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ARTICLE

The Influence of Comorbidities on Overall Survival Among Older Women Diagnosed With Breast Cancer

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Background Previous studies have shown that summary measures of comorbid conditions are associated with decreased overall survival in breast cancer patients. However, less is known about associations between specific comorbid conditions on the survival of breast cancer patients.

Methods The Surveillance, Epidemiology, and End Results–Medicare database was used to identify primary breast cancers diagnosed from 1992 to 2000 among women aged 66 years or older. Inpatient, outpatient, and physician visits within the Medicare system were searched to determine the presence of 13 comorbid conditions present at the time of diagnosis. Overall survival was estimated using age-specific Kaplan–Meier curves, and mortality was estimated using Cox proportional hazards models adjusted for age, race and/or ethnicity, tumor stage, cancer prognostic markers, and treatment. All statistical tests were two-sided.

Results The study population included 64034 patients with breast cancer diagnosed at a median age of 75 years. None of the selected comorbid conditions were identified in 37306 (58%) of the 64034 patients in the study population. Each of the 13 comorbid conditions examined was associated with decreased overall survival and increased mortality (from prior myocardial infarction, adjusted hazard ratio [HR] of death = 1.11, 95% CI = 1.03 to 1.19, $P = .006$; to liver disease, adjusted HR of death = 2.32, 95% CI = 1.97 to 2.73, $P < .001$). When patients of age 66–74 years were stratified by stage and individual comorbidity status, patients with each comorbid condition and a stage I tumor had similar or poorer overall survival compared with patients who had no comorbid conditions and stage II tumors.

Conclusions In a US population of older breast cancer patients, 13 individual comorbid conditions were associated with decreased overall survival and increased mortality.

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One in eight women will be diagnosed with breast cancer during her lifetime (1). Breast cancer is more common among older women, yet cancer survivors diagnosed at age 65 years or older still represent an understudied population in cancer research, and older cancer patients and patients with comorbid chronic conditions are often systematically excluded from clinical trials (2–6).

Older persons diagnosed with cancer often have comorbid conditions in addition to their primary cancer diagnosis (7–9). These conditions can be highly prevalent, such as hypertension and heart-related conditions, or less common, such as diabetes. Comorbid conditions may be considered when deciding treatment regimens and otherwise increase the patient's risk of death (10–12). Gaining a better understanding of the relationship between comorbid conditions and cancer survival and mortality may assist with the assessment of a patient's prognosis and treatment management.

The Surveillance, Epidemiology, and End Results (SEER) is a national population-based cancer registry that has been linked with Medicare data at the patient level. SEER provides detailed information on patient demographics and tumor characteristics, whereas the Medicare database offers information on health-care utilization leading up to and following cancer diagnosis. This linkage provides a large unified data source that enables analysis of the relationships between clinical information that is not routinely included in cancer registries and includes cancer-related outcomes.

Previous studies of breast cancer patients have found that the presence of comorbid conditions is statistically significantly associated with overall survival and all-cause mortality (11–18). However, most published reports on this subject have combined comorbid conditions into one summary measure (a comorbidity index), and few studies have assessed the individual associations between specific comorbid conditions and prognosis (11,12,17). In addition, no previous studies have assessed whether the relationships between comorbid conditions and survival after breast cancer are modified by other prognostic factors, such as age at diagnosis and tumor characteristics. Determining the specific influence of individual comorbidities on mortality can enable a better assessment of prognosis for breast cancer patients with these conditions.

CONTEXT AND CAVEATS

Prior knowledge

Previous reports have combined comorbidities into a summary measure and found that they are associated with poor overall survival and increased all-cause mortality in breast cancer patients.

Study design

The individual associations between 13 comorbidities and overall survival and all-cause mortality were investigated among breast cancer patients aged 65 years or older using data from the Surveillance, Epidemiology, and End Results cancer registry that had been linked with Medicare data for each patient.

Contribution

The large population size allowed the investigators to study the association between rare conditions and overall survival in older breast cancer patients in the United States and to assess the impact of age and tumor stage. All 13 comorbidities were associated with decreased overall survival and increased all-cause mortality in the study population. The age at diagnosis modified these relationships. Patients with comorbidities diagnosed with early-stage breast cancer had survival outcomes similar to or worse than that of patients with no comorbiditites diagnosed with later-stage tumors.

Implication

Comorbidities should be considered when determining prognosis for older breast cancer patients.

Limitations

The Medicare data, created for billing purposes, may not have included data about possible confounding factors such as smoking status, obesity, and physical activity level. Also, the severity of the comorbidity and the time since diagnosis were unknown and therefore not considered in the analyses.

From the Editors

The current study aims to measure the individual associations between specific comorbidities of interest and overall survival and all-cause mortality among older women diagnosed with breast cancer. We hypothesize that some comorbidities will be more strongly associated with survival and mortality and also that these associations may be modified by age.

Methods

Patient Population

The SEER program is a population-based tumor registry of selected geographic areas within the United States designed to be representative of the country's general population. Demographic data from SEER include sex, race, and dates of birth and death; tumor-specific data include diagnosis date, site, stage at diagnosis, and grade; and estrogen and progesterone receptor status of the tumor is reported for breast cancer patients. Surgical and radiation treatment within 4 months after cancer diagnosis are also included in the SEER database.

The following types of Medicare files from women aged 65 years or older were also included in this study: 1) the Medicare Provider Analysis and Review file containing inpatient hospital claims, 2) the Hospital Outpatient Standard Analytic file for outpatient claims, and 3) the Physician/Supplier file containing claims for physician visits. Medicare files were searched for diagnostic and procedure codes related to the comorbidities and treatments of interest. Codes for diagnoses and procedures are derived from the *International Classification of Diseases, Ninth Revision, Clinical Modification*; the Health Care Financing Administration Common Procedure Coding System; and Revenue Center codes (19,20). Medicare patients can also be enrolled in either a Fee-for-Service (FFS) or Health Maintenance Organization (HMO) plan. Because Medicare payments for HMO plans are not tied to specific clinical services, the claims files are not available for the 17% of Medicare recipients enrolled in such plans (21).

