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The Association Between Guideline-concordant Care and Risk for Breast Cancer and Non-breast Cancer Mortality Among Older Women with Breast Cancer

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Abstract: The purpose of this study is to determine how receipt of guideline-concordant care (GCC) is associated with breast cancer-specific mortality (BCSM) and non-breast cancer mortality (NBCM) among older women with breast cancer. The SEER-Medicare data was used to identify 142, 433 women age > 66 diagnosed with stage I-III breast cancer between 2007-2011. Receipt of GCC was determined according to evidence-based treatment guidelines. Cause-specific Cox proportional hazard multivariable regression models were used to estimate the association between GCC and the risk of BCSM, considering NBCM as a competing event, and NBCM, considering BCSM as a competing event, within five years of diagnosis or until end of follow-up. Among older women with breast cancer, 6.5% experienced BCSM and 11.9% experienced NBCM. GCC was associated with a 24% decreased risk of BCSM (AHR, 0.76; 95% CI, 0.71-0.82), but a 80% increased risk of NBCM (AHR, 1.80; 95% CI, 1.70-1.92). Receipt of adjuvant endocrine therapy was associated with an increased risk of BCSM and a decreased risk for NBCM. Receipt of chemotherapy was associated with an increased risk for BCSM and NBCM, while radiation therapy was associated with a decreased risk of NBCM. Women with a pre-existing dementia, arthritis, hypertension, stroke and increased comorbidity burden had an increased risk for BCSM. Most older breast cancer patients do not receive GCC, yet relatively few die from breast cancer. While GCC does decrease the risk of BCSM, the decision to treat should be made considering the patients existing health status, given that pre-existing comorbidity increases the risk for both BCSM and NBCM. Mortality differences associated with specific types of treatment may be attributed to patient selection for treatment based on worse cancer prognostic factors.

Keywords: Breast Cancer, Guideline-concordant Care, Survival

1. Background

Although the majority of older women diagnosed with breast cancer have less aggressive subtypes, [1, 2] older women experience worse breast cancer-specific mortality (BCSM) at every stage and sub-type, compared to younger women. [3] Older women with breast cancer are also at greater risk of non-breast cancer mortality (NBCM), especially those with greater comorbidity. [4] The concurrent increased risk for BCSM and NBCM may present challenges to the treatment decision making process for many older patients. While breast cancer treatment is primarily determined by evidence-based guidelines based on clinical characteristics and extent of disease spread, [5] other important considerations include patient preferences, health and age.

Yet, it is well documented that older breast cancer patients are often undertreated, as compared to their younger counterparts. [6, 7] In fact, a recent study reported that only 40% of women age > 66 years received treatment according to evidence-based guidelines, or guideline-concordant care (GCC), [8] possibly contributing to the

worse BCSS observed among older women. Primary reasons associated with lower rates of GCC include older age, greater comorbidity, treatment toxicity, decreased functional status and limited life-expectancy. [9-11] Moreover, epidemiological studies have reported conflicting findings as to whether or not receipt of GCC and specific treatments are associated with improved BCSM and/or NBCM among older women. [12-14] An important, but previously unconsidered factor is the concept of competing risks of death. Competing events, such as NBCM, are important to account for when estimating cause-specific endpoints such as BCSM, [15] especially given that over 70% of deaths among women age > 75 years with breast cancer, are due to non-breast cancer causes. [16] Therefore, the purpose of the current study is to investigate how GCC is associated with the risk of BCSM, considering NBCM as a competing event, and the risk of NBCM, considering BCSM as a competing event, among a large US population-based cohort of older women with breast cancer.

2. Methods

2.1. Data Source and Cohort Definition

The National Cancer Institute and Centers for Medicare and Medicaid Services collaborated to create the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The SEER cancer registry, representing 17 distinct tumor registries and 26% of the US population, is linked to Medicare claims for individuals age > 65 years using patient name, age, sex, date of birth, and social security number. [17] The linked database provides information regarding date of diagnosis, cancer site, stage, tumor characteristics, treatment, health conditions, health care use, patient enrollment and eligibility, selected demographic characteristics, and vital status information. For this study, the US Department of Health and Human Resource's 2009 Area Resource File (ARF) was additionally linked to the SEER-Medicare database to identify the area-level health resources using county and state identifiers. [18] Inclusion criteria for defining the study cohort included: female sex, age > 66 years at the date of diagnosis, breast cancers diagnosed in the years 2007 – 2011, breast cancer was first and only cancer diagnosed during the study time period, diagnoses that were pathologically confirmed, patients who were alive for a minimum of 366 days after the date of diagnosis, stage of diagnosis was I, II or III, and continuous enrollment in Medicare Parts A and B fee-for-service plan 12 months before and after the date of diagnosis. Patients were excluded if they were diagnosed at death or autopsy, diagnosed at stage 0 or stage IV, enrolled in a health maintenance organization (HMO) plan at any time in the 12 months before and after diagnosis or tumor size was missing. The final analytic sample of 142,382 women.

2.2. Measures

2.2.1. Outcomes

The primary study outcome was BCSM, with NBCM treated as a competing event, and the secondary outcome was NBCM, with BCSM treated as a competing event. Cause-specific mortality (BCSM) was ascertained using the SEER cause-specific death classification variable that determines cause of death by considering cause of death, sequence of tumor diagnosis, and site of primary tumor. This method reduces the risk for misclassification of the cause of death when using death certificate records. [19] All other causes of death were classified as NBCM. The follow-up period was for up to five years (1,830 days) after diagnosis or until the end of the study time-period (December 31st, 2013). Mortality events were identified using the Medicare date of death variable.

