

Incident comorbidities and all-cause mortality among 5-year survivors of Stage I and II breast cancer diagnosed at age 65 or older: a prospective-matched cohort study

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Abstract Five-year breast cancer survivors, diagnosed after 65 years of age, may develop more incident comorbidities than similar populations free of cancer. We investigated whether older breast cancer survivors have a similar comorbidity burden 6–15 years after cancer diagnosis to matched women free of breast cancer at start of follow-up and whether incident comorbidities are associated with all-cause mortality. In this prospective cohort study, 1,361 older 5-year early-stage breast cancer survivors diagnosed between 1990 and 1994 and 1,361 age- and health system-matched women were followed for 10 years. Adjudicated medical record review captured prevalent and

incident comorbidities during follow-up or until death as collected from the National Death Index. Older 5-year breast cancer survivors did not acquire incident comorbidities more often than matched women free of breast cancer in the subsequent 10 years [hazard ratio (HR) 1.0, 95 % confidence interval (95 % CI) 0.93, 1.1]. Adjusted for cohort membership, women with incident comorbidities had a higher mortality rate than those without incident comorbidities (HR 4.8, 95 % CI 4.1, 5.6). A breast cancer history continued to be a hazard for mortality 6–15 years after diagnosis (HR 1.3, 95 % CI 1.1, 1.4). We found that older breast cancer survivors who developed comorbidities had an increased all-cause mortality rate even after adjusting for age and prevalent comorbidity burden. Additionally, survivors acquire comorbidities at a rate similar to older women free of breast cancer. These results highlight the association between comorbidity burden and

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long-term mortality risk among older breast cancer survivors and their need for appropriate oncology and primary care follow-up.

Keywords Breast cancer · Survivorship · Comorbidity · Geriatrics · Managed care · Mortality

Abbreviations

AJCC	American Joint Committee on Cancer
BOW	Breast Cancer Treatment Effectiveness in Older Women cohort study
CCI	Charlson Comorbidity Index
CI	Confidence interval
HR	Hazard ratio
mCCI	Modified Charlson Comorbidity Index
SEER	Surveillance, epidemiology, and end results

Introduction

Breast cancer predominantly affects older women [1, 2], yet modest advances have been made in their survival relative to cohorts of younger breast cancer patients [3, 4]. An association between age and mortality has been found in older 5-year breast cancer survivors [4], and the development of incident comorbidities, such as congestive heart failure, is independently associated with aging and cancer therapy [5, 6]. It is unclear, however, whether older women who have undergone cancer therapy are more likely to develop comorbidities than older women without a history of cancer [7–9]. Furthermore, it is unknown whether incident comorbidities acquired in older breast cancer survivors are more often fatal than in comparable reference populations.

The unknown impact of incident comorbid disease following breast cancer and its treatment is an important barrier to improving survival among older women [6, 10]. Previous investigations suggest that older breast cancer survivors have increased comorbidity burden 3 years after diagnosis compared with women without breast cancer matched for age, prevalent comorbidities at baseline, and health system [11]. In a cohort of older breast cancer survivors followed for a median of 85 months after primary breast cancer, survivors experienced a 40 % higher all-cause mortality hazard for each unit increase in the Charlson Comorbidity Index (CCI) after accounting for

prevalent comorbidities at baseline and incident comorbidities during follow-up [12]. Limitations of these studies include differential loss to follow-up, selection bias, and misclassification associated with self-report of comorbid disease. Furthermore, no investigation has examined the impact of incident comorbidities following breast cancer treatment on 10-year all-cause mortality among older 5-year breast cancer survivors.

Therefore, we investigated whether incident comorbidities accumulate more frequently and rapidly among a cohort of older 5-year breast cancer survivors (aged ≥ 65 years at diagnosis) than among a comparison cohort matched for age and geography. We also assessed whether incident comorbidities impact all-cause mortality differently among survivors than matched comparators.

Methods

Setting, design, and subjects

This analysis was conducted in the longitudinal Breast Cancer Treatment Effectiveness in Older Women (BOW) cohort study, as previously described [13]. Eligible women were enrolled at one of six integrated healthcare systems within the Cancer Research Network [14]. This study was reviewed and approved by the Institutional Review Boards of each participating institution and at the Boston University Medical Center. The requirement for informed consent was waived.