The National Cancer Institute, the SEER program, and the Centers for Medicare and Medicaid Services have collaborated to link the SEER cancer registries and Medicare enrollment and claims files to produce the de-identified SEER–Medicare dataset. These two databases are periodically linked based on an algorithm consisting of an individual social security number, first and last name, sex, and dates of birth and death (22).

Female primary malignant cancers of the breast diagnosed at age 66 years or older and reported to SEER from January 1, 1992, through December 31, 2000, were eligible for study inclusion. Women aged 65 years were not included to allow for a 1-year period after Medicare enrollment during which comorbidities could be recorded in claims files for the period before breast cancer diagnosis. Women were excluded if they: 1) lacked full coverage of both Medicare Part A (covers hospital, skilled-nursing facility, hospice, and some home health care) and Part B (covers physician and outpatient services), 2) were enrolled in a Medicare HMO, 3) had an unknown month of cancer diagnosis, 4) had the same month of diagnosis of breast cancer and death, or 5) had records considered to have unreliable Medicare coding for a comorbid condition (e.g. bills that are not encoded by a clinician). These exclusions were to ensure that claims files were available for accurate detection of comorbidities and accurate calculation of survival time from diagnosis to death.

The outcomes of interest were overall survival and all-cause mortality. Survival time was measured from the date of diagnosis of breast cancer until the date of SEER-recorded death or the censor date of December 15, 2005. Because SEER does not include the exact day for date of diagnosis or death, the 15th of the month was arbitrarily assigned to the reported month and year.

Measurement of Comorbidity

The SEER database identifies whether another primary cancer had been diagnosed before the cancer of interest in this analysis. This field was used to determine whether a previous cancer constituted a comorbidity. All other comorbidities were searched in Medicare files for the period of 1 year before and 30 days after the cancer diagnosis. This long period before cancer diagnosis and short period after cancer diagnosis allows for substantial time to identify diagnoses representing comorbidities without capturing conditions that may result from the cancer treatment. Comorbidity codes had to be recorded in the Medicare files but not necessarily first diagnosed in the patient during this period. Diagnostic coding for comorbidities had to be included in the Medicare inpatient files

Table 1. Prevalence, 5-year survival rates, and hazard ratios of all-cause mortality by demographic and clinical characteristics in breast cancer patients aged 66 years or older, SEER-Medicare 1992–2000*

Characteristic	No. (%)	5-year survival rate, No. (%)		HR† (95% CI)
		No. (%)	95% CI	
Total	64 034 (100)	43 151 (67.4)	67.0 to 67.7	NA
Age, y				
66–74	28 812 (45.0)	22 618 (78.5)	78.0 to 79.0	1.0 (referent)
75–84	26 496 (41.4)	17 402 (65.7)	65.1 to 66.2	1.86 (1.81 to 1.91)
≥85	8726 (13.6)	3131 (35.9)	34.9 to 36.9	4.45 (4.32 to 4.58)
Race/ethnicity				
White	56 116 (87.6)	38 034 (67.8)	67.4 to 68.2	1.0 (referent)
Black	3901 (6.1)	2192 (56.2)	54.6 to 57.7	1.41 (1.35 to 1.46)
Hispanic	1927 (3.0)	1308 (68.4)	65.7 to 69.9	0.97 (0.91 to 1.04)
Other	1928 (3.0)	1493 (77.4)	75.5 to 79.2	0.66 (0.61 to 0.71)
Unknown	162 (0.2)	124 (76.5)	69.2 to 82.3	0.64 (0.49 to 0.82)
Stage				
I	33 017 (51.6)	26 025 (78.8)	78.4 to 79.3	1.0 (referent)
II	20 559 (32.1)	13 057 (63.5)	62.8 to 64.2	1.63 (1.59 to 1.67)
III and IV	5965 (9.3)	1664 (27.9)	26.8 to 29.0	4.53 (4.38 to 4.68)
Unknown	4493 (7.0)	2405 (53.5)	52.1 to 55.0	2.02 (1.94 to 2.11)
Grade				
1	10 519 (16.4)	8171 (77.7)	76.9 to 78.5	1.0 (referent)
2	22 729 (35.5)	16 314 (71.8)	71.2 to 72.4	1.25 (1.20 to 1.29)
3 and 4	16 859 (26.3)	10 113 (60.0)	59.2 to 60.7	1.72 (1.66 to 1.78)
Unknown	13 927 (21.8)	8553 (61.4)	60.6 to 62.2	1.63 (1.57 to 1.69)
ER status				
Positive	41 018 (64.1)	29 508 (71.9)	71.5 to 72.4	1.0 (referent)
Negative	7981 (12.5)	4742 (59.4)	58.3 to 60.5	1.33 (1.29 to 1.38)
Unknown/other	15 035 (23.5)	8901 (59.2)	58.4 to 60.0	1.41 (1.30 to 1.44)
Surgery				
Yes	60 153 (93.9)	42374 (70.4)	70.1 to 70.8	1.0 (referent)
No	2385 (3.7)	326 (13.7)	12.3 to 15.1	6.16 (5.89 to 6.43)
Unknown	1496 (2.3)	451 (30.2)	27.8 to 32.5	3.27 (3.09 to 3.47)
Chemotherapy				
Yes	9459 (14.8)	5948 (62.9)	61.9 to 63.8	1.0 (referent)
No	54 575 (85.2)	37 203 (68.2)	67.8 to 68.6	0.90 (0.88 to 0.93)
Radiation				
Yes	21 826 (34.1)	17 005 (77.9)	77.4 to 78.5	1.0 (referent)
No	42 208 (65.9)	26 146 (62.0)	61.5 to 62.4	1.72 (1.68 to 1.77)

* CI = confidence interval, ER = estrogen receptor, HR = hazard ratio. Calculations were based on log–log transformation.