2.2.2. Independent Variables

The main independent variable was receipt of GCC (yes or no). Receipt of GCC was determined for each woman by comparing the actual course of treatment received to the recommended course of treatment, according to age and clinical characteristics as per National Comprehensive Cancer Network (NCCN) Breast Cancer Clinical Practice Guidelines. [20] Information regarding how GCC was determine has been described elsewhere. [8] Specific types of tests and treatments studied were receipt of estrogen receptor (ER) and progesterone receptor (PR) testing, breast-conserving surgery (BCS), mastectomy, radiation therapy (RT), chemotherapy, initiation of chemotherapy within 120 days of diagnosis, and adjuvant hormone therapy (AET). Hormone receptor testing was estimated using a previously described method that considers documentation of a "positive", "negative", or "borderline" ER and PR status an indication that hormone receptor testing was conducted, and an "unknown" or "missing" status an indication that testing was not conducted. [21] Initiation of chemotherapy within 120 days of diagnosis, when indicated, was assessed according to joint American Society of Clinical Oncology (ASCO)/ NCCN quality measures. [22] These services were identified using International Classification of Diseases, 9th Revision (ICD-9) diagnostic and procedure codes and Healthcare Common Procedure Coding System (HCPCS)/Current Procedural Terminology (CPT) codes generic drug names (Table 1).

Table 1. *Claims Codes Used for Identifying Types of Treatment.*

Type of Treatment	ICD-9 Diagnostic	ICD-9 Procedure	HCPCS/CPT	Revenue Center	Generic Drug Name
Breast-Conserving Surgery		85.20-85.29	19120, 19125-19126, 19160, 19162, 19301-19302		
Mastectomy		85.33-85.36,	19140, 19180, 19182, 19300, 19303-		

Type of Treatment	ICD-9 Diagnostic	ICD-9 Procedure	HCPCS/CPT	Revenue Center	Generic Drug Name
		85.40-85.48	19307, 19200, 19220, 19240, 19260, 19271-19272		
Radiation Therapy	V58.0, V66.1, V67.1	92.20-92.39	77261-77799, G0256, G0261, G0173-G0174, G0243, G0251, G0338-G03340	0330, 0333	
Chemotherapy	V58.1, V66.2, V67.2,	99.25, 99.28	96400-96599, C8953-C8955, G0355-G0363, G902-G9032, J0640, J8510, J8520-J8521, J8530-J8999, J9000-J9999, Q0083-Q0085, S9329-S9331	0331, 0332, 0335	
Adjuvant Endocrine Therapy					tamoxifen, anastrozole, exemestane, letrozle

Other independent variables were year of diagnosis, age, pre-existing chronic conditions, frequency of primary care provider (PCP) visits, clinical prognostic factors, oncology care resources, and demographic characteristics. Specific pre-existing chronic conditions identified were anxiety, depression, dementia, arthritis, osteoporosis, diabetes, hypertension, hyperlipidemia, heart disease (includes coronary artery disease and cardiac arrhythmia), stroke, and chronic obstructive pulmonary disease (COPD), using methods described by the Multiple Chronic Conditions Working Group. [23] Comorbidity scores were calculated using the Klabunde adaptation of the Charlson Comorbidity Index (CCI) (score = 0, 1, > 2). [24] Frequency of PCP visits was calculated by counting the number of unique PCP claim dates recorded one year before diagnosis in the physician claims file and dividing by the lower and upper 50th percent median cutoff (low, high). Clinical prognostic factors included stage at diagnosis, tumor size, lymph node status, hormone receptor status, and tumor grade. Measures of oncology care resources were the density of area-level mammography screening centers and oncology treatment centers relative to each woman's location of residence, using data from the ARF, categorized by the lower and upper 50th percent median cutoff (low, high). Surgeon specialty was assessed using provider specialty claims codes 02, 49 (general) and 83, 90, 91, 98 (oncology) from the physician claims file variable "hcfaspec" (general only, oncology only, both). Demographic characteristics included race, marital status, metro status, and 2010 Census measures of area-level education and annual income.

2.3. Statistical Analysis

Pearson X^2 tests were used to compare survival outcomes by patient characteristics. Cause-specific Cox proportional hazard multivariable regression models were used to estimate the risk of BCSM, with NBCM events treated as a censored observations, and the risk of NBCM, with BCSM events treated as a censored observations. These cause-specific regression models were adjusted for all other study variables. Independent variables, ER testing and PR testing, were removed from the final regression models due to small cell sizes. Sub-distribution hazard models were used to estimate the cumulative incidence functions for BCSM and NBCM, stratified by receipt of GCC (yes or no) using the Fine and Gray method. [25] Parameter estimates are presented as adjusted hazard ratios (AHR) with their corresponding 95% confidence intervals (CI). *P* values < .05 were considered statistically significant. All analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC). This study was approved for exemption by the West Virginia Institutional Review Board.