BOW initially identified a cohort of older women (aged ≥ 65 years) diagnosed with early-stage invasive breast cancer [American Joint Committee on Cancer (AJCC) Stage I, IIA, or IIB] between 01/01/1990 and 12/31/1994 [15]. For this study, we restricted the cohort to 5-year survivors of primary breast cancer diagnosis ($n = 1,361$) [16]. For each survivor, we selected a comparison woman of the same age from the same health system, who was free of breast cancer at the matched survivor's date of breast cancer diagnosis (index date) and survived for 5 years after index date. Comparator women remained enrolled if they received a breast cancer diagnosis between the index date and start of observational follow-up.

Data collection and analytic variables

We collected data elements from electronic sources and through standardized medical record reviews conducted at each site by medical record abstractors trained via web-based technology who entered data directly into a computer-based, menu-driven data collection system [17, 18]. The medical record abstractor inter-rater reliability across sites was a weighted average of 95 % agreement (range

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89–98 %) [18]. A study of medical record reviews conducted during the 5 years after breast cancer diagnosis showed good inter-rater reliability for the CCI [19] and little bias from comorbidity misclassification [20]. Women were followed from 5 years after their cancer diagnosis until death, health system disenrollment, or through 15 years after index date, whichever occurred first.

All-cause mortality

We obtained date of death using the National Death Index through December 31, 2009.

Comorbidity

We collected from medical records information on incident comorbid conditions included in the CCI [19]. We estimated the CCI, updated continually, for years 6–15 after index date. Prevalent breast cancer was not included in the CCI; however, incident primary breast cancers were scored during follow-up for both cohorts. The CCI only captures some of the comorbidities identified as potential late effects of breast cancer treatment. We therefore collected incident occurrences of pulmonary emboli and osteoporotic fractures of the hip, wrist, and vertebra during follow-up, excluding fractures diagnosed as secondary to metastatic breast cancer. We calculated a modified Charlson Comorbidity Index (mCCI) score using the CCI with the addition of pulmonary emboli and osteoporotic fractures (assigned index weight of one point).

Demographic data

Age was categorized as 70–74, 75–79, and 80+ years at the beginning of follow-up. We gathered information on race and ethnicity using the National Cancer Institute surveillance, epidemiology, and end results (SEER) coding instructions [21]. Women of Hispanic ethnicity were identified and grouped into SEER race categories. For those with unknown ethnicity, the patient's last name was identified via a validated computer program search to assign ethnicity [13].

Statistical analyses

We tabulated the distribution of demographic factors, breast cancer treatment characteristics (survivor cohort only), prevalent comorbidities at beginning of follow-up (5 years after index date), and incident comorbidities acquired during years 6–15 after index date.

To compare the incidence of comorbidities among survivors with the comparison cohort during follow-up, we fit Cox proportional hazards regression models to estimate

hazard ratios (HRs) and 95 % confidence interval (95 % CI) bounds for each comorbidity separately as well as for a dichotomous composite (presence/absence) of any incident comorbidity we ascertained. HRs were adjusted for age category, health system, and existence of any prevalent comorbidity.

We tabulated the distribution of all-cause mortality by age group and cohort type. We fit an Anderson–Gill Cox proportional hazard model, adjusting for age group, cohort, and presence of any comorbidity at beginning of follow-up to examine the effect of acquiring incident comorbidities on all-cause mortality among survivors. Additional Anderson–Gill Cox proportional hazard models were fit to each individual cohort, adjusting for age group and presence of any comorbidity at beginning of follow-up, to determine the adjusted HRs of covariates within each cohort. Incident comorbidity (presence/absence) was included in the models as a time-varying covariate to account for accumulation of time between incident comorbidity and the censoring event. All statistical analyses were performed in SAS version 9 (SAS Institute, Cary, NC).