† Cox proportional hazards model was used to calculate values.

or had to occur at least two times 30 days apart in the outpatient and/or physician files.

The comorbidities of interest in this analysis are the 19 conditions included in the Charlson index (23,24), adapted by Deyo and Klabunde (25,26) to be used with administrative claims data. The Charlson index has been validated as a predictor of short- and long-term mortality and specifically for use with breast cancer (27). The Charlson index has five conditions that have two categories of severity that were combined for the purposes of our analysis. The conditions assessed in this study include: cerebrovascular disease (stroke), chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, dementia, diabetes, liver disease, myocardial infarction, paralysis (hemiplegia, hemiparesis, or paraplegia), peripheral vascular disease, previous cancer (except for nonmelanoma skin cancer), rheumatoid arthritis, and ulcers (chronic gastric or duodenal ulcers). We also assessed HIV status to determine if an individual had any comorbid conditions, but because there were only three patients diagnosed with HIV, separate data are not presented for this comorbidity, leaving 13 conditions specifically examined in this analysis. In addition, the Charlson Comorbidity Index Score was used as a summary measure of comorbidity in which each comorbidity is assigned a weight based on the association with survival, and the weights were then summed. SAS (SAS Institute, Cary, NC) programming to identify diagnostic and procedure codes for these comorbidities is available on the SEER–Medicare website (28).

Cancer Treatments

Fields for surgical treatment of breast cancer and radiation provided within 4 months after breast cancer diagnosis are available in the SEER database, but chemotherapy is not coded. Medicare files were therefore searched for chemotherapy within 6 months of diagnosis and for radiation codes within 9 months of diagnosis. These periods were chosen based on published articles of chemotherapy (29–31) and radiation therapy (30,32,33) to capture treatment for primary and not recurrent disease. Radiation treatment was counted if it occurred in either SEER or Medicare (33). The *International Classification of Diseases, Ninth Revision*,

Table 2. Comorbidities among breast cancer patients aged 66 years or older: prevalence, 5-year survival rates, and hazard ratios of all-cause mortality of the SEER–Medicare 1992–2000 population*

Comorbidities	No. (%)	5-year survival rate		Crude HR (95% CI)	Age-adjusted HR (95% CI)	Partially adjusted HR† (95% CI)	Fully adjusted HR‡ (95% CI)
		No. (%)	95% CI				
Total patients	64 034 (100)	43 151 (67.4)	67.0 to 67.7	NA	NA	NA	NA
Comorbidities							
None	37 306 (58.3)	27 956 (74.9)	74.5 to 75.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Previous cancer	10 422 (16.3)	6386 (61.3)	60.3 to 62.2	1.61 (1.56 to 1.66)§	1.48 (1.44 to 1.52)§	1.55 (1.50 to 1.60)§	1.27 (1.23 to 1.30)§
Myocardial infarction	1091 (1.7)	525 (48.1)	45.1 to 51.0	2.38 (2.21 to 2.55)§	2.14 (2.00 to 2.31)§	2.16 (2.01 to 2.32)§	1.11 (1.03 to 1.19)||
Congestive heart failure	4280 (6.7)	1405 (32.8)	31.4 to 34.2	3.68 (3.55 to 3.82)§	2.76 (2.66 to 2.87)§	2.55 (2.46 to 2.65)§	1.70 (1.64 to 1.76)§
Peripheral vascular disease	1638 (2.6)	718 (43.8)	41.4 to 46.2	2.69 (2.54 to 2.86)§	2.16 (2.04 to 2.29)§	2.18 (2.05 to 2.31)§	1.36 (1.28 to 1.44)§
Cerebrovascular disease	2742 (4.3)	1232 (44.9)	43.1 to 46.8	2.65 (2.53 to 2.78)§	2.16 (2.06 to 2.26)§	2.08 (1.99 to 2.18)§	1.35 (1.28 to 1.42)§
COPD	5669 (8.8)	2987 (52.7)	51.4 to 54.0	2.13 (2.06 to 2.21)§	2.11 (2.04 to 2.19)§	2.14 (2.07 to 2.22)§	1.52 (1.47 to 1.58)§
Dementia	887 (1.4)	168 (18.9)	16.4 to 21.6	5.72 (5.33 to 6.14)§	3.47 (3.23 to 3.73)§	2.79 (2.59 to 3.00)§	1.96 (1.82 to 2.10)§
Paralysis	388 (0.6)	138 (35.6)	30.8 to 40.3	3.52 (3.16 to 3.93)§	2.73 (2.44 to 3.04)§	2.58 (2.31 to 2.88)§	1.23 (1.09 to 1.38)§
Diabetes	8332 (13.0)	4631 (55.6)	54.5 to 56.6	1.97 (1.91 to 2.03)§	1.97 (1.91 to 2.03)§	1.90 (1.85 to 1.96)§	1.41 (1.36 to 1.45)§
Chronic renal failure	590 (0.9)	139 (23.6)	20.2 to 27.1	4.90 (4.49 to 5.35)§	4.52 (4.14 to 4.94)§	4.42 (4.04 to 4.83)§	2.20 (2.02 to 2.41)§
Liver disease	186 (0.3)	59 (31.7)	25.2 to 38.5	3.46 (2.94 to 4.06)§	3.78 (3.22 to 4.44)§	4.04 (3.44 to 4.76)§	2.32 (1.97 to 2.73)§
Stomach ulcer	705 (1.1)	387 (54.9)	51.1 to 58.5	1.91 (1.74 to 2.10)§	1.73 (1.57 to 1.89)§	1.71 (1.56 to 1.88)§	1.12 (1.02 to 1.23)#
Rheumatoid arthritis	1246 (2.0)	747 (60.0)	57.2 to 62.6	1.70 (1.58 to 1.83)§	1.65 (1.53 to 1.78)§	1.71 (1.58 to 1.84)§	1.27 (1.18 to 1.37)§
Charlson comorbidity index score							
0	37 306 (58.3)	27 956 (74.9)	74.5 to 75.4	1.0 (referent)	1.0 (referent)	1.0 (referent)	NA
1	17946 (28.0)	11 392 (63.5)	62.8 to 64.2	1.54 (1.50 to 1.57)§	1.45 (1.41 to 1.48)§	1.45 (1.41 to 1.48)§	NA
2	5639 (8.8)	2787 (49.4)	48.1 to 50.7	2.34 (2.25 to 2.42)§	2.13 (2.06 to 2.21)§	2.12 (2.05 to 2.20)§	NA
≥3	3143 (4.9)	1016 (32.3)	30.7 to 34.0	3.69 (3.54 to 3.84)§	3.24 (3.11 to 3.38)§	3.19 (3.06 to 3.32)§	NA