3. Results

3.1. Unadjusted Analysis

At follow-up, 6.5% of older women had experienced BCSM, 11.9% experienced NBCM and the majority did not receive GCC (Table 2). Among women who received GCC, a greater proportion were alive at follow-up (42.2%), than experienced BCSM (33.2%) or NBCM (26.1%). Whereas, greater proportions of women who did not receive GCC experienced BCSM (66.8%) or NBCM (73.9%), than living at follow-up (57.8%). Greater proportions of women who were hormone receptor negative experienced BCSM (27.5%), than NBCM (9.2%) or were alive (10.2%). Among those who received chemotherapy, a greater proportion experienced BCSM (46.1%), than NBCM (16.9%) or were alive (28.8%). Greater proportions of women who received AET or RT were still alive at follow-up, than experienced BCSM or NBCM.

Table 2. *Comparison of Characteristics among Older Women Diagnosed with Breast Cancer by 5-Year Survival Outcomes.*

SEER-Medicare, 2007-2011							
	BCSM	%	NBCM	%	Alive	%	p
All	9,222	6.5	16,962	11.9	116,199	81.6	
Receipt of GCC							< 0.001
Yes	3,064	33.2	4,423	26.1	49,072	42.2	
No	6,158	66.8	12,539	73.9	67,127	57.8	
Year of Diagnosis							< 0.001
2007	2,846	30.9	4,109	24.2	17,573	15.1	
2008	1,176	12.7	2,795	16.5	24,205	20.9	

SEER-Medicare, 2007-2011							
	BCSM	**%**	**NBCM**	**%**	**Alive**	**%**	**p**
2009	3,569	38.7	3,595	21.2	24,196	20.8	
2010	1,109	12.0	4,571	27.0	24,641	21.2	
2011	522	5.7	1,892	11.1	25,584	22.0	
Age & Health							
Age at Diagnosis							< 0.001
66-69	1,942	21.1	719	4.2	26,344	22.7	
70-74	1,548	16.8	1,579	9.3	32,904	28.3	
75-79	2,010	21.8	3,950	23.3	27,098	23.3	
> 80	3,722	40.3	10,714	63.2	29,853	25.7	
PCP Visits							< 0.001
Low	3,963	43.0	6,599	38.9	54,042	46.5	
High	5,259	57.0	10,363	61.1	62,157	53.5	
Anxiety							< 0.001
Yes	259	2.8	2,611	15.4	9,131	7.9	
No	8,963	97.2	14,351	84.6	10,7068	92.1	
Depression							< 0.001
Yes	773	8.4	2,584	15.2	9,021	7.8	
No	8,449	91.6	14,378	84.8	107,178	92.2	
Dementia							< 0.001
Yes	1,369	14.8	3,849	22.7	2,605	2.2	
No	7,853	85.2	13,113	77.3	113,594	97.8	
Arthritis							< 0.001
Yes	3,666	39.8	4,093	24.1	32,614	28.1	
No	5,556	60.2	12,869	75.9	83,585	71.9	
Osteoporosis							< 0.001
Yes	939	10.2	1,326	7.8	14,336	12.3	
No	8,283	89.8	15,636	92.2	101,863	87.7	
Diabetes							< 0.001
Yes	3,289	35.7	7,336	43.2	35,528	30.6	
No	5,933	64.3	9,626	56.8	80,671	69.4	
Hypertension							< 0.001
Yes	7,965	86.4	14,791	87.2	93,471	80.4	
No	1,257	13.6	2,171	12.8	22,728	19.6	
Hyperlipidemia							< 0.001
Yes	5,218	56.6	10,498	61.9	77,844	67.0	
No	4,004	43.4	6,464	38.1	38,355	33.0	
Heart Disease							
Yes	3,991	43.3	9,420	55.5	38,536	33.2	
No	5,231	56.7	7,542	44.5	77,663	66.8	
Stroke							< 0.001
Yes	1,035	11.2	3,275	19.3	6,701	5.8	
No	8,187	88.8	13,687	80.7	109,498	94.2	
COPD							< 0.001
Yes	1,547	16.8	4,158	24.5	11,636	10.0	
No	7,675	83.2	12,804	75.5	104,563	90.0	
Charlson Comorbidity Index							< 0.001
0	4,540	49.2	7,281	42.9	71,484	61.5	
1	2,982	32.4	5,106	30.1	31,946	27.5	
> 2	1,700	18.4	4,575	27.0	12,769	11.0	
Clinical Prognostic Factors							
Stage at Diagnosis							< 0.001
I	1,178	12.8	7,643	45.1	67,350	58.0	
II	4,638	50.3	7,328	43.2	39,743	34.2	
III	3,406	36.9	1,991	11.7	9,106	7.8	
Tumor Size							< 0.001
< 1 cm	527	5.7	2,670	15.7	32,843	28.3	
< 2 cm	1,981	21.5	6,461	38.1	47,584	40.9	
2 - 5 cm	4,615	50.0	6,904	40.7	33,238	28.6	
> 5 cm	2,099	22.8	927	5.5	2,534	2.2	
Lymph Nodes							< 0.001
Positive	4,297	46.6	3,903	23.0	28,450	24.5	
Negative	4,925	53.4	13,059	77.0	87,749	75.5	
Hormone Receptor Status							< 0.001
ER and/or PR Positive	5,395	58.5	14,811	87.3	99,525	85.6	
ER and PR Negative	2,538	27.5	1,561	9.2	11,812	10.2	
Borderline/Unknown	1,289	14.0	590	3.5	4,862	4.2	