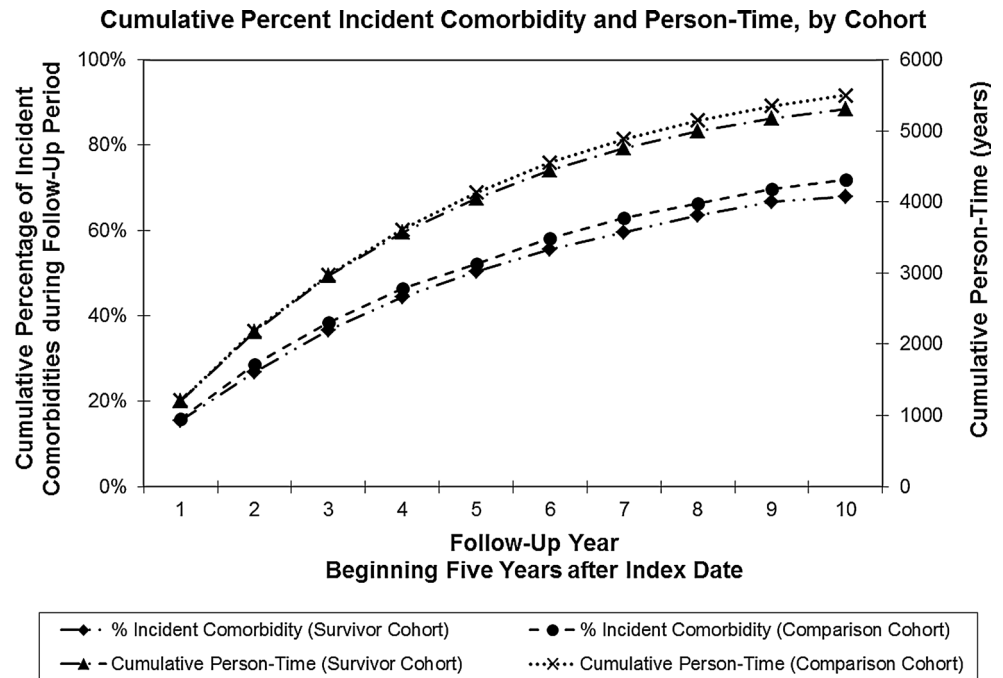
Results

We identified 1,361 breast cancer survivors who met the eligibility criteria (5-year survivors diagnosed with early-stage breast cancer at age 65 years and older) and were followed beginning 5 years after diagnosis for a median of 3.3 years (total person-years = 5,679). In the comparison cohort, 1,361 women were matched to the breast cancer cohort and were followed for a median of 3.7 years after 5-year survival (total person-years = 6,062). The accumulation of person-time during follow-up is shown in Fig. 1 (right axis) for each cohort. Age was evenly distributed across age categories, and women were predominately Caucasian in both the survivor (82 %) and comparison cohorts (84 %, Table 1). Follow-up was censored in 319 women for disenrollment from the healthcare system and in 278 women for death.

Breast cancer

Within the survivor cohort, 60 % of women were diagnosed with AJCC Stage I breast cancer ($n = 812$) and the remaining 40 % were diagnosed with Stage IIA or IIB breast cancer ($n = 549$). About half of the women received breast-conserving surgery ($n = 648$, $n = 523$ of whom also received radiation therapy) while the other half underwent mastectomy ($n = 699$). Less than 10 % of the survivor cohort received chemotherapy ($n = 121$) and two-thirds received adjuvant tamoxifen ($n = 905$).

Fig. 1 Accumulation of person-time and incident comorbidities in older 5-year early breast cancer survivors and matched comparison cohort. Cumulative percentage of incident comorbidities for each year during the 10-year follow-up period beginning 5 years after index date is plotted on *left* y-axis for survivor cohort (*dash-dot-dot line with diamond marker*) and comparison cohort (*dashed line with circle marker*). Cumulative person-time in years for the same period is plotted on the *right* y-axis for survivor cohort (*dash-dot line with triangle marker*) and comparison cohort (*dotted line with cross marker*)



Prevalent comorbidities at initiation of follow-up period

At the beginning of follow-up, the prevalence of comorbidities was similar in the cohorts (Table 1). The five most common prevalent conditions in the survivor and comparison cohorts were diabetes (15 vs. 12 %), chronic pulmonary disease (13 vs. 14 %), congestive heart failure (10 vs. 8.6 %), cerebrovascular disease (7.1 vs. 7.2 %), and history of malignancy other than breast cancer (8.2 vs. 5.5 %). Other comorbidities frequencies were similar in the cohorts. For prevalent comorbidity score, the mCCI score was calculated using the traditional CCI comorbidity index weights (Table 2) with the addition of pulmonary emboli and osteoporotic fractures (each given an index weight of one point). At the beginning of follow-up, 54 % of survivors and 55 % of comparators were free of prevalent comorbidities (mCCI = 0). Only 8.7 % of women in each cohort had a mCCI \geq 3 (Table 1).