* CI = confidence interval; COPD = chronic obstructive pulmonary disease, HR = hazard ratio, NA = not applicable.

† Adjusted for age, race and/or ethnicity, stage, grade, estrogen receptor status, surgery, chemotherapy, and radiation with Cox proportional hazards modeling.

‡ Adjusted for age, race and/or ethnicity, stage, grade, estrogen receptor status, surgery, chemotherapy, radiation, and all other individual comorbid conditions with Cox proportional hazards modeling.

§ Indicates $P < .001$, determined by a two-sided χ^2 test.

|| Indicates $P < .01$, determined by a two-sided χ^2 test.

# Indicates $P < .05$, determined by a two-sided χ^2 test.

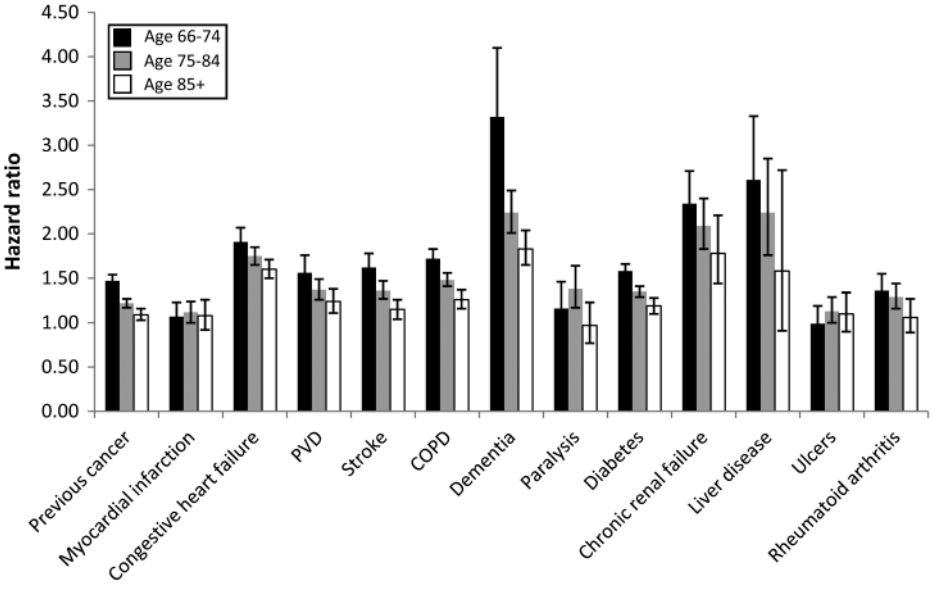


Figure 1. Adjusted hazard ratios of comorbidities on all-cause mortality, stratified by age category, among breast cancer patients aged 66 years or older, Surveillance, Epidemiology, and End Results–Medicare 1992–2000. The hazard ratios were fully adjusted for race and/or ethnicity, stage category, grade category, estrogen receptor status, surgery, chemotherapy, radiation, and all other comorbid conditions. COPD = chronic obstructive pulmonary disease, PVD = peripheral vascular disease.

Clinical Modification diagnostic and procedure codes; Health Care Financing Administration Common Procedure Coding System codes; and Revenue Center codes used to identify chemotherapy and radiation treatment in Medicare are included in the Appendix.