SEER-Medicare, 2007-2011							
	BCSM	**%**	**NBCM**	**%**	**Alive**	**%**	**p**
Tumor Grade							< 0.001
Well Differentiated	378	4.1	3,684	21.7	28,519	24.5	
Moderately Differentiated	2,661	28.8	8,226	48.5	52,016	44.8	
Poorly Differentiated	4,940	53.6	4,057	23.9	28,341	24.4	
Undifferentiated/Unknown	1,243	13.5	995	5.9	7,323	6.3	
Oncology Care Resources							
Mammography Screening Centers							< 0.001
Low	3,019	32.7	8,658	51.0	63,966	55.1	
High	6,203	67.3	8,304	49.0	52,233	44.9	
Oncology Treatment Centers							< 0.001
Low	3,051	33.1	8,740	51.5	64,563	55.6	
High	6,171	66.9	8,222	48.5	51,636	44.4	
Specialty of Treating Surgeon (s)							< 0.001
General Only	1,305	14.2	4,273	25.2	13,450	11.6	
Oncology Only	407	4.4	933	5.5	7,580	6.5	
Both	7,510	81.4	11,756	69.3	95,169	81.9	
Demographic Characteristics							
Race/Ethnicity							< 0.001
White	6,092	66.1	12,440	73.3	88,254	75.9	
Black	2,814	30.5	4,064	24.0	20,202	17.4	
Hispanic/Latino	231	2.5	178	1.0	4,406	3.8	
Other	85	0.9	280	1.7	3,337	2.9	
Education							< 0.001
< 15% college degree	3,681	39.9	6,320	37.3	44,272	38.1	
> 15% college degree	5,541	60.1	10,642	62.7	71,927	61.9	
Annual Income							0.003
< $35,000	3,381	36.7	5,951	35.1	40,535	34.9	
> $35,000	5,841	63.3	11,011	64.9	75,664	65.1	
Marital Status							< 0.001
Yes Married/Partnered	976	10.6	4,642	27.4	39,531	34.0	
No not Married/Partnered	8,246	89.4	12,320	72.6	76,668	66.0	
Metro Status							< 0.001
Non-metro	308	3.3	1,774	10.5	7,315	6.3	
Metro	8,914	96.7	15,188	89.5	108,884	93.7	
Tests & Treatments							
ER Status Tested							< 0.001
Yes	8,291	89.9	16,371	96.5	111,334	95.8	
No	931	10.1	591	3.5	4,865	4.2	
PR Status Tested							< 0.001
Yes	8,291	89.9	16,365	96.5	111,005	95.5	
No	931	10.1	597	3.5	5,194	4.5	
Received AET							< 0.001
Yes	3,717	40.3	7,000	41.3	59,989	51.6	
No	5,505	59.7	9,962	58.7	56,210	48.4	
Type of Surgery							< 0.001
BCS	3,930	42.6	10,069	59.4	72,546	62.4	
Mastectomy	2,553	27.7	3,105	18.3	23,258	20.0	
BCS and Mastectomy	1,524	16.5	2,878	17.0	17,439	15.0	
No Surgery	1,215	13.2	910	5.3	2,956	2.6	
Received Radiation Therapy							< 0.001
Yes	4,757	51.6	5,708	33.7	71,275	61.3	
No	4,465	48.4	11,254	66.3	44,924	38.7	
Received Chemotherapy							< 0.001
Yes	4,253	46.1	2,862	16.9	33,442	28.8	
No	4,969	53.9	14,100	83.1	82,757	71.1	
Time to Chemotherapy							< 0.001
Appropriate	2,819	30.6	1,520	9.0	23,812	20.5	
Not Appropriate	1,434	15.5	1,342	7.9	9,630	8.3	
No Chemotherapy	4,969	53.9	14,100	83.1	82,757	71.2	

Abbreviations: GCC, guideline-concordant care; BCSM, breast cancer specific mortality; NBCM, non-breast cancer mortality; PCP, primary care physician; ER, estrogen receptor; PR, progesterone receptor; AET, adjuvant endocrine therapy; COPD, chronic obstructive pulmonary disease.

3.2. Breast Cancer-Specific Mortality

In the multivariate analysis, women who received GCC had a 24% lower risk of BCSM (AHR, 0.76; 95% CI, 0.71-0.82), than those who did not receive GCC (Table 3). Women with a CCI > 2 (AHR, 3.10; 95% CI, 2.81-3.43) or with

dementia (AHR, 3.57; 95% CI, 3.30-3.87) were more than three times as likely to experience BCSM. Those with arthritis, hypertension and stroke also had a higher risk for BCSM. Women who were lymph node positive had a decreased risk of BCSM (AHR, 0.58; 95% CI, 0.54- 0.62), while those who were later stage, with larger tumors, hormone receptor negative or with moderately and poorly differentiated tumors had increased risk for BCSM. Women who received AET had a 59% increased risk of BCSM (AHR, 1.59; 95% CI, 1.50-1.68). Receipt of chemotherapy was also associated with an increased risk for BCSM (AHR, 1.18; 95% CI, 1.08-1.29). Women of black race, Hispanic/Latino ethnicity, and other race had a decreased risk of BCSM, compared to white women. At five years (1830 days), the cumulative incidence of BCSM was significantly greater among women who did not receive GCC [(HR, 0.054; 95% CI, 0.052-0.056); Gray's test $p < 0.0001$] (Figure 1).

