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Increased Mortality Risk among Early Stage Hormone Receptor Positive Breast Cancer Patients Who Did Not Receive Adjuvant or Neoadjuvant Therapy

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Abstract

Background: Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) is the most common biologic subtype of breast cancer. Although adjuvant therapy has demonstrated a survival benefit in clinical trials, its use is poorly understood in the real-world among elderly breast cancer patients since age is a barrier to receiving adjuvant therapy. An examination of treatment patterns and outcomes associated with receipt of adjuvant/neoadjuvant therapy among elderly HR + HER2-breast cancer patients was undertaken. *Methods*: There were 18,470 HR + HER2-breast cancer patients from the linked SEER-Medicare database. Patients were diagnosed with stage I-III disease between 1/1/2007-12/31/2011, ≥66 years, enrolled in Medicare Parts A, B and D, and underwent breast cancer surgery after diagnosis. Time-varying Cox proportional hazards regression assessed overall survival. *Results*: There were 13,670 (74%) patients treated with adjuvant/neoadjuvant therapy and 4800 (26%) untreated. Compared to treated patients, untreated patients were older, had earlier stage, lower grade, smaller tumors, poorer performance, higher comorbidity score, and less use of a 21-gene recurrence score (RS) assay ($p < 0.0001$). In the survival model, increasing age, stage, tumor size, tumor grade, comorbidity score and poor performance were significantly associated with higher mortality risks, while use of an RS assay was associated with lower risks. The Cox model showed a 48% higher risk of death in untreated compared to treated patients. In a subset of 8967 patients with stage I disease, tumor size < 2.0 cm and grade 1/2; untreated patients had a 22% higher risk of death compared to treated patients. *Conclusions*: Older patients with favorable clinical characteristics (earlier stage, smaller tumor, lower grade) are less likely to be treated and have a

higher risk of death compared to adjuvant/neoadjuvant treated patients. An unmet need among older breast cancer patients persists.

Keywords

Hormone Receptor Positive Breast Cancer, Elderly Patients, Adjuvant Therapy, Survival

1. Introduction

Breast cancer is the most common invasive cancer in women and the second leading cause of death from cancer among women in the United States [1]. One-percent of breast cancer occurs in men [2] [3]. Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) is the most common biologic subtype of breast cancer occurring in post-menopausal women and men [3], and accounts for about 73% of incident cases [4]. About 50% of women diagnosed with breast cancer are over the age of 65 [5]. Breast cancer mortality has declined over the past few decades because of advances in awareness, earlier detection, and adjuvant treatments [6] [7].

In general, patients with early-stage breast cancer undergo primary breast cancer surgery with or without radiation therapy. The National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant endocrine therapy for postmenopausal women with HR+ breast cancer for a five-year period following diagnosis [8]. The decision to add chemotherapy to adjuvant endocrine therapy is individualized based on patient factors such as age, tumor size, tumor grade, lymph node involvement, and the results of prognostic multigene assays like the 21-gene Recurrence Score (RS) assay [9] [10] [11]. Recent updates in the American Joint Committee on Cancer Criteria (AJCC) for breast cancer staging manual (8^{th} edition) have incorporated biomarkers and prognostic panel data to guide clinical decision-making.

The benefit of adjuvant therapy is poorly understood among older patients with breast cancer since age is a barrier to receiving adjuvant therapy and older patients are underrepresented in clinical trials [12] [13]. Observational studies have demonstrated that breast cancer mortality increases with age [14] and older age and comorbidities are associated with less aggressive treatment in non-metastatic breast cancer [13] [15]. We aimed to contribute to the existing evidence by examining adjuvant therapy patterns and survival outcomes among HR+HER2-, stage I-III patients with breast cancer using the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database.

2. Methods

2.1. Data Source

The SEER-Medicare database has been described previously [16]. The SEER

program, supported by the National Cancer Institute (NCI), collects data from diverse geographic tumor registries and is representative of about 26% of the U.S. population. The Medicare program is administered by the Centers for Medicare and Medicaid Services (CMS) and covers 97% of the U.S. population for patients aged 65 years and older. The SEER participants who were diagnosed with cancer at age 65 years or above are matched to their Medicare files through an agreement between the NCI and the CMS resulting in a 93% match rate. All Medicare beneficiaries receive Part A coverage (inpatient care, skilled nursing, home healthcare and hospice care) and approximately 95% of beneficiaries subscribe to Part B (outpatient and physician services) and this is combined with the clinical, demographic and cause of death information in SEER. The database linkage used in this study included cancer cases diagnosed until 2011 with their Medicare claims through 2013. Institutional review board (IRB) approval was waived by the New England IRB because the National Institutes of Health's Office of Human Subjects Research has determined that analyses using SEER-Medicare data are exempt from requiring further IRB review and approval.