Statistical Methods

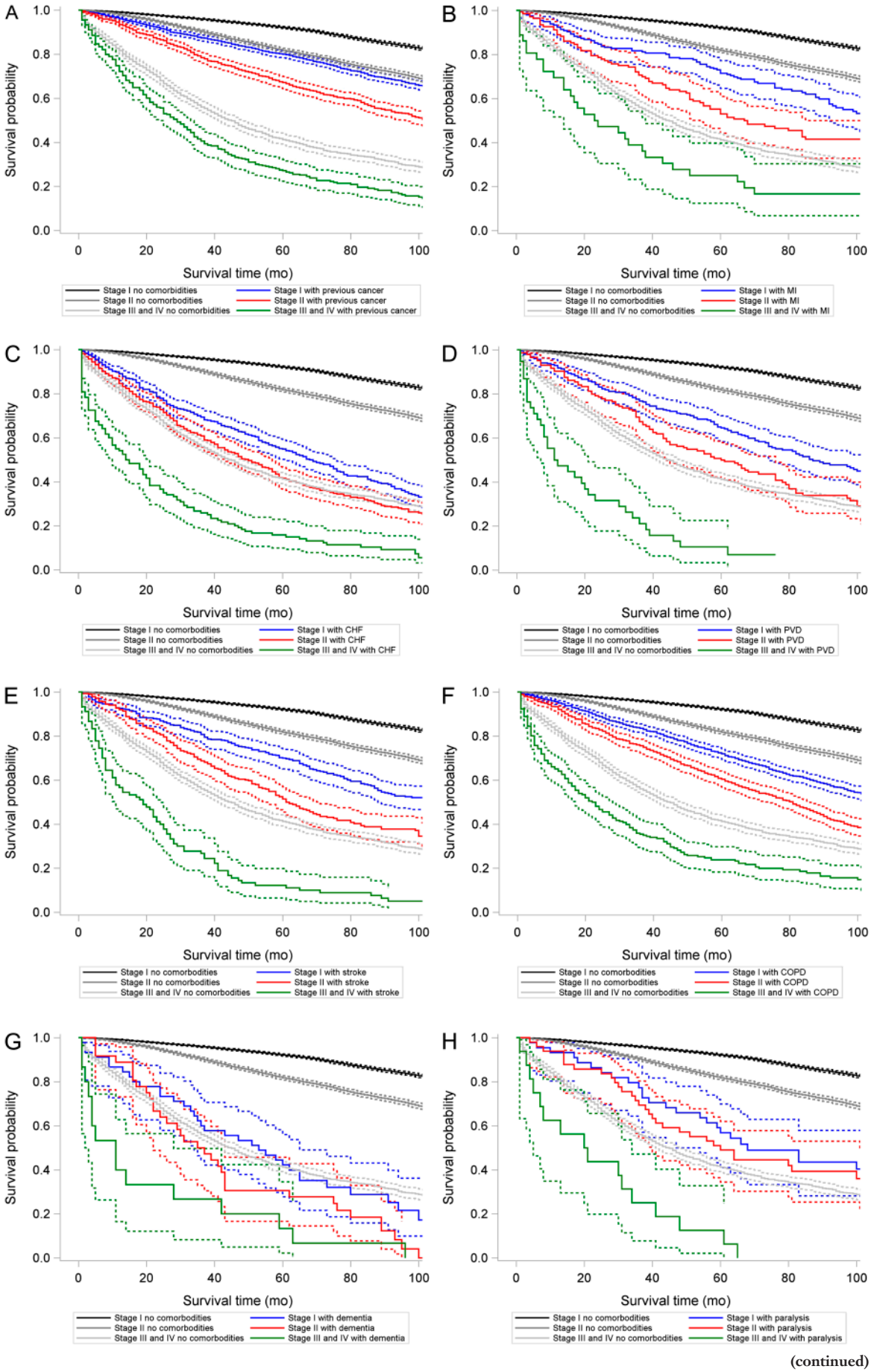
Proportions, 5-year overall survival rates, and hazard ratios (HRs) for all-cause mortality according to specific patient characteristics were calculated. Multivariable Cox proportional hazards models were used to estimate the association between selected comorbidities and all-cause mortality in the form of crude and adjusted hazard ratios and 95% confidence intervals (CIs). Partially adjusted models controlled for age (66–74 years, 75–84 years, and 85 years or more), race and/or ethnicity (white, black, Hispanic, other, or unknown), stage (I, II, III and IV, or unknown), grade (1, 2, 3 and 4, or unknown), estrogen receptor status (yes, no, or unknown), surgery (yes, no, or unknown), chemotherapy (yes or no), and radiation treatment (yes or no). Fully adjusted models also controlled for the presence of all other comorbidities (13 yes or no conditions). Stratified analyses were conducted to determine if the relationships between comorbidities and survival were modified by age. Unadjusted Kaplan–Meier survival curves were generated for selected comorbidities and stratified by presence of comorbidity and stage category (stage I, II, and III and IV) for women diagnosed with breast cancer. Missing or unknown data values were grouped into their own category and included in Cox proportional hazards models. Two approaches were used to determine whether missing data on predictors contributed to the results. Records with missing or unknown values for any variable of interest were excluded from the analyses, and the R package NestedCohort was used to weight records with known values of age, race and/or ethnicity, and death status to account for records with missing data (34). SAS version 9.1 and 9.2 were used for analysis. All statistical tests were two-sided and a P value less than .05 was considered to be statistically significant.

Results

A total of 96954 women aged 66 years or older and diagnosed with malignant breast cancer between January 1, 1992, and December 31, 2000, were potentially eligible for the study. One-third of women (32920 women or 34.0%) were excluded because of the following (some patients were excluded for more than one reason): being in a Medicare HMO (22106 women or 22.8%), unreliable diagnosis coding (3878 women or 4.0%), not having both Medicare Part A and B (5332 women or 5.5%), month and year of death were the same as that of diagnosis (2521 women or 2.6%) and/or unknown month of diagnosis (679 women or 0.7%). Women who were excluded from the study were younger than patients chosen for the study (median age = 74 vs 75 years), were more likely to be Hispanic (6.8% vs 3.0%), less likely to be white (78.4% vs 87.6%), more likely to have higher tumor stage (12.2% had stage III or IV vs 9.3%) or unknown tumor stage (10.7% vs 7.0%), and less likely to have undergone surgery (87.4% vs 93.9%). A total of 64034 patients met the study inclusion criteria. Excluding records with unknown or missing values and using R to account for missing and unknown data values did not influence the study findings.

The median follow-up time was 104 months and the median age at diagnosis was 75 years. A breast cancer diagnosis was made for 28812 study participants (45.0%) aged 66–74 years, 26496 (41.1%) aged 75–84 years, and 8726 (13.6%) aged 85 years or older. The majority of patients were white (56116 women or 87.6%), 33017 tumors (51.6%) were stage I, 20559 tumors (32.1%) were stage II, 5965 tumors (9.3%) were stage III and IV, and the stage was unknown for 4493 tumors (7.0%) (Table 1). Most patients (60153 or 93.9%) underwent some type of surgery, 21826 (34.1%) were treated with radiation, and 9459 (14.8%) were treated with chemotherapy.