Incident comorbidities during follow-up period

In the survivor cohort, 355 women acquired one comorbidity, while 570 women acquired more than one comorbidity. A total of 383 women in the comparison cohort acquired one comorbidity and 595 women acquired more than one comorbidity. The most common incident comorbidities in the survivor and comparison cohorts were dementia (18 vs. 19 %), osteoporotic fracture (17 vs. 17 %), congestive heart failure (14 vs. 16 %), cerebrovascular disease (11 vs. 13 %), and diabetes (11 vs. 8.6 %, Table 2).

The cohorts did not accumulate incident comorbidities at different rates during the follow-up period (HR 1.0 adjusted for age and prevalent comorbidities, 95 % CI 0.93, 1.1; Fig. 1, left axis). Compared with the comparison cohort, survivors had no notable difference in individual incident comorbidities during the 10-year follow-up period except for diabetes (HR 1.4, 95 % CI 1.1, 1.8) and myocardial infarction (HR 0.75, 95 % CI 0.57, 0.99, Table 2).

Association between incident comorbidity and mortality

Among women who acquired incident comorbidities, 21 % died within the next 2 years and 57 % survived through end of follow-up. The time-varying model inclusive of survivors and comparators found that a breast cancer diagnosis was associated with increased mortality in years 6–15 after diagnosis, compared with matched women (HR 1.3, 95 % CI 1.1, 1.4, Table 3). Regardless of cohort, mortality was also associated with having any prevalent comorbidity at the beginning of follow-up (HR 1.8, 95 % CI 1.6, 2.1) and with the development of incident comorbidities during follow-up (HR 4.8, 95 % CI 4.1, 5.6). As expected, older age was also associated with mortality hazard, even after accounting for breast cancer history, prevalent comorbidities, and incident comorbidities (Table 3). In the models fit to each cohort separately (Table 4), the adjusted mortality HR after an incident comorbidity was nearly twofold greater in the comparison cohort (HR 7.2, 95 % CI 5.6, 9.3) than the survivor cohort

Table 1 Characteristics of older 5-year survivors of early breast cancer and matched comparison cohort

	Breast cancer survivor cohort ^a (<i>n</i> = 1,361)		Comparison cohort ^b (<i>n</i> = 1,361)		
	No.	%	No.	%	
Sociodemographic					
Age category at beginning of follow-up (years)					
70–74	502	37	502	37	
75–79	417	31	417	31	
80+	442	32	442	32	
Race/ethnicity					
Caucasian, non-Hispanic	1,115	82	1,147	84	
African-American, non-Hispanic	137	10	125	9.2	
Hispanic	72	5.3	62	4.6	
Asian/Pacific Islander	37	2.7	27	2.0	
Native American	0	0	0	0	
Comorbidity burden at beginning of follow-up					
Prevalent comorbidities included in mCCI ^c (index weight)					
Myocardial infarction	(1)	80	5.9	80	5.9
Congestive heart failure	(1)	140	10	117	8.6
Peripheral vascular disease	(1)	60	4.4	67	4.9
Cerebrovascular disease	(1)	96	7.1	98	7.2
Dementia	(1)	64	4.7	76	5.6
Chronic pulmonary disease	(1)	172	13	184	14
Connective tissue disease	(1)	36	2.6	62	4.6
Ulcer disease	(1)	75	5.5	73	5.4
Diabetes	(1)	202	15	169	12
Mild liver disease	(1)	7	0.51	6	0.44
Hemiplegia	(2)	24	1.8	25	1.8
Moderate or severe renal disease	(2)	17	1.2	15	1.1
Diabetes with end organ damage	(2)	31	2.3	31	2.3
Leukemia, lymphoma or tumor ^d	(2)	112	8.2	75	5.5
Moderate or severe liver disease	(3)	14	1.0	2	0.15
AIDS	(6)	0	0.00	0	0.00
Metastatic solid tumor	(6)	6	0.44	4	0.29
Modified Charlson Comorbidity Index^e					
mCCI 0		741	54	755	55
mCCI 1–2		502	37	487	36
mCCI 3+		118	8.7	119	8.7

^a Older 5-year survivors diagnosed 1990–1994 with early Stage I and II breast cancer at age 65 or older followed for 10 years beginning 5 years after index date (date of breast cancer diagnosis)

^b Comparison cohort matched for health system and age, who were free of breast cancer at matched index date and followed for 10 years beginning 5 years after index date

^c Women may be counted in multiple comorbidities

^d Prevalent breast cancer at index date excluded. ^ePrevalent breast cancer at index date excluded from modified Charlson Comorbidity Index (mCCI), which is calculated from the sum of comorbidity weights listed in the table (Charlson et al. [19])

(HR 3.7, 95 % CI 3.0, 4.5). All other covariate estimates were similar between cohort models.