2.2. Study Population

See **Figure 1** for the schematic of the inclusion/exclusion process. Patients with a first primary breast cancer diagnosis were identified using SEER cancer site variables labeled "breast" by International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes, C50.0-C50.9. We included patients with AJCC stage I, II, or III invasive breast cancer from SEER. Patients, ≥66 years with a first primary breast cancer diagnosed between January 1, 2001 and December 31, 2011 were then linked to their Medicare claims for the years 2000 through 2013. Patients needed to be enrolled in Medicare Parts A and B for a full 12 months prior to diagnosis date and were excluded if breast cancer was diagnosed at the time of death or autopsy, and if enrolled in a health maintenance organization (HMO) any time within the 12 months prior to diagnosis as HMO claims are not available in the dataset.

In July 2006, Medicare coverage was expanded to include prescription drugs under Medicare Part D. We had to further restrict our sample to patients diagnosed between 2007-2011 and enrolled in Part D for at least 1 month in the year after diagnosis date in order to capture patients eligible for adjuvant endocrine therapy. Patients also underwent breast cancer surgery (lumpectomy and mastectomy) within 6 months after diagnosis. Those who received oral or infused neoadjuvant/adjuvant systemic therapy from diagnosis up to 6 months after breast cancer surgery were part of the "treated" group while those who did not were classified as "untreated". The final analytic cohort included 18,470 patients with HR + HER2-breast cancer.

2.3. Study Variables

Patient demographics (age, race/ethnicity, marital status, income, education level

and geographic region) and tumor characteristics (stage, grade, size, and histology) at the time of breast cancer diagnosis were extracted from the SEER registry file. SEER does not contain a measure of functional status, such as Eastern Cooperative Oncology Group (ECOG), we therefore used a proxy for functional status by Davidoff *et al.* [17]. This surrogate for functional status utilized Medicare claims to identify the following categories of healthcare services that are associated with poor functional status and difficulty in ambulation: oxygen and related respiratory supplies, wheelchair, walkers and supplies, home health services, and hospitalization, skilled nursing, or long-term care facility stays during the 12 months prior to diagnosis date. The National Cancer Institute (NCI) comorbidity index [18] assessed comorbidity burden using diagnosis and procedure codes in the Medicare claims files to identify the 15 non-cancer comorbidities from the Charlson Comorbidity Index [19]. A weight is assigned to each condition based on its 2-year mortality risk and these weights are summed to obtain an index for each patient. The index accounts for the number and severity of the conditions, with higher scores indicating a greater burden of comorbid disease. The NCI comorbidity index was also constructed using claims in the 12 months prior to diagnosis date.

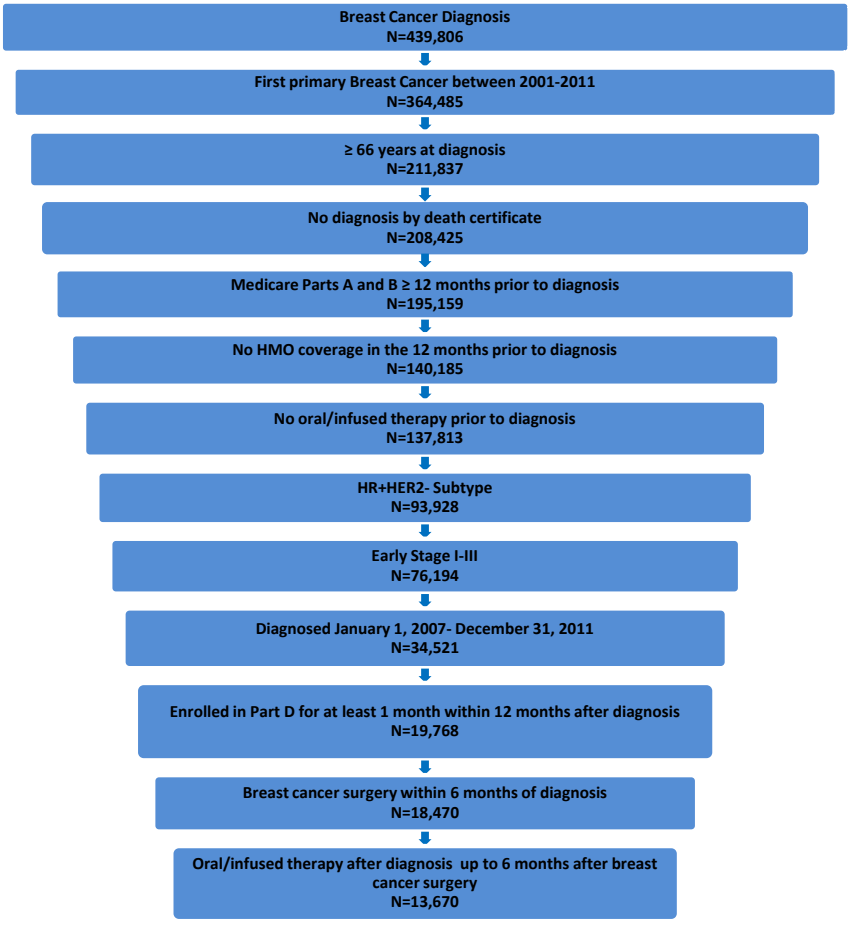

Figure 1. Schematic of inclusion/exclusion process.