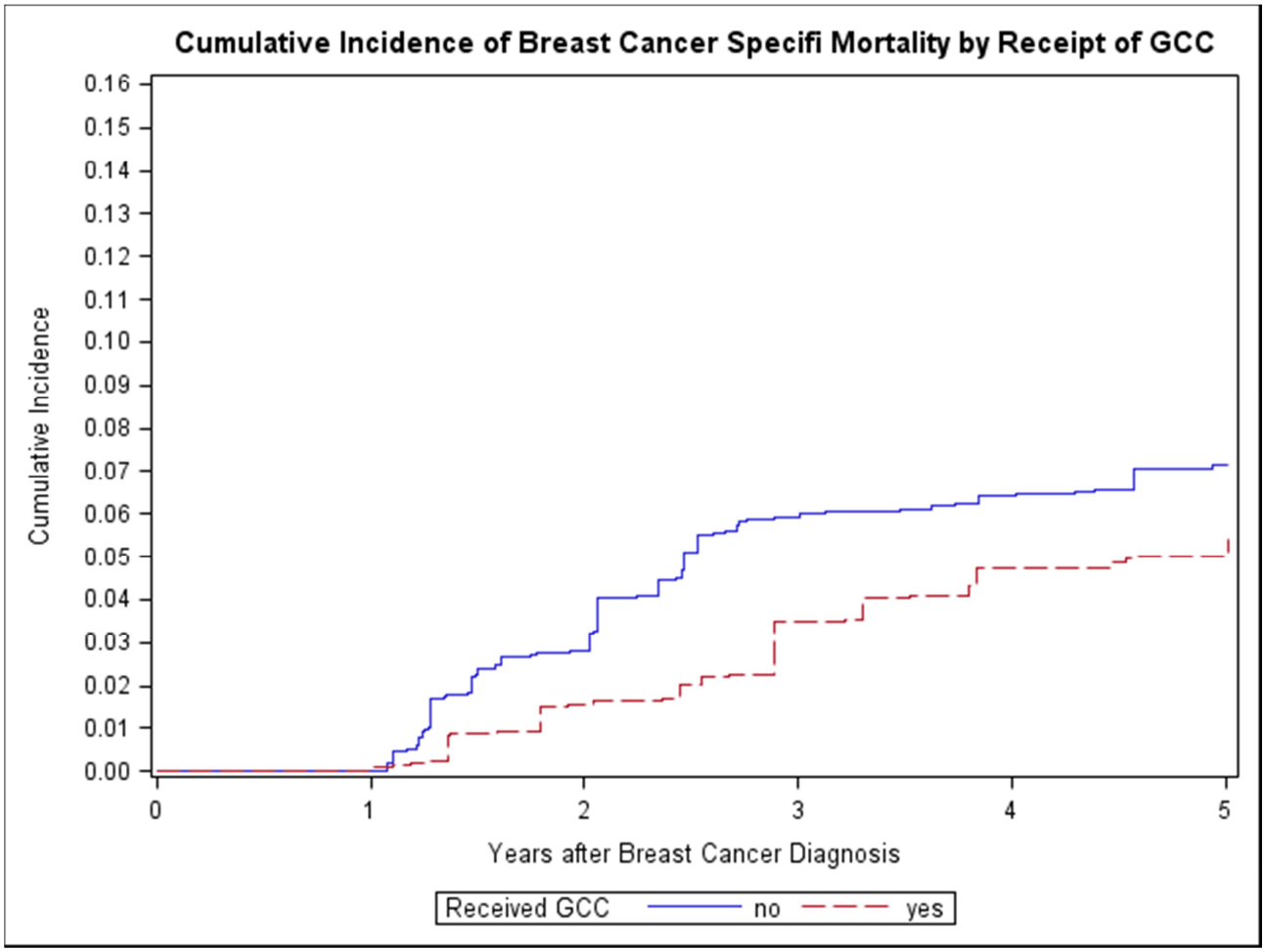

Figure 1. *Competing Risks Cumulative Incidence of Breast Cancer Specific Mortality.*

Table 3. *Adjusted Cause-Specific Cox Proportional Hazard Models for Older Women Diagnosed with Breast Cancer.*

SEER-Medicare, 2007-2011						
	BCSM vs. Alive			**NBCM vs. Alive**		
	AHR	**95% CI**	**Sig.**	**AHR**	**95% CI**	**Sig.**
Adjusted Hazard Ratio						
Receipt of GCC						
Yes	0.76	[0.71, 0.82]	***	1.80	[1.70, 1.92]	***
No	1.00	—		1.00	—	
Year of Diagnosis						
2007	1.00	—		1.00	—	
2008	0.42	[0.39, 0.46]	***	0.77	[0.73, 0.81]	***
2009	1.17	[1.10, 1.24]	***	0.69	[0.66, 0.73]	***
2010	0.14	[0.13, 0.16]	***	0.98	[0.94, 1.03]	
2011	0.18	[0.16, 0.20]	***	0.38	[0.35, 0.40]	***
Age & Health						
Age at Diagnosis						
66-69	1.00	—		1.00	—	