Discussion

In this study of 5-year breast cancer survivors diagnosed at age 65 or older, older survivors did not develop more comorbidities 6–15 years after diagnosis and treatment than age-matched women free of breast cancer. However, despite comparable incident comorbidity development, survivors were slightly more likely to die in the 10-year follow-up period beginning 5 years after cancer diagnosis and treatment independent of age and prevalent comorbidity burden. In both cohorts, newly acquired comorbidities were strongly associated with all-cause mortality.

The results of our study are concordant with prior literature investigating comorbidities in older breast cancer survivors and their association with mortality. Previous studies concluded that despite an increased comorbidity frequency within 1 year of diagnosis [11, 22], survivors have the same comorbidity burden 5 years after diagnosis as matched women free of breast cancer [11]. We observed an equivalent prevalent comorbidity burden among both cohorts at start of follow-up. Additionally, the rate of acquired comorbidities in our survivor cohort was also similar to another survivor cohort [23]. Our work extends this earlier survivor comorbidity burden research by investigating comorbidity burden in a population of older breast cancer survivors matched with a comparison cohort from the same source population over a longer survival period than previously studied. We have previously observed within this cohort that starting at diagnosis, women who receive left-sided radiotherapy have increased rates of cardiovascular disease [24], which may account for increased rates of cardiovascular comorbidities in our population. Similarly, anthracycline chemotherapy is associated with cardiovascular toxicity [25]; however, we did not have specific regimen information to further investigate this within our population. A study investigating the impact of comorbidities among older 5-year breast cancer survivors found a low to moderate comorbidity burden was associated with a twofold mortality risk, whereas a severe comorbidity burden was associated with a threefold risk mortality compared with survivors without comorbidities [26]. Other studies have suggested that increased comorbidity burden is associated with increased all-cause mortality risk in older breast cancer survivors [12, 27, 28]; however, none of these prior studies included a matched comparison group. In our study, we found that acquiring any comorbidity in years 6–15 after index date was associated with a 4.8-fold increase in mortality hazard after adjusting for cohort membership.

Table 2 Incident comorbidities after 10 years of follow-up in older 5-year early breast cancer survivors and matched comparison cohort

	Breast cancer survivor cohort ^a (n = 1,361)		Comparison cohort ^b (n = 1,361)		Adjusted hazard ratio		
	No.	%	No.	%	Adj HR ^c	(95 % CI)	
Any incident comorbidity acquired in 10-year observation period	870	64	911	67	1.0	(0.93, 1.1)	
Frequency of incident comorbid conditions and adjusted hazard ratios from individual models ^d (index weight)							
Myocardial infarction	(1)	91	6.7	123	9.0	0.75	(0.57, 0.99)
Congestive heart failure	(1)	197	14	219	16	0.92	(0.76, 1.1)
Peripheral vascular disease	(1)	76	5.6	93	6.8	0.84	(0.62, 1.1)
Cerebrovascular disease	(1)	145	11	176	13	0.85	(0.68, 1.1)
Dementia	(1)	248	18	257	19	1.0	(0.85, 1.2)
Chronic pulmonary disease	(1)	112	8.2	127	9.3	0.92	(0.72, 1.2)
Connective tissue disease	(1)	29	2.1	24	1.8	1.3	(0.74, 2.2)
Ulcer disease	(1)	46	3.4	53	3.9	0.92	(0.62, 1.4)
Diabetes	(1)	149	11	117	8.6	1.4	(1.1, 1.8)
Mild liver disease	(1)	8	0.59	10	0.73	0.85	(0.33, 2.1)
Hemiplegia	(2)	35	2.6	50	3.7	0.72	(0.47, 1.1)
Moderate or severe renal disease	(2)	79	5.8	83	6.1	1.0	(0.74, 1.4)
Diabetes with end organ damage	(2)	76	5.6	66	4.9	1.2	(0.88, 1.7)
Leukemia, lymphoma or tumor ^e	(2)	123	9.0	115	8.7	1.1	(0.87, 1.5)
Moderate or severe liver disease	(3)	4	0.29	5	0.37	0.82	(0.22, 3.1)
AIDS	(6)	0	0	0	0	–	–
Metastatic solid tumor	(6)	37	2.7	31	2.3	1.2	(0.77, 2.0)
Pulmonary embolism ^f	(1)	11	0.81	19	1.4	0.61	(0.29, 1.3)
Osteoporotic fracture ^f	(1)	231	17	238	17	1.0	(0.83, 1.2)