Estrogen receptor (ER) and progesterone receptor (PR) status have been collected by SEER since 1990 and ER and PR results were combined and analyzed jointly as HR status. The year 2010 is the most recent year for which HER2 was available in the dataset. Therefore, we used the presence of Medicare claims for HER2 targeted therapies, *i.e.*, trastuzumab (Herceptin®, Roche) and lapatinib (Tykerb, GSK) as a proxy for HER2 positive status and absence of these claims implied HER2 negative status. A case was defined as HR+HER2- if ER and/or PR were positive and HER2 were negative.

Medicare began covering multigene RS assays in February 2006. A modified algorithm from Dinan *et al.* [20] was used to identify claims for RS assays using Healthcare Common Procedural Coding System (HCPCS) code 84,999 (unlisted chemistry procedure) and provider ID corresponding to Genomic Health within the time period of 2 months before diagnosis to 12 months after diagnosis.

Patients who had breast cancer surgery (lumpectomy and mastectomy) were identified by searching Medicare claims for ICD-9 procedure codes and Current Procedural Terminology (CPT) procedure codes from initial diagnosis date of first primary breast cancer up until 6 months after diagnosis. ICD-9 and CPT procedure codes for radiation therapy within 12 months after diagnosis date were also captured in Medicare claims.

We identified Medicare claims associated with oral hormonal therapy and intravenous chemotherapy from breast cancer diagnosis up to 6 months after breast cancer surgery. The Medicare claims data contain information on each agent administered and date administered, but do not indicate whether the agent is being used in the neoadjuvant, adjuvant, or later-line setting or whether it's part of a sequential or combination regimen. Thus, we developed an algorithm to separate claims into regimen lines. All agents administered preoperatively from diagnosis date were considered to be part of a single neoadjuvant regimen line. Patients were considered to have received adjuvant therapy if administered between breast cancer surgery date and up to 6 months after. Chemotherapy followed by hormonal therapy without a 120-day gap in therapy was considered sequential adjuvant therapy. If a gap in therapy of at least 120 days occurs, then this would indicate the end of adjuvant therapy to avoid capturing treatment for metastatic or recurrent disease.

2.4. Statistical Analysis

Baseline characteristics of the study population were described using frequencies and percentages. The Chi-square test for categorical variables and ANOVA or t-test for continuous variables were used to test for differences between groups (treated versus untreated). A p-value of <0.05 was considered statistically significant. Multivariable logistic regression modeling examined the effect of demographic and clinical factors on the odds of receiving neoadjuvant/adjuvant therapy.

All cause overall survival (OS) was measured from date of breast cancer sur-

gery to date of death. Death date was captured through 2013 using Medicare enrollment files. If the Medicare date of death was missing, then the SEER date of death was used. Patients were censored at the end of the follow-up period (December 31, 2013) or until Medicare claims were no longer available. Crude survival was estimated using Kaplan-Meier survival curves and the log-rank test was applied to compare neoadjuvant/adjuvant treated patients with untreated patients. A time-varying Cox proportional hazards regression model was built to estimate the relative risk of mortality between neoadjuvant/adjuvant treated patients and untreated patients. In the model, neoadjuvant/adjuvant therapy was used as a time-dependent factor to account for variation in treatment initiation between patients and to minimize the introduction of immortal time bias into the analysis (period of follow-up time during which death cannot occur) [21]. To determine the extent to which age plays a role in treatment receipt and prognosis, we conducted a subgroup survival analysis among 8967 patients who had more favorable clinical characteristics (stage I disease, tumor size < 2.0 cm and tumor grade 1/2) to compare neoadjuvant/adjuvant treated with untreated patients.

3. Results

3.1. Treatment Patterns

There were 13,670 (74%) patients who received adjuvant/neoadjuvant treatment with hormonal and/or chemotherapy (Treated) and 4800 (26%) patients who did not (Not Treated). Receipt of adjuvant/neoadjuvant therapy (Treated) increased over the study time-period from 72% in 2007 to 77% in 2011 ($p < 0.0001$). Of the treated patients, 11016 (81%) received hormonal therapy only, 1981 (15%) received chemotherapy only and lastly, 673 (5%) received sequential therapy with chemotherapy followed by hormonal therapy. Overall, only 16% of the study population had a RS assay and the rates of testing increased over the study time-period from 6% in 2007 to 24% in 2011 ($p = 0.0002$). In regards to treatment rates in association with RS assays; the rates of sequential chemotherapy followed by hormonal therapy decreased from 6% in 2007 to 5% in 2011, the use of hormonal therapy increased from 60% in 2007 to 73% in 2011, and chemotherapy only remained consistent at 11% throughout the time period ($p = 0.0017$; data not shown).