SEER-Medicare, 2007-2011						
	BCSM vs. Alive			NBCM vs. Alive		
	AHR	95% CI	Sig.	AHR	95% CI	Sig.
70-74	0.71	[0.66, 0.77]	***	1.53	[1.40, 1.68]	
75-79	1.39	[1.29, 1.50]	***	4.59	[4.59, 5.40]	***
> 80	1.27	[1.29, 1.50]	***	7.79	[7.18, 8.45]	***
PCP Visits						
Low	1.00	—		1.00	—	
High	1.09	[1.03, 1.14]	***	0.84	[0.81, 0.87]	***
Anxiety						
Yes	0.26	[0.23, 0.30]	***	1.65	[1.57, 1.74]	***
No	1.00	—		1.00	—	
Depression						
Yes	0.87	[0.80, 0.96]	**	1.20	[1.14, 1.26]	***
No	1.00	—		1.00	—	
Dementia						
Yes	3.67	[3.39, 3.97]	***	3.11	[2.96, 3.27]	***
No	1.00	—		1.00	—	
Arthritis						
Yes	1.25	[1.19, 1.31]	***	0.61	[0.59, 0.64]	***
No	1.00	—		1.00	—	
Osteoporosis						
Yes	0.83	[0.77, 0.90]	***	0.55	[0.52, 0.59]	***
No	1.00	—		1.00	—	
Diabetes						
Yes	0.64	[0.59, 0.69]	***	1.58	[1.51, 1.66]	***
No	1.00	—		1.00	—	
Hypertension						
Yes	1.53	[1.42, 1.64]	***	1.09	[1.03, 1.14]	**
No	1.00	—		1.00	—	
Hyperlipidemia						
Yes	0.63	[0.60, 0.66]	***	0.95	[0.92, 0.99]	**
No	1.00	—		1.00	—	
Heart Disease						
Yes	1.11	[1.05, 1.16]	***	1.35	[1.31, 1.41]	***
No	1.00	—		1.00	—	
Stroke						
Yes	1.89	[1.76, 2.04]	***	1.70	[1.63, 1.78]	***
No	1.00	—		1.00	—	
COPD						
Yes	0.96	[0.89, 1.03]		2.54	[2.42, 2.67]	***
No	1.00	—		1.00	—	
Charlson Comorbidity Index						
0	1.00	—		1.00	—	
1	1.86	[1.73, 2.00]	***	0.69	[0.65, 0.73]	***
> 2	3.10	[2.81, 3.43]	***	1.13	[1.13, 1.28]	***
Clinical Prognostic Factors						
Stage at Diagnosis						
I	1.00	—		1.00	—	
II	3.81	[3.42, 4.24]	***	1.43	[1.32, 1.54]	***
III	15.39	[13.57, 17.44]	***	1.78	[1.61, 1.96]	***
Tumor Size						
< 1 cm	1.00	—		1.00	—	
< 2 cm	1.36	[1.23, 1.50]	***	1.34	[1.28, 1.41]	***
2 - 5 cm	1.33	[1.18, 1.49]	***	1.15	[1.06, 1.25]	***
> 5 cm	4.29	[3.79, 4.86]	***	2.15	[1.93, 2.39]	***
Lymph Nodes						
Positive	0.58	[0.54, 0.62]	***	1.09	[1.03, 1.16]	**
Negative	1.00	—		1.00	—	
Hormone Receptor Status						
ER and/or PR Positive	1.00	—		1.00	—	
ER and PR Negative	3.75	[3.50, 4.01]	***	0.71	[0.67, 0.76]	***
Borderline/Unknown	2.37	[2.18, 2.57]	***	0.71	[0.65, 0.78]	***
Tumor Grade						
Well Differentiated	1.00	—		1.00	—	

SEER-Medicare, 2007-2011						
	BCSM vs. Alive			**NBCM vs. Alive**		
	AHR	**95% CI**	**Sig.**	**AHR**	**95% CI**	**Sig.**
Moderately Differentiated	2.46	[2.18, 2.78]	***	0.95	[0.91, 0.99]	*
Poorly Differentiated	4.85	[4.29, 5.48]	***	1.03	[0.98, 1.09]	
Undifferentiated/Unknown	4.80	[4.20, 5.48]	***	0.81	[0.75, 0.87]	***
Oncology Care Resources						
Mammography Screening Centers						
Low	1.00	—		1.00	—	
High	1.01	[0.74, 1.38]		1.14	[0.96, 1.34]	
Oncology Treatment Centers						
Low	1.00	—		1.00	—	
High	2.23	[1.63, 3.03]	***	1.10	[0.96, 1.34]	
Specialty of Treating Surgeon (s)						
General Only	1.00	—		1.00	—	
Oncology Only	0.53	[0.46, 0.60]	***	1.07	[0.99, 1.16]	
Both	1.08	[1.01, 1.16]	*	1.03	[0.99, 1.08]	
Socio-Demographic Characteristics						
Race						
White	1.00	—		1.00	—	
Black	0.65	[0.61, 0.69]	***	0.92	[0.88, 0.96]	***
Hispanic/Latino	0.69	[0.59, 0.77]	***	0.38	[0.32, 0.44]	***
Other	0.73	[0.58, 0.92]	***	0.87	[0.77, 0.98]	*
Education						
< 15% college degree	1.00	—		1.00	—	
> 15% college degree	0.96	[0.91, 1.00]		1.05	[1.01, 1.09]	*
nnual Income						
< $35, 000	1.00	—		1.00	—	
> $35, 000	0.96	[0.92, 1.01]		0.98	[0.95, 1.02]	
Marital Status						
Yes Married/Partnered	1.00	—		1.00	—	
No not Married/Partnered	3.24	[3.01, 3.49]	***	0.90	[0.86, 0.93]	***
Metro Status						
Non-metro	2.71	[2.32, 3.29]	***	1.48	[1.36, 1.60]	***
Metro	1.00	—		1.00	—	
Tests & Treatments						
Received AET						
Yes	1.59	[1.49, 1.68]	***	0.57	[0.54, 0.59]	***
No	1.00	—		1.00	—	
Type of Surgery						
BCS	1.00	—		1.00	—	
Mastectomy	0.89	[0.83, 0.96]	***	0.54	[0.51, 0.57]	***
BCS and Mastectomy	0.72	[0.67, 0.78]	***	1.11	[1.06, 1.17]	***
No Surgery	1.42	[1.29, 1.56]	***	0.84	[0.77, 0.91]	***
Received Radiation Therapy						
Yes	1.03	[0.97, 1.10]		0.43	[0.41, 0.46]	***
No	1.00	—		1.00	—	
Received Chemotherapy						
Yes	1.18	[1.08, 1.29]	***	1.48	[1.38, 1.58]	***
No	1.00	—		1.00	—	
ime to Chemotherapy						
Appropriate	1.51	[1.37, 1.66]	***	0.45	[0.41, 0.48]	***
Not Appropriate	1.00	—		1.00	—	
No Chemotherapy	—	—		—	—	

* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; Abbreviations: AHR, adjusted hazard ratio; BCSM, breast cancer specific mortality; NBCM, non-breast cancer mortality; PCP, primary care physician; ER, estrogen receptor; PR, progesterone receptor; AET, adjuvant endocrine therapy; COPD, chronic obstructive pulmonary disease.

3.3. Non-Breast Cancer Mortality

Women who received GCC had an 80% increased risk for NBCM (AHR, 1.80; 95% CI, 1.70-1.92), compared to those who did not receive GCC. Women who received AET (AHR, 0.57; 95% CI, 0.54-0.59) or RT (AHR, 0.43; 95% CI, 0.41-0.46) had a decreased risk for NBCM, while women who received chemotherapy had a 48% increased risk for NBCM (AHR, 1.48; 95% CI, 1.38-1.58). The five-year cumulative incidence of NBCM was significantly greater for those who did not receive GCC [(HR, 0.078; 95% CI, 0.076-0.080); Gray's test $p < 0.0001$] (Figure 2).

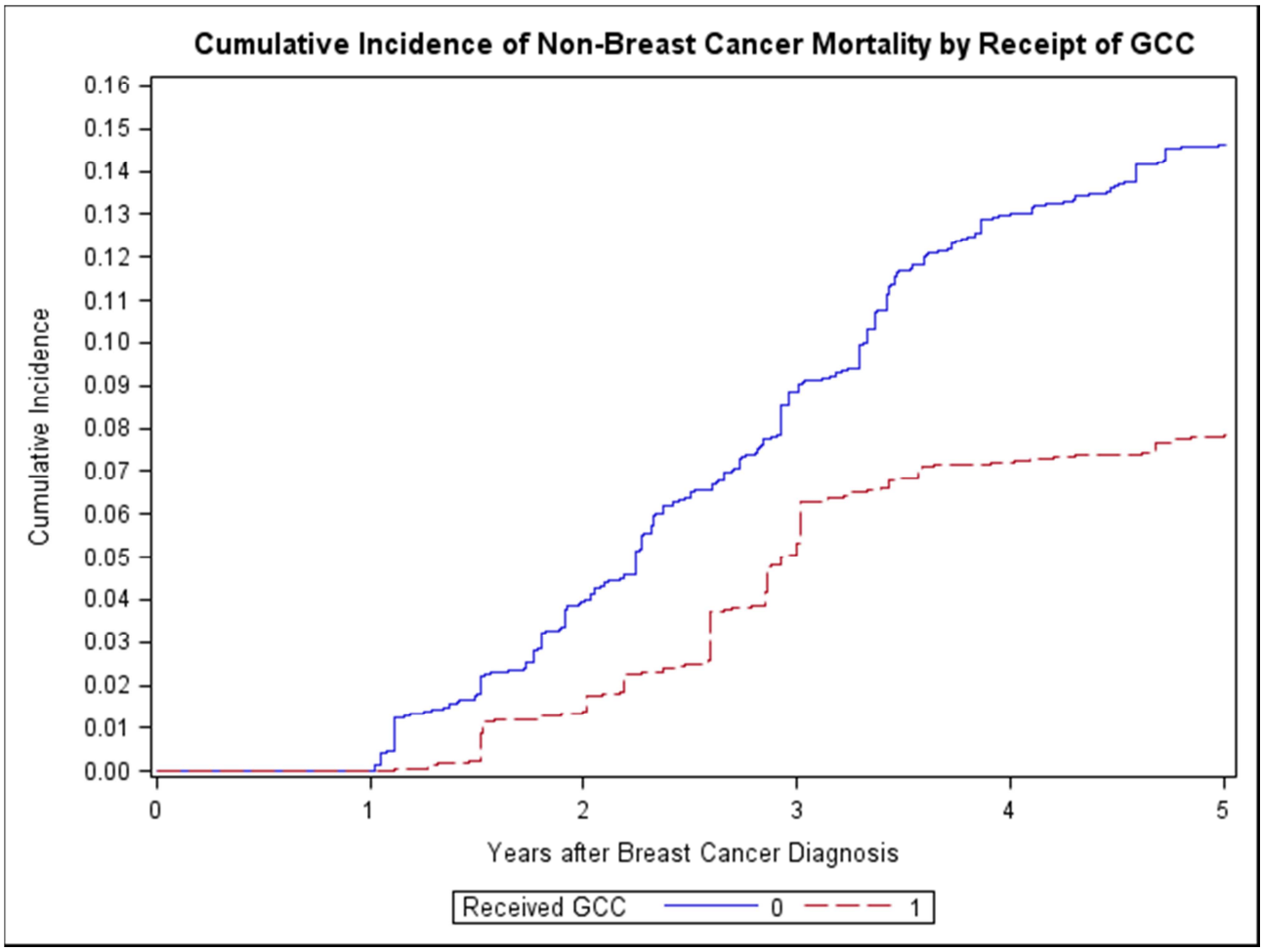

Figure 2. *Competing Risks Cumulative Incidence Non-Breast Cancer Mortality.*

4. Discussion

Although undertreatment has been well document among older women with breast cancer, the competing risks of BCSM and NBCM may complicate breast cancer treatment decisions and create uncertainty regarding the benefits and harms of GCC for this patient population. Therefore, this study sought to determine how receipt of GCC is associated with the risk of BCSM, considering NBCM as a competing event, and NBCM, considering BCSM as a competing event. Among 142,382 elderly women with stage I – III breast cancer, the majority did not receive GCC, but only 6.5% experienced BCSM. Yet, women who did receive GCC had a 22% decreased risk for BCSM, but a 69% increased risk for NBCM. The difference in the associated risk between GCC and BCSM and NBCM, may be explained by the trade-off of benefits and harms of specific types of treatment. In addition to increased intolerance of side-effects that include nausea, vomiting, diarrhea, neutropenia, and fatigue, chemotherapeutic agents, especially anthracycline-based agents, have a known risk for cardiotoxic and hepatotoxic effects, [10,11] in older patients with geriatric syndromes, pre-existing chronic conditions, or impaired organ function, and increased risk for treatment-related mortality. Similarly, this study found that women who received chemotherapy had a 34% increased risk of NBCM. This suggests that chemotherapy may have greater harms than benefits for many older breast cancer patients. An unexpected finding was that AET was associated with a greater than a 50% increased risk for BCSM. Over 84% of women in this study had hormone receptor positive tumors, but less than 50% received AET. Side effects of AET include accelerated bone-loss, musculoskeletal pain, metabolic syndrome, vasomotor, genitourinary, mood, and sleep disturbances. [26, 27] Given these side effects, low risk of recurrence for hormone receptor positive tumors and limited life-expectancy, many older women may not initiate AET. It's plausible that the many of the older women with breast cancer who took AET were not healthy enough for other treatments or were diagnosed with later stage disease, and thus already at an increased risk for BCSM. Similarly, a study by Kimmick and colleagues (2017) observed higher rates of BCSM among women age > 70 years who received chemotherapy, compared to younger women and adjusting for race and tumor characteristics. [14]