^a Older 5-year survivors diagnosed 1990–1994 with early Stage I and II breast cancer at age 65 or older followed for 10 years beginning 5 years after index date (date of breast cancer diagnosis)

^b Comparison cohort matched for health system and age, who were free of breast cancer at matched index date and followed for 10 years beginning 5 years after index date

^c Hazard ratio (HR) adjusted for study site location, age, and presence of prevalent comorbidity. *CI* confidence interval

^d Women may be counted in multiple comorbidities

^e Prevalent breast cancer at index date excluded in modified Charlson Comorbidity Index (CCI)

^f Comorbidities added to original CCI to create modified CCI (Charlson et al. [19])

Our work addresses a gap in the literature by determining the effect of incident comorbidities on mortality in a population of older 5-year breast cancer survivors 15 years after diagnosis in a prospective-matched cohort study. Importantly, we found that older 5-year survivors continue to have a slightly increased hazard of mortality, even after adjusting for covariates of age, race/ethnicity, prevalent comorbidity, and incident comorbidity during years 6–15 after diagnosis and treatment. This finding emphasizes the importance of all women receiving proper treatment regardless of age, comorbid conditions, or breast cancer history. Although follow-up was censored for healthcare system disenrollment, survivors generally remain with the insurer who covered their diagnosis and treatment. Thus, disenrollment is likely due to factors beyond women's control, and loss to follow-up is not likely to be differential.

No earlier studies have compared a cohort of older breast cancer survivors with a population-based-matched comparison cohort. As noted previously, the adjusted HR for incident comorbidity in the comparison cohort was nearly twofold greater than that of the survivor cohort (Table 4). We endeavored to explain this result through a series of analyses, none of which were illuminating and are therefore not presented here. Possible explanations of the observed interaction include selection bias associated with surviving breast cancer and its treatment and/or surveillance bias associated with more in-depth investigation and management of incident conditions. Deaths from causes other than breast cancer may be more affected by age and comorbidity; the mortality hazard in the comparator group may therefore be more influenced by age comorbidity than the survivor group in which the effects of age and comorbidity are diluted by breast cancer deaths. Conversely, as the first-

Table 3 All-cause mortality after 10 years of follow-up in older 5-year early breast cancer survivors and matched comparison cohort

	Total deaths, <i>n</i>	Adjusted HR ^c	(95 % CI)
Age category at index date (years)			
70–74	263	1 (ref)	–
75–79	289	1.3	(1.1, 1.6)
80+	508	2.8	(2.4, 3.3)
Cohort			
Breast cancer survivors ^a	593	1.3	(1.1, 1.4)
Comparison ^b	467	1 (ref)	–
Any prevalent comorbidity (at 5 years after index date)	614	1.8	(1.6, 2.1)
Incident comorbidity (6–15 years after index date)	773	4.8	(4.1, 5.6)

^a Older 5-year survivors (*n* = 1,361) diagnosed 1990–1994 with early Stage I and II breast cancer at age 65 or older followed for 10 years beginning 5 years after index date (date of breast cancer diagnosis)

^b Comparison cohort (*n* = 1,361) matched for health system and age, who were free of breast cancer at matched index date and followed for 10 years beginning 5 years after index date

^c Hazard ratio (HR) adjusted for study site location, age, and presence of prevalent comorbidity. *CI* confidence interval

Table 4 All-cause mortality stratified by cohort (older 5-year early breast cancer survivors and matched comparison cohort)