Specific comorbidities with the highest prevalence (Table 2) were previous cancer (16.3%), diabetes (13.0%), chronic obstructive pulmonary disease (8.8%), congestive heart failure (6.7%), and stroke (4.3%). Liver disease had the lowest prevalence (0.3%) among the study population. Fifty-eight percent of the study



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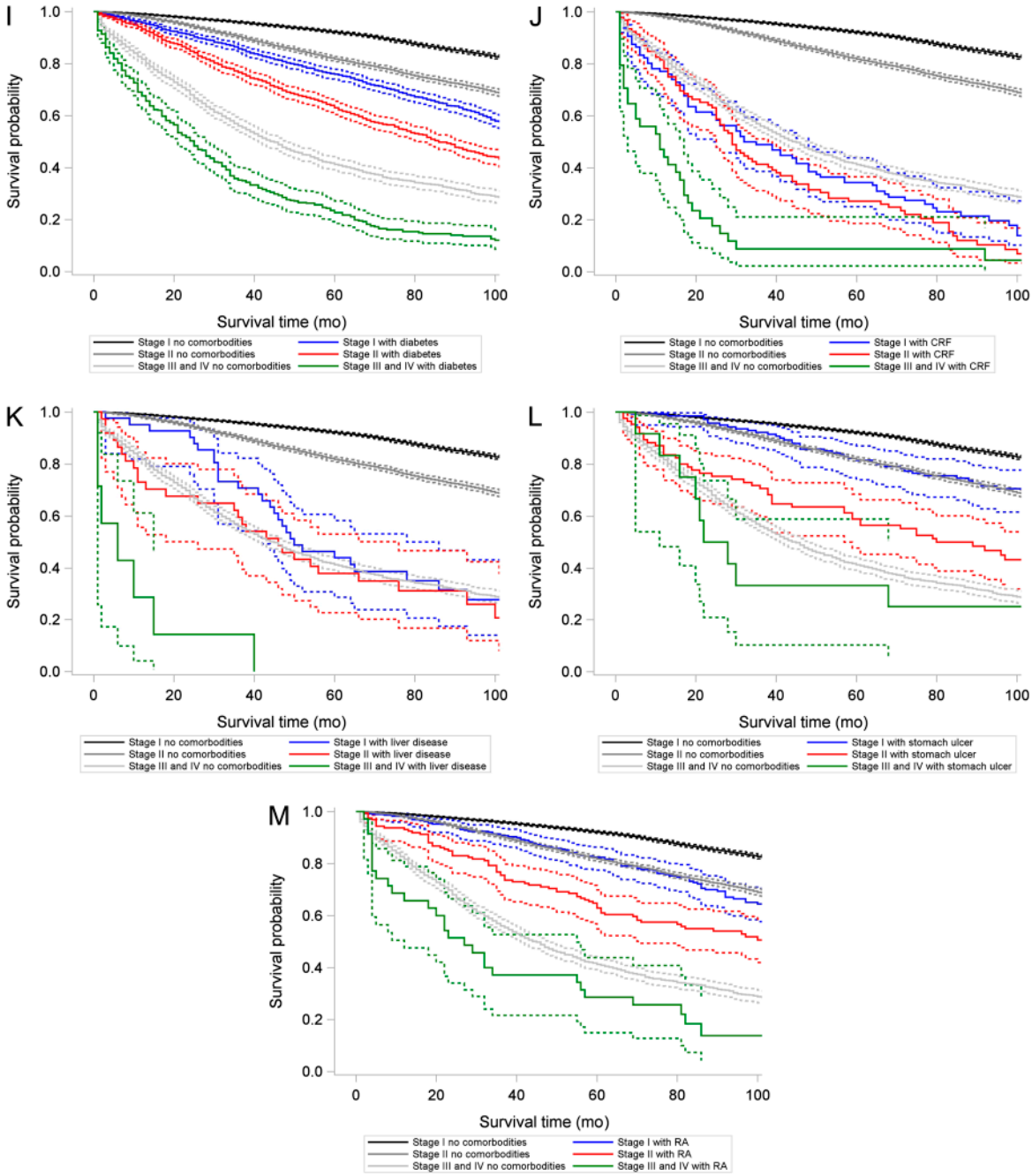

Figure 2. Kaplan–Meier survival curves by stage and each of 13 selected comorbid conditions (**A**–**M**) among women diagnosed with breast cancer at age 66–74 years, from the Surveillance, Epidemiology, and End Results–Medicare 1992–2000 database. CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, MI = myocardial infarction, PVD = peripheral vascular disease, RA = rheumatoid arthritis.

population had none of the selected comorbidities, 28.0% had one comorbidity, 8.8% had two comorbidities, and 4.9% had three or more of the conditions.

In univariate analysis, 5-year overall survival rates were highest for those patients of younger age, earlier tumor stage, lower tumor grade, positive estrogen receptor status (Table 1), and having no comorbidities (Table 2). Age was the largest confounding factor. Adjustment for age as a continuous variable (data not shown) produced results virtually identical to the age group-adjusted analyses shown in Table 2. All mortality hazard ratios for comorbidities in the fully adjusted models, which adjusted for other comorbid conditions, were smaller than those calculated by partially adjusted models (Table 2). Partially and fully adjusted hazard ratios of comorbidities were all positive and statistically significant (eg, fully adjusted hazard ratios: for myocardial infarction, HR of death = 1.11, 95% CI = 1.03 to 1.19, $P = .006$; for liver disease, HR of death = 2.32, 95% CI = 1.97 to 2.73, $P < .001$). Other comorbidities with the highest fully adjusted hazard ratios include chronic renal failure (HR of death = 2.20, 95% CI = 2.02 to 2.41, $P = .001$), dementia (HR of death = 1.96, 95% CI = 1.82 to 2.10, $P < .001$),