3.2. Patient Characteristics

Table 1 shows the distribution of patient characteristics by treatment group. The mean age at diagnosis was 75.6 years and approximately 1% of the cohort were men (n = 170). Compared to treated patients, untreated patients were older, with about 60% over the age of 75. Untreated patients were also more likely to be widowed (41.1% vs. 33.3%) compared to treated patients. In regards to clinical characteristics, a greater proportion of untreated patients were diagnosed with stage I disease (70.3% vs. 56.2%), grade 1 tumors (35.0% vs. 29.1%) and 71.5%

vs. 62.8% had small tumor size of <2.0 cm compared to treated patients. Untreated patients were also less likely to have received radiotherapy, had poorer performance, a higher comorbidity burden, and were less likely to have genomic testing for risk of recurrence ($p < 0.0001$).

In the adjusted logistic regression model (Table 2), increasing age, being unmarried and having indicators of poor performance decreased the odds of receiving neoadjuvant/adjuvant therapy; while male gender, later stage, higher tumor grade, radiotherapy and genomic testing increased the odds of receiving neoadjuvant/adjuvant therapy.

Table 1. Baseline demographic and clinical characteristics by treatment status.

Characteristics	Total N = 18,470		Treated N = 13,670		Not Treated N = 4800		*p*-value
	n	%	n	%	n	%	
Age at Diagnosis							
66 - 70	5423	29.4	4466	32.7	957	19.9	<0.0001
71 - 75	4619	25.0	3676	26.9	943	19.6	
76 - 80	3871	21.0	2810	20.6	1061	22.1	
>80	4557	24.7	2718	19.9	1839	38.3	
Mean Age (95% CI)	75.55	75.4 - 75.6	74.67	74.6 - 74.8	78.03	77.8 - 78.2	<0.0001
Sex							
Male	170	0.9	140	1.0	30	0.6	0.0127
Female	18,300	99.1	13,530	99.0	4770	99.4	
Race/ethnicity							
White	15,945	86.3	11,742	85.9	4203	87.6	0.0006
Black	1269	6.9	941	6.9	328	6.8	
Other/Unknown	1256	6.8	987	7.2	269	5.6	
Marital Status							
Single	1648	8.9	1204	8.8	444	9.3	<0.0001
Married	7525	40.7	5857	42.8	1668	34.8	
Separated/Divorced	2001	10.8	1483	10.8	518	10.8	
Widowed	6525	35.3	4553	33.3	1972	41.1	
Unknown	771	4.2	573	4.2	198	4.1	
% of adults with some college education							
0 - 50	5376	29.1	4123	30.2	1253	26.1	<0.0001
51 - 100	12,751	69.0	9306	68.1	3445	71.8	
Unknown	343	1.9	241	1.8	102	2.1	
Median Income Quartiles							
1-Low	4532	24.5	3449	25.2	1083	22.6	0.0013
2	4532	24.5	3294	24.1	1238	25.8	
3	4529	24.5	3321	24.3	1208	25.2	
4-High	4531	24.5	3364	24.6	1167	24.3	

Continued

Unknown	346	1.9	242	1.8	104	2.2	
Geographic region							
Midwest	1467	7.9	1047	7.7	420	8.8	0.0003
Northeast	1042	5.6	815	6.0	227	4.7	
South	7076	38.3	5289	38.7	1787	37.2	
West	8885	48.1	6519	47.7	2366	49.3	
Stage at Diagnosis							
Stage I	11,061	59.9	7687	56.2	3374	70.3	<0.0001
Stage II	5908	32.0	4699	34.4	1209	25.2	
Stage III	1501	8.1	1284	9.4	217	4.5	
Histology							
Ductal	13,017	70.5	9673	70.8	3344	69.7	<0.0001
Lobular	2242	12.1	1737	12.7	505	10.5	
Mixed	2036	11.0	1498	11.0	538	11.2	
Others	1175	6.4	762	5.6	413	8.6	
Tumor Grade							
Grade 1	5659	30.6	3977	29.1	1682	35.0	<0.0001
Grade 2	8990	48.7	6740	49.3	2250	46.9	
Grade 3/4	3083	16.7	2432	17.8	651	13.6	
Unknown	738	4.0	521	3.8	217	4.5	
Tumor Size							
<2.0 cm	12,010	65.0	8580	62.8	3430	71.5	<0.0001
2.0 - 4.9 cm	5499	29.8	4319	31.6	1180	24.6	
≥5.0 cm	919	5.0	739	5.4	190[a]	4.0	
Unknown	42	0.2	32	0.2			
Poor Performance Indictors							
No	16,350	88.5	12,291	89.9	4059	84.6	<0.0001
Yes	2120	11.5	1379	10.1	741	15.4	
NCI Comorbidity Score							
0	10,481	56.7	7876	57.6	2605	54.3	<0.0001
1	4661	25.2	3444	25.2	1217	25.4	
2	1868	10.1	1352	9.9	516	10.8	
≥3	1460	7.9	998	7.3	462	9.6	
RS Assay							
No	15,460	83.7	11,066	81.0	4394	91.5	<0.0001
Yes	3010	16.3	2604	19.0	406	8.5	
Radiation within 1 year of diagnosis							
No	7785	42.1	5301	38.8	2484	51.8	<0.0001
Yes	10,685	57.9	8369	61.2	2316	48.3	

[a]Cells with counts of less than 11 are combined in compliance with the National Cancer Institute data use agreement for small cell sizes.

