefore, we presented the results with a linear cardiac risk score effect for simplicity.

Statistical Analyses

We compared breast carcinoma survivors and comparison patients with respect to categorical and continuous demographic and health variables, using chi-squared tests and analysis of variance, respectively. We then used multivariate Cox regression to model the hazard of hospitalization for first AMI in breast carcinoma survivors versus comparison patients, adjusting for demographic and health variables. Among patients who did not experience the event of interest, those who died before the end of the observation period were censored at death and the remaining patients were censored at study termination (December 31, 1998).

We then examined whether the association between breast carcinoma survivorship and AMI risk varied with the cohorts' cardiac risk to evaluate for 1) possible differential health among breast carcinoma patients and comparison patients and 2) a possible etiologic role for tamoxifen. We restricted our analyses to women with invasive breast carcinoma (i.e., Stage I and II disease), the group with the highest probability of tamoxifen exposure, and to non-breast carcinoma comparison patients. We then used Cox regression to model time to hospitalization for AMI and included an interaction term of breast carcinoma survivorship multiplied by the CRF score, adjusting for the other demographic and disease variables from the previous model. The interaction term tests whether the effect of breast carcinoma survivorship on risk of incident AMI varied with CRFs.

To assess whether breast carcinoma survivors are systematically healthier than comparison patients, potentially related to 1) having an illness that was screening detected, 2) having survived one life-threatening diagnosis and its treatment or 3) having a higher probability of regular medical care, we evaluated the cohort for incident hospitalizations for a causally distinct illness, pneumonia. A hazard reduction in pneumonia among breast carcinoma survivors might suggest that any hazard reduction in AMI was spurious and related to confounding by better underlying health status and/or better medical care.

Finally, we conducted two sensitivity analyses to address concerns that 1) there might be differential positioning of the AMI diagnostic codes in the MEDPAR file for breast carcinoma survivors relative to comparison patients that would lead to a spuriously low rate of events among the survivors and 2) breast carcinoma survivors may be more likely to die of AMIs outside of a hospital and thus our restriction to the MEDPAR file for outcome ascertainment would again lead to a spuriously low rate of events among the survivors.

All analyses were performed using STATA 7.0 software (Stata, College Station, TX). The research was approved and conducted in accordance with the University of Chicago Institutional Review Board regulations.

RESULTS

Cohort Characteristics

Table 1 presents the demographic and disease-related characteristics of the breast carcinoma survivors and comparison patients. A higher proportion of breast carcinoma survivors were white and resided in zip code regions with higher median incomes. The breast carcinoma survivors more often had claims in each of the three Medicare files during the 24-month look-back period and had slightly lower comorbidity scores. Breast carcinoma survivors and comparison patients had similar rates of each of the three risk factors and CRF scores. Table 2 contains censoring proportions by exposure status for the cohort. More breast carcinoma survivors exited the cohort due to early death without the outcome of interest (0.07 vs. 0.04; $P < 0.001$).

Time to Acute Myocardial Infarction Analyses

Modeling time to hospitalization for first myocardial infarction, the hazard of AMI for breast carcinoma survivors compared with controls, adjusting for age and race, was 0.74 (95% CI, 0.56–0.98). From a multivariate Cox proportional hazards model that further adjusted for socioeconomic status, geographic region, cohort entry year, and comorbidity, the hazard of AMI for breast carcinoma survivors compared with controls was 0.66 (95% CI, 0.49–0.88). In addition, living in a zip code in the highest quartile of median income was associated with reduced risk. High amounts of comorbidity, as measured by CS ascertained from ICD-9-CM codes within MEDPAR, NCH, and OUTPT

TABLE 1
Characteristics of Cohort by History of Breast Carcinoma (n = 29,145)

Variable	Breast carcinoma history (n = 5,980)	No breast carcinoma history (n = 23,165)	P value
Age (yrs) (mean)	67.5 (SD ± 0.29)	67.5 (SD ± 0.28)	0.056
Race (proportion)			< 0.001
White	0.88	0.79	
African-American	0.05	0.07	
Other	0.07	0.12	
Unknown	<0.01	0.01	
Zip code income (median)	$39,122	$36,432	< 0.001
Geographic region (proportion)			< 0.001
California	0.20	0.27	
Connecticut	0.15	0.11	
Michigan	0.16	0.14	
Hawaii	0.04	0.04	
Iowa	0.16	0.13	
New Mexico	0.04	0.05	
Washington	0.13	0.08	
Utah	0.05	0.05	
Georgia	0.07	0.07	
Unknown	0.00	0.07	
Cohort yr (proportion)			< 0.001
1993	0.11	0.18	
1994	0.14	0.17	
1995	0.17	0.15	
1996	0.24	0.16	
Breast carcinoma AJCC stage (proportion)			
Stage 0 (DCIS)	0.17	-	
Stage I	0.48	-	
Stage II	0.34	-	
Breast carcinoma diagnosis < 5 yrs (proportion)	0.43	-	
Two-yr look-back variables (ages 65–66) continuous Charlson scores[a] (mean)			
MEDPAR file	0.98	0.99	0.923
No previous claims (proportion)			
MEDPAR file	0.83	0.86	< 0.001
NCH file	0.13	0.18	< 0.001
OUTPT file	0.28	0.43	< 0.001
All three files	0.11	0.16	< 0.001
Diagnoses for cardiac risk factors during ages 65–66			
AMI Previous	0.02	0.02	0.589
Diabetes	0.15	0.14	0.302
Emphysema	0.015	0.015	0.731
Cardiac risk factor score (mean)	0.19	0.18	0.341