In addition to the increased risk of mortality that some cancer treatments pose to older patients, increased comorbidity burden and specific types of pre-existing chronic conditions were also found to increase the risk for mortality. Women with pre-existing dementia, diabetes, hypertension,

heart disease and stroke had an increased risk for both BCSM and NBCM. Previous research has shown greater comorbidity burden from chronic conditions to increase the risk for BCSM and NBCM. [28, 29] Not only do these conditions directly increase the risk for NBCM, but they can also indirectly increase the risk of BCSM. [4, 14, 28] The presence of these conditions may increase the risk for treatment-related toxicity and complications, resulting in modified treatment regimens, or discontinuation of treatment, or omission of treatment all-together.

Unexpected findings from this study were that women who were lymph node positive and of black and Hispanic/Latina races had decreased lower risk of BCSM, compared to women who were lymph node negative or of white race. The association between race and BCSM is more difficult to interpret, but may be explained by study inclusion/exclusion criteria and adjusted hazard models controlling for receipt of specific types of treatments and GCC. It is well documented that black women with breast cancer experience poorer breast cancer survival. [30] These survival disparities are largely attributed to the greater prevalence of aggressive breast cancer subtypes diagnosed among black women and treatment disparities. This study may have limited observed survival disparities due to treatment variations by controlling for receipt of specific types of treatments, as well as, GCC in hazard models. Additionally, study criteria that excluded women enrolled in HMO plans, types of plans that are often used to manage sicker, higher cost patients, may have selected for a healthier study sample.

This study examined both BCSM and NBCM in association with a comprehensive examination of GCC, types of treatments, numerous prevalent chronic conditions, clinical, oncology resource, and demographic characteristics using a large population-based data set. Complex algorithms were used to determine receipt of GCC by calculating the correct course of care according to each patient's tumor characteristics and comparing that to the actual care received. Yet, several limitations should be kept in mind when interpreting the results of this study. This study did not measure completion of RT or chemotherapy, only the initiation of therapy. As the SEER program only began recording information about the status of the human epidermal growth factor 2 (HER2/neu) protein until breast cancer cases diagnosed in 2011, this study did not assess treatment for HER2/neu positive tumors. Nor does SEER-Medicare collect information regarding results of any Oncotype testing that may influence treatment choices.

5. Conclusion

In conclusion, even though less than half of older women receive GCC, relatively few died from breast cancer. Pre-existing chronic conditions often complicate treatment decisions and increase the risk for both BCSM and NBCM. While receipt of GCC decreases the risk of BCSM, the decision to treat should be made considering the patients existing health status, as specific types of cancer treatments, such as chemotherapy, increase the risk of NBCM. The risk and benefits of cancer treatment to the patient's health should be carefully considered before deciding the best course of treatment for each woman.

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