Table 2. Logistic regression model of factors associated with the odds of not receiving neoadjuvant/adjuvant treatment.

Characteristic	All Patients[a] N = 18,470			
	N	OR	95% CI	*p* value
Age at Diagnosis				
66 - 70 (ref)	5423			
71 - 75	4619	1.14	1.028 - 1.262	<0.0001
76 - 80	3871	1.58	1.426 - 1.758	0.0232
>80	4557	2.61	2.353 - 2.897	<0.0001
Sex				
Female (ref)	18,300			
Male	170	0.61	0.403 - 0.922	0.0190
Race/ethnicity				
White (ref)	15,945			
Black	1269	1.08	0.936 - 1.25	0.0021
Others	1256	0.71	0.615 - 0.828	<0.0001
Marital Status				
Married (ref)	7525			
Separated/Divorced	2001	1.18	1.05 - 1.334	0.0913
Single	1648	1.20	1.062 - 1.374	0.0476
Widowed	6525	1.09	1.001 - 1.186	0.9867
Unknown	771	0.99	0.826 - 1.185	0.1753
Stage at Diagnosis				
Stage I (ref)	11,061			
Stage II	5908	0.51	0.450 - 0.572	0.1233
Stage III	1501	0.31	0.253 - 0.376	<0.0001
Grade				
Grade 1 (ref)	5659			
Grade 2	8990	0.91	0.841 - 0.985	0.2243
Grade 3/4	3083	0.80	0.714 - 0.897	0.0001
Unknown	738	1.10	0.919 - 1.317	0.0241
Tumor Size				
<2.0 cm	12,010			
2.0 - 4.9 cm	5499	1.06	0.935 - 1.197	0.0674
≥5.0 cm	919	1.21	0.968 - 1.503	0.6109
Unknown	42	2.10	0.984 - 4.501	0.0840
Poor Performance Indicators				

Continued

No (ref)	16,350			
Yes	2120	1.34	1.195 - 1.492	<0.0001
NCI Comorbidity Score				
0 (ref)	10,481			
1	4661	0.98	0.900 - 1.065	0.1715
2	1868	1.00	0.885 - 1.125	0.5390
≥3	1460	1.13	0.989 - 1.296	0.0463
RS Assay				
No (ref)	15,460			
Yes	3010	0.53	0.45 - 0.66	<0.0001
Radiotherapy				
No (ref)	7785			
Yes	10,685	0.70	0.648 - 0.751	<0.0001

[a] Model also includes geographic region, education, income, year of diagnosis, and histology.

In a subgroup analysis comparing treated patients who received hormonal therapy, chemotherapy-only, and sequential therapy (chemotherapy followed by hormonal therapy); patients who received hormonal therapy were more likely to be older than 75 (46% vs. 21% and 22%; $p < 0.0001$), more likely widowed (35% vs. 26% and 27%; $p < 0.0001$), have stage I disease (64% vs. 23% and 26%; $p < 0.0001$), tumor grade I (32%, 16% and 16%; $p < 0.0001$), tumor size < 2.0 cm (68% vs. 40% and 41%; $p < 0.0001$), poorer performance (11% vs. 6% and 7%; $p < 0.0001$), and NCI comorbidity score ≥ 2 (18% vs. 14% and 16%; $p = 0.0010$) compared to patients who received chemotherapy-only and sequential therapy respectively (data not shown). Patients who received chemotherapy-only were more likely to have had radiotherapy (73% vs. 59% and 57%; $p < 0.0001$) compared to patients who received hormonal therapy and sequential therapy.

3.3. Survival Outcomes

The mean and median follow-up time for the overall cohort was 48.3 months (95% CI: 48.1 - 48.6) and 47.6 months (95% CI: 32.9 - 64.1) respectively. The median overall survival time was not reached in the analysis and the mean unadjusted OS from all cause of death was 65.4 months (95% CI: 65.1 - 65.6) for the overall population. As shown in **Figure 2**, the mean unadjusted OS was longer for treated patients (66.6 months; 95% CI: 66.3 - 66.8) compared to untreated patients (61.5 months; 95% CI: 61.0- 62.1; log rank $p < 0.0001$). The mean unadjusted OS was similar for patients treated with hormonal therapy (65.0 months; 95% CI: 64.7 - 65.3) and chemotherapy only (65.3 months; 95% CI: 64.6 - 66.1) and slightly shorter for sequential therapy (60.3 months; 95% CI: 59.1 - 61.5), log rank $p = 0.3274$.