SD: standard deviation; AJCC: American Joint Committee on Cancer; DCIS: ductal carcinoma in situ; MEDPAR; Medicare Provider Analysis and Review file; NCH: National Claims History file; OUTPT: Outpatient Standard Analytic file; AMI: acute myocardial infarction.

[a] Scores were calculated from patients in the cohort with claims during 2-year look-back period in the Medicare file.

files, were associated with increased hazard of AMI. Table 3 contains selected parameters from the full Cox model. Figure 1 shows the cumulative incidence of AMI during the study period for breast carcinoma survivors and comparison patients.

Interaction of Survivorship and Cardiac Risk

To evaluate whether incident AMIs varied among breast carcinoma survivors according to their previous cardiac risk, we used multivariate Cox regression to model time to AMI among a subset of our sample (i.e., women with a > 50% chance of having received tamoxifen [women with Stage I and II disease]) and comparison patients (n = 28,104). To do this, we evaluated the independent effect of the CRF score on time to AMI, simultaneously controlling for all variables in the previous model (Table 3). Using the Cox proportional hazards model, we found that breast carcinoma

TABLE 2
Censoring Proportions for Cohort (n = 29,145)[a]

Event/censoring	Breast carcinoma history	No breast carcinoma history
AMI	0.009	0.015
Death	0.068	0.036
Right censored	0.922	0.948
Total	1.000	1.000

AMI: acute myocardial infarction.
[a] $P < 0.001$ for this comparison.

TABLE 3
Adjusted Hazard of Hospitalization for Acute Myocardial Infarction in the Observation Period (n = 29,145)[a]

Variable	HR	95% CI
History of breast carcinoma	0.66	0.49–0.88
Age	1.01	0.72–1.42
Race		
White	1.00	(Referent)
African-American	0.82	0.54–1.24
Other	0.94	0.64–1.39
Unknown	0.63	0.15–2.57
Zip code median income		
First quartile	1.00	(Referent)
Second quartile	0.91	0.69–1.20
Third quartile	0.85	0.61–1.16
Fourth quartile	0.67	0.47–0.97
Unknown	0.87	0.54–1.41
Charlson comorbidity score		
MEDPAR CS = 0	1.00	(Referent)
MEDPAR CS = 1	1.41	1.14–3.48
MEDPAR CS > 1	2.88	1.82–4.56
No MEDPAR claims previous	0.90	0.62–1.31
NCH CS = 0	1.00	(Referent)
NCH CS = 1	1.65	1.25–2.18
NCH CS > 1	2.34	1.76–3.13
No NCH claims previous	0.78	0.51–1.18
OUTPT CS = 0	1.00	(Referent)
OUTPT CS = 1	1.24	0.91–1.69
OUTPT CS > 1	1.70	1.18–2.44
No OUTPT claims previous	1.01	0.78–1.31

HR: hazard ratio; CI: confidence interval; MEDPAR: Medicare Providor Analysis and Review file; NCH: National Claims History file; OUTPT: Outpatient Standard Analytic file.
[a] All dichotomous variables are coded as 0 = absent and 1 = present. Model is adjusted for geographic region and year of entry into the cohort (coefficients not reported).