and congestive heart failure (HR of death = 1.70, 95% CI = 1.64 to 1.76, $P < .001$). Analysis of patients diagnosed with only a single comorbidity (ie, excluding those with multiple comorbidities) resulted in hazard ratios for all-cause mortality that were generally lower than the partially adjusted model but higher than the fully adjusted model for each comorbidity (data not shown). Compared with patients who had no comorbidities, hazard ratios of death increased as the Charlson Comorbidity Index Score increased (adjusted HR: for a score of 1, HR = 1.45, 95% CI = 1.41 to 1.48, $P < .001$; for a score of 2, HR = 2.12, 95% CI = 2.05 to 2.20, $P = .001$; and for a score of ≥3, HR = 3.19, 95% CI = 3.06 to 3.32, $P = .001$).

Younger patients were more likely to have no comorbidities; 18310 (63.6%) patients aged 66–74 years had no comorbidities compared with 14637 (55.2%) and 4359 (50.0%) patients aged 75–84 years and 85 years or older, respectively. In general, the prevalence of each type of comorbidity increased with age. Consistently across most of the comorbidities, the adjusted hazard ratios of the comorbidities decreased as age increased (Figure 1) statistically significantly for all comorbidities except ulcers and rheumatoid arthritis. Omitting records with missing values from multivariable analysis did not change the study findings (data not shown).

Across all of the comorbid conditions, patients aged 66−74 years with stage I tumors who had these conditions had survival curves similar to patients with stage II tumors who had no comorbidities (Figure 2). Similar trends were observed in the Kaplan–Meier survival curves for patients aged 75–84 years and 85 years or older (data not shown). In all of these graphs, the curves representing patients with no comorbidities for stage I, stage II, and stage III and IV tumors are the same. The most common pattern of survival, shown for myocardial infarction, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, and diabetes, for patients with earlier stage cancers and comorbidities was to have survival outcomes that were shifted about one stage higher compared with patients without comorbidities. For more severe comorbidities (eg, dementia, chronic renal failure, and liver disease), the survival outcomes of patients with stage I and stage II tumors who had the specific comorbid condition resembled that of patients with stage III and IV tumors who did not have the specific conditions. The number of patients at risk at different time points after breast cancer diagnosis is presented in Table 3.

Discussion

Our analysis found an association between thirteen individual comorbidities and the overall survival and all-cause mortality of older female breast cancer patients. The presence of comorbid conditions in this population is substantially associated with decreased survival and is quantitatively similar to that of breast cancer stage. The hazard ratios of all-cause mortality depend on the specific comorbidity and statistically significantly decline with increasing age for 11 of the 13 comorbidities included in this study.

It is well established that breast cancer patients with comorbidities have a poorer prognosis than patients without comorbidities (11–18), but previous studies have used only a summary measure of comorbidities such as the Charlson Comorbidity Index Score. Although a comorbidity index can be useful for research purposes, measuring the specific hazard ratio of comorbidities can help delineate clinically meaningful differences that exist between cancer patients. For example, we found that conditions such as liver disease, chronic renal failure, dementia, and congestive heart failure produce the highest hazard ratios of all-cause mortality and that patients with these conditions diagnosed at stage I have survival experiences similar to those of patients with stage III and IV tumors lacking any coexisting disease. Interestingly, in this study, the hazard ratios of all-cause mortality for individual comorbidities differed somewhat from the weights assigned to each comorbidity in the Charlson Comorbidity Index Score. This observation agrees with other publications that have suggested that comorbidity indices may not always be adequate predictors of survival, as the influence of comorbid conditions may vary depending on the population and disease of interest (35–38).

Only three other studies have assessed the individual effects of specific comorbidities on breast cancer mortality (11,12,17), with two of these studies having a substantial overlap in study populations. Louwman et al. (12) analyzed patients in the Eindhoven Cancer Registry who were diagnosed from 1995 to 2001 at any age and Janssen-Heijnen et al. (17) studied patients in the Eindhoven Cancer Registry with stage I–III tumors diagnosed from 1995 to 2004 among women aged 50 years or older and included other cancer sites as well. Our study findings were similar to these previous studies in terms of which comorbidities had the highest hazard ratios. However, we identified more comorbidities that had a statistically significant association with overall mortality. The largest of these previous studies included approximately 9000 breast cancer patients, whereas our study population is almost seven times larger. The large size of our study population allowed us to assess the impact of rarer conditions and to see whether the relationship between comorbidities and all-cause mortality differed by age and tumor stage.

Our study population is large because SEER was used to identify cancer patients. SEER participation has expanded greatly since its inception. The population covered by SEER is intended to be comparable to the general US population and is true in regards to measures of poverty and education. However, the SEER population is somewhat more urban and has a higher proportion of foreign-born people than the general population. SEER continually monitors and evaluates their data to ensure high quality. The program's standard for registry completeness for incident cancers is 98% (21).

We determined that age at diagnosis often modifies the relationships between comorbidities and all-cause mortality. This interaction has not been previously studied among breast cancer patients. Three separate studies among patients with prostate, colorectal, and head and neck cancers found that comorbidity indices modified overall survival more for younger age-groups (39–41). Froehner et al. (42) also determined that age modifies the relationship between a comorbidity index and prostate cancer survival with a comorbidity index having the greatest effect among men aged 63–69 years. Only one previous study, reported by Gross et al. (43), measured comorbidities at the individual level and assessed interactions with age. Similar to our results, age modified the relationship between survival among colon cancer patients and three specific comorbidities including heart disease, chronic obstructive pulmonary disease, and diabetes.