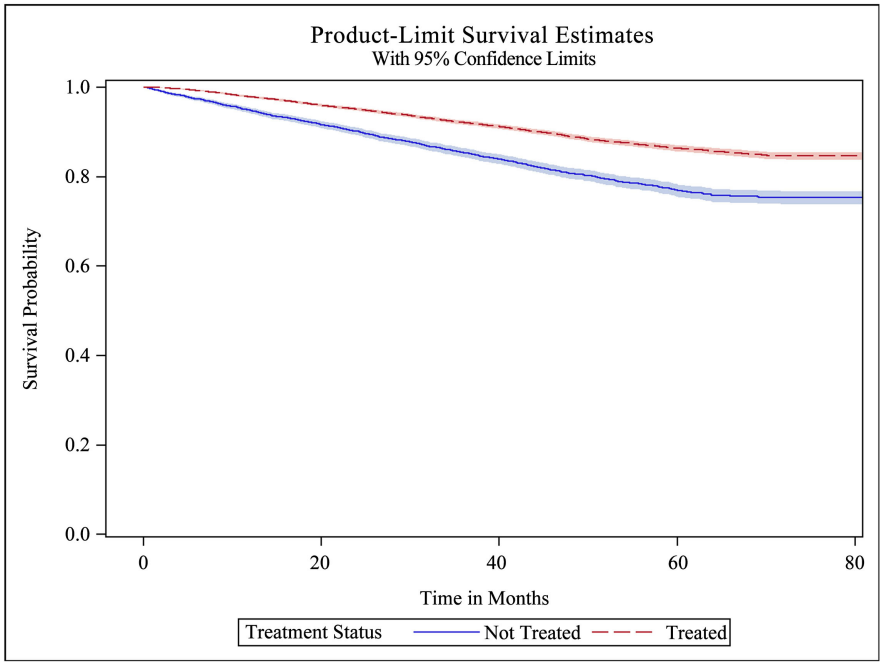

Figure 2. Unadjusted Kaplan-Meier curve of overall survival by treatment status.

Adjusting for demographic and clinical characteristics in **Table 3**, untreated patients exhibited a 48% higher risk of death compared to treated patients. Increasing age, male gender, being widowed, poor performance, increasing stage, increasing tumor size, increasing tumor grade, and increasing comorbidity score were significantly associated with higher mortality risks. Receipt of genomic testing was associated with a 45% reduction in mortality risk. Prior radiotherapy was associated with a 41% reduction in mortality risk, and black African ancestry was associated with a 16% reduction in mortality risk compared to whites, after adjusting for all other variables in the model. In a subset of 8967 patients with stage I disease, tumor size < 2.0 cm and tumor grade 1 or grade 2; untreated patients had a 22% higher risk of death compared to treated patients. In the subset of treated patients, those receiving sequential chemotherapy plus hormonal therapy exhibited a 26% (HR = 1.26; 95% CI: 1.01 - 1.58) higher risk of death compared to hormonal therapy alone, and there was no mortality risk difference with chemotherapy-only (HR = 1.10; 95% CI: 0.94 - 1.30) compared to hormonal therapy, after adjusting for demographic and clinical characteristics (data not shown).

4. Discussion

We evaluated the predictors of neoadjuvant/adjuvant therapy receipt and survival among Medicare beneficiaries diagnosed with HR + HER2-breast cancer and found that older patients with more favorable disease characteristics (earlier stage, smaller tumor size, lower tumor grade) were less likely to receive neoadjuvant/adjuvant therapy and had a higher risk of death compared to neoadjuvant/adjuvant treated patients, controlling for other competing causes of mortal-

ity such as age, co-morbidity burden, and poor performance. Our multivariate survival model also demonstrated that after adjusting for tumor characteristics and neoadjuvant/adjuvant treatment, increasing co-morbidity score was associated with increasing mortality risk, similar to a recent study [22]. The logistic regression model demonstrated that increasing age was associated with lower likelihood of therapy independent of performance status, co-morbidities and tumor characteristics, suggesting that physicians may be under-treating otherwise healthy older patients. Older patients represent a heterogeneous population in terms of fitness, and chronological age alone should not contraindicate life-prolonging or curative treatment.

Table 3. Time-varying Cox model of overall mortality risk in the total population and the stage/size/grade subpopulation.