survivorship remained an important and significant predictor of AMI (hazard ratio [HR] 0.68; 95%CI, 0.50–0.92) and that the CRF score strongly predicted AMI. That is, with each 1 point increase in the CRF score, the hazard of hospitalization for AMI increased by 73% (HR 1.73; 95%CI, 1.40–2.13). We then added to this model an interaction term that consisted of the breast carcinoma survivorship variable multiplied by the CRF score. In this Cox model, the interaction between the breast carcinoma survivorship and CRF was statistically significant. For example, the hazard reduction in AMI for breast carcinoma survivors was weak for those with no CRFs and strengthened with increased cardiac risk. That is, breast carcinoma survivors experienced a 43% reduction in CRF-related hazard of AMI relative to comparison patients (HR 0.57; 95% CI, 0.34–0.96). For example, the hazard of AMI among breast carcinoma survivors with no CRFs is not different from comparison patients with no CRFs (HR 0.87; 95% CI, 0.60–1.25). However, the hazard of AMI among breast carcinoma survivors with one CRF is substantially lower compared with comparison patients with one CRF (HR 0.50; 95% CI, 0.32–0.79). Table 4 contains selected parameters from the full Cox model that incorporates the CRF score as well as selected parameters from the full Cox model that incorporates the CRF score and breast carcinoma survivorship interaction.

Evaluation for the Healthy Survivor Effect

To evaluate whether breast carcinoma survivors were systematically healthier than comparison patients, we used Cox proportional hazards regression to model time to first pneumonia admission, simultaneously adjusting for all the variables in Table 3. We found a nonsignificantly elevated hazard of 1.22 (95% CI, 0.90–1.67) for pneumonia admission for breast carcinoma survivors relative to comparison patients.

Sensitivity Analyses

In the first sensitivity analysis, we evaluated the possibility that our results were confounded by differential positioning of the MEDPAR AMI diagnostic codes. In our main analyses, MEDPAR files were evaluated for AMI codes only in the first diagnostic position using the method of Krumholz et al.[33] Because a diagnosis of breast carcinoma might take primacy over AMI in the list of 10 diagnoses provided for each hospitalization catalogued in the MEDPAR file, we might have underestimated AMI among breast carcinoma survivors. When we broadened our ascertainment of AMI to include all 10 diagnostic positions per hospitalization per patient, our results did not change (HR 0.66; 95% CI, 0.49–0.88).

In the second sensitivity analysis, we evaluated whether our results were confounded by the possibility that breast carcinoma survivors were less likely to be hospitalized for rapid death from AMIs than were the comparison patients. For the breast cancer survivors, we considered the cause of death from death certificates, which had been linked to SEER records for censored observation, and found that 11 patients had died of AMI. We then changed these patients' designation to AMI from censored and reestimated the model. Cause of death information was not available

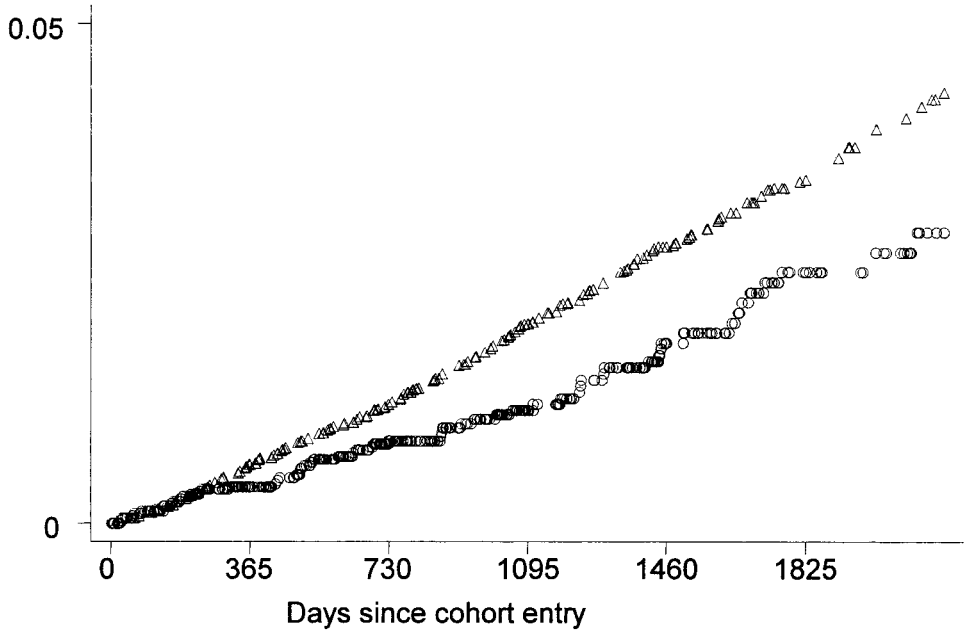

FIGURE 1. Adjusted cumulative incidence of hospitalization for acute myocardial infarction for breast carcinoma survivors (circles) and comparison patients (triangles). Data show the adjusted cumulative incidence of AMI hospitalization for breast carcinoma survivors and comparison patients with the following covariates: the patients were white women aged 70 years who entered the cohort in 1993, resided in California in zip code regions with the highest quartile of median income, and had a Charlson comorbidity score of 1.