Table 3. Number of patients at risk by stage and selected comorbid condition among women diagnosed with breast cancer at ages 66–74 years, SEER–Medicare 1992–2000

	No. of patients at risk*					
Comorbidity	**0 mo**	**20 mo**	**40 mo**	**60 mo**	**80 mo**	**100 mo**
No comorbidities						
Stage I	10058	9874	9609	9280	6811	5057
Stage II	5750	5529	5128	4723	3220	2313
Stage III and IV	1501	1110	806	626	399	261
Previous cancer						
Stage I	2420	2267	2095	1941	1347	979
Stage II	1137	1014	873	767	508	352
Stage III and IV	313	193	120	86	48	30
Myocardial infarction						
Stage I	196	171	158	143	92	58
Stage II	136	111	92	75	48	33
Stage III and IV	36	20	12	9	5	3
Congestive heart failure						
Stage I	467	383	315	257	145	85
Stage II	375	287	217	157	94	59
Stage III and IV	120	52	28	19	11	4
Peripheral vascular disease						
Stage I	254	220	189	165	94	65
Stage II	144	120	92	73	40	26
Stage III and IV	38	15	6	4	0	0
Cerebrovascular disease						
Stage I	389	344	305	273	184	134
Stage II	288	243	191	151	88	57
Stage III and IV	90	44	22	11	8	3
COPD						
Stage I	1333	1221	1094	965	630	415
Stage II	767	658	564	466	279	160
Stage III and IV	206	110	70	49	28	19
Dementia						
Stage I	45	35	26	20	10	5
Stage II	36	28	16	11	7	1
Stage III and IV	15	5	4	2	1	0
Paralysis						
Stage I	44	39	31	26	18	14
Stage II	49	42	32	25	17	12
Stage III and IV	16	9	4	2	0	0
Diabetes						
Stage I	1807	1672	1518	1375	873	571
Stage II	1351	1189	1006	863	519	330
Stage III and IV	358	205	119	84	37	24
Chronic renal failure						
Stage I	96	61	45	33	17	9
Stage II	92	61	36	25	12	5
Stage III and IV	34	8	3	3	2	1
Liver disease						
Stage I	41	38	29	19	10	6
Stage II	37	25	20	14	8	5
Stage III and IV	7	1	1	0	0	0
Stomach ulcer						
Stage I	140	138	128	115	82	61
Stage II	85	66	55	50	39	24
Stage III and IV	12	9	4	4	3	3
Rheumatoid arthritis						
Stage I	290	276	262	239	153	97
Stage II	159	138	116	103	70	44
Stage III and IV	35	22	13	10	7	3

* The number of patients at risk at different times after breast cancer diagnosis.

Our study has several potential limitations. Medicare data were created for billing purposes and may lack the precision needed for clinical research. For example, data on possible confounding factors such as smoking, body fatness (body mass index or percentage body fat), physical activity, and functional status are not available in the database. Recipients of Medicare can seek care from outside providers, such as long-term care or an oral prescription for Tamoxifen, which was not in the past covered by Medicare. In addition, both cancer treatment and treatment for comorbid conditions have improved since the time this study began. Data on medical history before enrolling in Medicare are also not available. The measurement of comorbidities does not consider the severity of diagnosis or how long the patient has had each condition. In addition, if a person has a comorbid condition that is not listed in Medicare, it would result in misclassification of the comorbidity status. However, comorbidity prevalence was defined using inpatient, outpatient, and physician files with restriction criteria that have been shown to be comparable to hospital medical records (44).

Approximately one-third (34%) of the potentially eligible study participants were excluded, most often because they were enrolled in an HMO and Medicare files were not available. Differences do exist between the population characteristics of HMO and FFS Medicare health-care delivery system subscribers—patients who are enrolled in HMOs are generally younger, healthier, diagnosed at an earlier stage, and have better overall survival compared with FFS patients (21,45). Although these differences between HMO patients and FFS patients could potentially influence the relationships between comorbidity and overall survival, there is no data to support this hypothesis. Our study findings are therefore most applicable to the population of Medicare FFS patients because this population is used in the present analysis. In addition, the number of patients in the study receiving chemotherapy was low (14.8%) and consistent with other Medicare patient series (46,47). The relatively low number of patients receiving chemotherapy in our study population may be because of the substantial drop-off in the use of adjuvant therapies that occurs with advancing age (46–49). Finally, our study population included a number of records with missing or unknown values for stage, grade, and estrogen receptor status. However, the use of two different methods to account for missing or unknown values indicated that missing records had no influence on the study findings.

In this study, analyses of Kaplan–Meier survival curves demonstrate that comorbidities can be as important as stage in predicting breast cancer survival. Comorbidities are associated with survival to the extent that patients with these comorbid conditions diagnosed with early-stage breast cancer have survival similar to or worse than that of patients with no comorbidities diagnosed with later-stage tumors. This finding suggests that including comorbid conditions in the assessment of prognosis in both observational research and patient care may be important and that careful attention to the effective management of comorbid conditions, as well as to the management of a patient's cancer, may result in longer overall survival for older breast cancer patients.

Appendix

Appendix Table 1. Codes used to identify chemotherapy and radiation treatment in Medicare files*

Treatment	*ICD*-9 diagnostic codes	*ICD*-9 procedure codes	HCPCS codes	Revenue center codes
Chemotherapy	V58.1, V66.2, V67	99.25	96400–96499, 96500–96599, Q0083–Q0085, 51720, J8510, J8520, J8521, J8530-J8999, J9000-J9999	331, 332, 335
Radiation	V58.0, V66.1, V67.1	92.21–92.33, 92.39	77401–77499, 77520, 77523, 77750–77799, G0256, G0261	330, 333, 339

* *ICD*-9 = *International Classification of Diseases, Ninth Revision*; HCPCS = the Health Care Financing Administration Common Procedure Coding System.

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