	All Patients[a] N = 18,470			Stage/Size/Grade Subset[a, b] N = 8967		
Characteristic	**N**	**HR**	**95% CI**	**N**	**HR**	**95% CI**
Subpopulation						
Treated (ref)	13,670			6175		
Not Treated	4800	1.476	1.35 - 1.61	2792	1.217	1.05 - 1.41
Age at Diagnosis						
66 - 70 (ref)	5423			2747		
71 - 75	4619	1.189	1.03 - 1.38	2374	1.348	1.04 - 1.75
76 - 80	3871	1.615	1.40 - 1.86	1890	1.691	1.31 - 2.18
>80	4557	2.720	2.39 - 3.10	1956	3.111	2.45 - 3.95
Sex						
Female (ref)	18,300			8926		
Male	170	1.507	1.11 - 2.05	41	2.928	1.55 - 5.54
Race/ethnicity						
White (ref)	15,945			7911		
Black	1269	0.843	0.73 - 0.98	450	0.872	0.63 - 1.20
Others	1256	0.776	0.65 - 0.93	606	0.713	0.51 - 0.99
Marital Status						
Married (ref)	7525			3973		
Separated/Divorced	2001	1.067	0.91 - 1.25	978	0.943	0.71 - 1.24
Single	1648	1.129	0.97 - 1.32	718	1.027	0.76 - 1.38
Widowed	6525	1.203	1.09 - 1.33	2928	1.244	1.05 - 1.48
Unknown	771	1.123	0.91 - 1.39	370	0.740	0.46 - 1.19
Stage at Diagnosis						
Stage I (ref)	11,061					
Stage II	5908	1.241	1.08 - 1.42			

Continued

Stage III	1501	2.389	2.02 - 2.83			
Histology						
Grade						
Grade 1 (ref)	5659					
Grade 2	8990	1.124	1.01 - 1.25			
Grade 3/4	3083	1.533	1.36 - 1.73			
Unknown	738	1.282	1.05 - 1.57			
Tumor Size						
<2.0 cm	12,010					
2.0 - 4.9 cm	5499	1.318	1.15 - 1.51			
≥5.0 cm	919	1.588	1.32 - 1.91			
Unknown	42	2.772	1.67 - 4.60			
Poor Performance Indicators						
No (ref)	16,350			8217		
Yes	2120	1.735	1.57 - 1.92	750	2.026	1.69 - 2.43
NCI Comorbidity Score						
0 (ref)	10,481			5366		
1	4661	1.349	1.22 - 1.49	2260	1.708	1.43 - 2.04
2	1868	1.790	1.58 - 2.02	802	2.264	1.81 - 2.83
≥3	1460	2.489	2.20 - 2.81	539	3.483	2.78 - 4.36
RS Assay						
No (ref)	15,460			7607		
Yes	3010	0.546	0.45 - 0.66	1360	0.745	0.55 - 1.01
Radiotherapy						
No (ref)	7785			3385		
Yes	10,685	0.591	0.54 - 0.65	5582	0.578	0.49 - 0.67

[a] Model also includes geographic region, education, income, year of diagnosis, and histology, [b] Subset of patients with stage I disease, tumor size < 2.0 cm and grade 1/2.

The primary element of curative therapy for early-stage breast cancer is surgery. The International Society of Geriatric Oncology (SIOG) panel recommends radiation therapy and adjuvant systemic treatment after breast-conserving surgery in all older patients with breast cancer [23]. The decision to use adjuvant chemotherapy should not be based on age, but on several factors that include comorbidities, functional status, life expectancy, treatment tolerance, patient preference and risk for local recurrence [24] [25]. Although adjuvant systemic therapy has clear benefits in patients with HR+ early breast cancer [26], the treatment rate in our older aged cohort was low. Prior studies show that patients

over the age of 80 are only half as likely as younger patients to have a discussion about tamoxifen with their physicians due to physician concerns about side effects and treatment adherence [27] [28].

Overall, only 16% of our study population had genomic testing and this was associated with a higher likelihood of receiving neoadjuvant/adjuvant therapy as well as a 45% reduction in mortality risk compared to patients who did not have the test. A recent meta-analysis of 15 studies that investigated the impact of RS assays on adjuvant treatment decisions, reported that the additional information provided by the test changed the recommendation for adjuvant treatment in 30% of cases with the majority being a de-escalation of chemoendocrine therapy to adjuvant endocrine therapy alone [29]. In our study, we found that the rates of sequential therapy with chemotherapy followed by hormonal therapy decreased, while the use of hormonal therapy increased in association with the RS assay. Other trials showed that the benefit of adding chemotherapy to tamoxifen was mainly seen in patients with a high RS and no significant benefit from the addition of chemotherapy was noted in the low and intermediate RS risk groups [11] [30]. However, given the nature of administrative claims data, we were unable to determine results of RS assays and RS score risk groups. In addition, RS assays are usually ordered for patients who are candidates for chemotherapy use. It's possible that the higher mortality risk observed in the non-RS assay group was due to poorer fitness and tolerability concerns that also precluded them from chemotherapy use and RS assay testing. A recent sub analysis from the MINDACT study demonstrated that 24% of patients with node negative small tumors (<1 cm) who were identified as clinical low risk, but genomic high risk, derived a benefit from chemotherapy [31]. While another study found that patients with indolent threshold (ultralow-risk) on the 70-gene assay genomic test have a significantly low risk of mortality after surgery without adjuvant systemic treatment [32]. This adds further support that tumor biology is an important factor when considering adjuvant treatments.