TABLE 4
Adjusted Hazard of Hospitalization for Acute Myocardial Infarction in the Observation Period According to Breast Carcinoma Survivorship and Cardiac Risk Factors in Women with History of Invasive Breast Carcinoma Versus Comparison Patients (n = 28,104)[a]

Variable	HR	95% CI
Model 1		
Breast carcinoma survivorship	0.68	0.50–0.92
CRF (per risk factor)	1.73	1.40–2.13
Model 2		
Breast carcinoma survivorship	0.87	0.60–1.25
CRF (per risk factor)	1.83	1.48–2.26
Breast carcinoma survivorship × CRF	0.57	0.34–0.96

HR: hazard ratio; CI: confidence interval; CRF: cardiac risk factor.

[a] All dichotomous variables are coded as 0 = absent and 1 = present. Explanatory variables include a history of breast carcinoma and the cardiac risk factor score ranging from 0 to 3. The model is adjusted for age, race, income, geographic region, year of entry into the cohort, and comorbidity using the three Charlson comorbidity score-based indices for each patient derived from the Medicare Provider Analysis and Review file, National Claims History file and Outpatient Standard Analytic Medicare file (coefficients not reported).

for comparison events. For the unlikely scenario that the out of hospital deaths from AMIs occurred only among the breast carcinoma survivors, the hazard of AMI increased to 0.79 (95% CI, 0.60–1.03).

DISCUSSION

Compared with otherwise similar patients, elderly women who have survived early-stage postmenopausal breast carcinoma have a 34% lower hazard of hospitalization for AMI. The magnitude of this cardiac risk reduction is similar to the magnitude of the cardiac risk reduction reported in other cohort studies utilizing SERMs.[20–24] Breast carcinoma survivorship and risk of AMI varied with patients' baseline cardiac risk in a manner that may be consistent with previous clinical trials utilizing tamoxifen and raloxifene.[23,24] Survivorship was associated only with reduced risk of AMI among women with CRFs. This interaction effect and the lack of risk reduction in admissions for a causally unrelated illness (pneumonia) suggest that the beneficial effect of breast carcinoma survivorship on AMI risk is not mediated by better overall health and/or better medical care.

Our results have significant public health and epidemiologic implications. The public health implications are clear. We have identified a subset of women who have a 34% reduction in the disease that accounts for the largest number of deaths in elderly women in the U.S. Therefore, these patients and this phenomenon merit further study. Further work might elucidate the mechanism behind this risk reduction in breast carcinoma survivors and be leveraged to improve the cardiovascular health of the general population. That is, if tamoxifen can explain the risk reduction, then SERMs may well have a role in cardiac as well as breast carcinoma prevention.[39] These results resonate with previous findings of favorable osteoporosis risk in breast carcinoma survivors[16] and suggest that breast carcinoma survivors may have better health outcomes than other women regarding certain noncancer dimensions. However, future research should also evaluate the rates of unfavorable estrogen and tamoxifen-

related conditions like deep vein thrombosis and stroke in breast carcinoma survivors.

In addition, we pursued a novel line of epidemiologic inquiry that yielded results that question the stark dichotomies of "health" and "disease." Our results suggest that the presence of one serious illness may be protective (through, perhaps, a combination of etiology and treatment) of another serious and more common illness. This study may serve as a model for evaluating the interactions between nonmalignant disease and malignancy and its treatment.

Given the constraints of claims data, our analyses does not reveal the mechanism for this decreased risk. Such an explanation would require data enriched with clinical variables that neither SEER records nor claims data contain, like life-time estrogen exposure and tamoxifen use. In addition, claims data provide limited race coding, information on HMO enrollees is inconsistently available, and many clinical variables are lacking (e.g., CRFs of family history, smoking, hypertension, hyperlipidemia).[40–43] The socioeconomic status measure employed in this study is suboptimal given that the zip code represents an indeterminate combination of both individual and neighborhood socioeconomic characteristics.[44–46] Our study may also be limited by our cohort construction. It is possible that the effect we observed is not related to biologic factors, but instead to left truncation. That is, if the initial treatment of breast carcinoma accelerates cardiac risk (e.g., through the physiologic stress of surgery), then our cohort may be enriched with breast carcinoma survivors with a low cardiac risk.

The findings of the current study demonstrate that elderly women with a history of postmenopausal breast carcinoma have a 34% lower hazard of hospitalization for AMI relative to comparison patients without a history of breast carcinoma. The dependency of this risk reduction on CRFs may be consistent with a possible SERM effect. These findings have clinical implications for breast carcinoma survivors and may have public health implications for other women. The risk reduction in the disease that accounts for the majority of deaths in elderly women invites further research to determine its underlying mechanism.

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