	Breast cancer survivors ^a		Comparison cohort ^b	
	Adjusted HR ^c	(95 % CI)	Adjusted HR ^c	(95 % CI)
Age category at index date (years)				
70–74	1 (ref)	–	1 (ref)	–
75–79	1.2	(0.92, 1.4)	1.6	(1.2, 2.0)
80+	2.6	(2.1, 3.1)	3.4	(2.7, 4.3)
Any prevalent comorbidity (at 5 years after index date)	1.7	(1.4, 2.0)	2.0	(1.7, 2.4)
Incident comorbidity (years 6–15 after index date)	3.7	(3.0, 4.5)	7.2	(5.6, 9.3)

^a Older 5-year survivors (*n* = 1,361) diagnosed 1990–1994 with early Stage I and II breast cancer at age 65 or older followed for 10 years beginning 5 years after index date (date of breast cancer diagnosis)

^b Comparison cohort (*n* = 1,361) matched for health system and age, who were free of breast cancer at matched index date and followed for 10 years beginning 5 years after index date

^c Hazard ratio (HR) adjusted for health system, age, and presence of prevalent comorbidity. *CI* confidence interval

matched comparison cohort study to investigate these outcome measures, it is potentially a spurious finding that may not be confirmed in future studies.

Our measure of comorbidity burden, the CCI, was originally designed to include fatal comorbid conditions [19]. The included diseases were selected based on mortality data from decades ago and may not represent the most important comorbidities in this population [29]. Quan et al. [30] re-weighted the CCI with more recent administrative data and found no large change in the association between CCI and mortality. We captured additional comorbidity data for pulmonary emboli and osteoporotic fractures, which have been determined to occur in older cancer survivors [31, 32]. There is no gold standard measure of comorbidity in cancer populations [6, 29]; as such, we calculated the mCCI given our access to data and methods of data collection. Importantly, older survivors have an incremental increase in mortality driven primarily by new comorbidity burden acquired 6–15 years after diagnosis and treatment. These findings highlight the importance of care coordination between oncology and primary care providers and appropriate long-term follow-up in older breast cancer survivors [33, 34].

The strengths of our study include a well-matched comparison cohort with high-quality data obtained through adjudicated medical record collection with good inter-rater reliability [17, 20]. We repeatedly collected comorbidity data that allowed us to implement time-varying analyses while accounting for censored events, which is critical in longitudinal studies. Our work utilized an index of comorbidity burden previously associated with all-cause mortality in breast cancer patients [19]. Additionally, our analyses extended the follow-up period observing older breast cancer survivors to determine the association of incident comorbidities and mortality.

This study is not without limitations, however. The possibility of a more complete medical history obtained in the survivor cohort versus the comparison cohort may have led to information bias. Prior studies have shown that comorbidities are similar among women with and without breast cancer at diagnosis [35] and 5 years after diagnosis [11, 22], and our measures of comorbidity burden are therefore unlikely to have substantially different information quality. Additional unmeasured parameters, such as body mass index, may leave residual confounding in the findings of the association between comorbidity burden and mortality [22]. While this survivor cohort had breast cancer diagnoses between 1990 and 1994, the standards of care and primary treatment for early-stage invasive breast cancer in older women have only changed modestly since this cohort was identified. Epidemiologic studies of the rate of late effects of more current treatments will need to be conducted in a new survivorship cohort after an appropriate person-time has accumulated. While our study investigated early-stage survivors with low prevalence of receipt of radiation therapy and chemotherapy, the inclusion of

advanced-stage breast cancer survivors in future studies may provide more insight into the late effects of radiation therapy and chemotherapy. We sought to enroll a diverse population of survivors and purposefully undersampled eligible non-Hispanic white women at the largest health system site [13]; however, our resultant survivor population consisted of a higher proportion of non-Hispanic white women than in the general population, which may limit conclusions drawn for other races and ethnicities.

The results of this study demonstrate that comorbidity burden in older breast cancer survivors is similar to age-matched women free of breast cancer in an extended observational period of 6–15 years after cancer diagnosis and treatment. Furthermore, older survivors retain a marginal increase in mortality rate 6–15 years after diagnosis, even after adjusting for age and comorbidity burden. It is important, therefore, that patients receive optimal breast cancer therapy regardless of age and comorbidity. Additionally, as the rates of 5- and 10-year breast cancer survival increase [2] and the population ages, these findings underscore the importance of preventing and treating the comorbidities in older survivors of breast cancer as well as in older women in general.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study complies with the current laws of the United States of America. This study was reviewed and approved by the Institutional Review Boards of each participating institution and at the Boston University Medical Center.

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