Interestingly, our finding that patients of black African ancestry have lower mortality risk compared to white patients is discordant with prior research. African American women have lower incidence of breast cancer but worse survival when compared to white women [33] [34] [35]. Many have postulated that the survival disparity is related to access to healthcare, treatment differences or socioeconomic factors [36] [37] [38] and race alone is seen as an independent predictor of survival [39]. However, a more recent SEER-Medicare analysis confirmed that after matching patients on treatment as well as demographics, comorbidities, and tumor characteristics at presentation, there was very little difference in survival between black and white women [40].

Receipt of treatment and survival varied by marital status, similar to patterns observed in prior oncology research [41] [42]. In the current study unmarried status, especially widowhood were predictive of not receiving neoadjuvant/adjuvant treatment and was associated with a higher risk of mortality. Male

patients made up about 1% of our study population [2] and were more likely to receive neoadjuvant/adjuvant therapy, but had a higher mortality risk compared to females. Breast cancer in males was long thought to have a less favorable outcome than in females [43] [44]. However, others have found little gender difference in survival when matched for age, stage and grade [3] [45] [46]. Further research is warranted to better understand the disparity of nonclinical factors on receipt of cancer therapy to ensure appropriate cancer care and improve outcomes for all patients.

5. Strengths & Limitations

A major strength of this study is that it is a large population-based sample that allows longitudinal evaluation of outcomes that may not be possible in clinical trials. Further, cancer occurs disproportionately in older patients and the dataset is a valuable tool to study patients who have been historically underrepresented in clinical trials. However, it is important to acknowledge the limitations of this retrospective, observational study using administrative claims data. The first limitation relates to missing data for HER2 status prior to the year 2010. Medicare does not pay for targeted therapy without a positive HER2 test result so we used the presence of claims for HER2 targeted therapy as a proxy for HER2+ status and the absence of these claims to indicate HER2-status. The magnitude and direction of the potential bias introduced by the missing data are unknown as patients who tested HER2+ and did not receive targeted therapy could have been misclassified into the HER2-group. It is possible that because untreated HER2+ cancers pose a higher morality risk, this potential misclassification would bias the results by increasing apparent mortality in the untreated group.

The second limitation involves an imputation method for performance status since the database does not include a direct measure for ECOG performance status. We identified diagnostic and procedure codes for specific healthcare resource use that have been shown to be predictive of functional status. Although this surrogate for poor performance may not adequately assess functional status for all patients in our study, it improves the validity of this observational study by attempting to control for such an important confounding variable.

Third, Medicare claims data are created for payment purposes and although we are able to detect who received the RS assay, we do not know the results of the test or patients RS risk groups. The decision to forgo therapy in the older individual often involves many factors such as patient and family preferences, and/or physician concerns for poor tolerance of therapy due to comorbidity and declining organ function [47]; and the SEER-Medicare database does not take into account these physician and patient preferences with regard to treatment. Similarly, patients in the oral hormonal therapy group may be susceptible to misclassification bias as the data derived from administrative claims provide information on medications that were filled, but does not reflect actual medication exposure. To minimize the impact of these potentially misclassified individuals

in the oral hormonal therapy group, we required evidence of at least two prescriptions and no gaps of at least 120 days between prescriptions to increase the likelihood that patients are actually taking the medicine.

Fourth, the use of overall survival as an endpoint should be interpreted with caution. Although overall survival is the most reliable and available survival measure, it may not be specific enough to provide information on survival related to breast cancer treatment. Therefore, it's not clear if the higher survival we observed among treated patients is due to fewer deaths from other competing causes or fewer deaths from breast cancer treatment. Finally, the data presented here are limited to Medicare enrollees and patients enrolled in HMO represent a gap in the SEER-Medicare database. HMO enrollees tend to be younger and healthier than beneficiaries in fee-for-service plans resulting in a biased loss of information using the Medicare claims data [16].

6. Conclusion

Older patients with HR + HER2-resected breast cancer who have favorable disease characteristics (earlier stage, smaller tumor size and lower tumor grade) were less likely to receive adjuvant/neoadjuvant therapy with hormonal and/or chemotherapy. Untreated patients with favorable disease characteristics had a significantly higher risk of death compared to treated patients, after controlling for comorbidities, poor performance and other patient characteristics. Additional research is needed to determine why adjuvant/neoadjuvant therapies are omitted among the older "fit" breast cancer patient population.

Author Contributions

Study Concepts: SS-H, CR;
Study Design: SS-H, AS, PC, FM, CR;
Data Acquisition: SS-H, CR;
Quality Control of Data and Algorithms: SS-H, FM;
Data Analysis and Interpretation: SS-H, AS, PC, FM, CR;
Statistical Analysis: SS-H, FM;
Manuscript Preparation: SS-H;
Manuscript Editing: SS-H, AS, PC, FM, CR;
Manuscript Review: SS-H, AS, PC, FM, CR.

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lance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

Conflicts of Interest

AS, PC and CR are employees of Genentech and shareholders of Roche. SSH and FM work for Q.D. Research in a research and consulting capacity.

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