Population-based recurrence rates among older women with HR-positive, HER2-negative early breast cancer: Clinical risk factors, frailty status, and differences by race

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ABSTRACT

Background: Multiple independent risk factors are associated with the prognosis of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer (BC), the most common BC subtype. This study describes U.S. population-based recurrence rates among older, resected women with HR+/HER2- early BC.

Methods: We conducted a retrospective cohort study of older women diagnosed with incident, invasive stages I–III HR+/HER2- BC who underwent surgery to remove the primary tumor using the Surveillance, Epidemiology, and End Results (SEER)-Medicare Linked Database (2007–2015). SEER records and administrative health claims data were used to ascertain patient and tumor-specific characteristics, treatment, and frailty status. Cumulative incidences of BC recurrence were estimated using a validated algorithm for administrative claims data. Multivariable Fine-Gray competing risk models estimated adjusted subdistribution hazards ratios and 95 % confidence intervals for associations with BC recurrence risk.

Results: Overall, 46,027 women age ≥65 years were included in our analysis. Over a median follow up of 7 years, 6531 women experienced BC recurrence with an estimated 3 and 5-year cumulative incidence rates of 10 % and 16 %, respectively. Higher 3- and 5-year cumulative incidences were observed in women with larger tumor size (5+ cm, 21 % and 28 %), lymph node involvement (4+ nodes, 27 % and 37 %), and with frail health status at diagnosis (13 % and 20 %). Independent of these clinical risk factors, Black, Hispanic and American Indian/Alaskan Native women had significantly increased BC recurrence risks.

Conclusions: Rates of recurrence in HR+/HER2- early BC differs by several patient and clinical factors, including high-risk tumor characteristics. Racial differences in BC outcomes deserve continued attention from clinicians and policymakers.

1. Introduction

An estimated 3.8 million women living in the United States (U.S.) have a history of breast cancer (BC), of which a majority are over 65 years of age [1]. Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) BC is the most common BC subtype, and are mostly diagnosed at local (64 %) or regional (27 %) stages of disease [2]. Despite highly effective BC

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treatments and favorable five-year relative survival of >90 % for HR+/HER2-disease, these women remain at risk for BC recurrence [3]. Recurrence risks in HR+/HER2- BC vary according to health status and clinical subgroups; however, more detailed evidence on current population-based recurrence rates among older women with BC is needed, including recurrence risks associated with frailty [4,5],

Several studies have estimated recurrence rates in this population of BC survivors. In a meta-analysis of 10,801 women from randomized trials, 5- and 10-year recurrence rates were 12.6 % and 19.3 %, respectively, in BC patients treated with breast-conserving surgery and adjuvant radiotherapy [6]. Larger real-world, US population-based longitudinal studies examining BC recurrence among women with stages I-II BC report cumulative incidence rates between 10 % and 20 %, depending on clinical characteristics, health conditions, and rates of surveillance mammography [7–11]. While these and other studies based on trial data characterize BC recurrence rates and clinical factors with worse prognosis, real-world data with information from specific age groups and health conditions among older women remains sparse, even for the most common BC subtype (i.e., HR+/HER2-).

Describing population-based BC recurrence rates is particularly salient for guiding treatment decisions among older women, who often have comorbid conditions that affect how treatment may be tolerated and prognosis [12]. This study sought to: (i) describe and characterize BC recurrence rates among older women in the U.S. with HR+/HER2-early BC undergoing potentially curative surgery; (ii) provide annualized BC recurrence rates across multiple clinical subgroups, risk factors, and health status (i.e., frailty) among older women; and (iii) estimate excess risks for adverse BC outcomes in relation to the above-mentioned characteristics after accounting for treatment patterns.

2. Material and methods

2.1. Data sources

This was a population-based, retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) Medicare Linked Database, from 18 reporting regions, accounting for 28 % of the U.S. population. Data from SEER records were linked to Medicare enrollment records and Medicare administrative claims data from inpatient, outpatient, and pharmacy services [13]. This study was approved by the institutional review board of the University of Illinois at Chicago.

2.2. Study population

Women diagnosed with first primary stages I-III HR+/HER2- BC between January 1, 2007 and September 30, 2014 were identified. Women who were not continuously enrolled in both Medicare Part A and B plans for at least 12 months before and after cancer diagnosis and who received HER2-targeted therapies including trastuzumab, ado-trastuzumab, emtansine and/or pertuzumab were excluded. Analyses were restricted to female patients who received cancer-directed surgery to enhance specificity of case identification processes in building the analytical cohort (Fig. 1).

2.3. Outcomes

The primary outcome of interest was the occurrence of a first BC recurrence event. A validated algorithm was adapted specifically for use with SEER-Medicare using detailed diagnosis and procedure codes to identify BC recurrence; the validation processes reported elsewhere [14,15]. Assessment of BC recurrence (at-risk time)

started following a delayed entry [16] at 365 days post-cancer diagnosis to mitigate misclassification and enhance specificity (sensitivity and specificity of 69 % and 99 %, respectively) [17,18].

2.4. Covariates

Information on age at diagnosis, race/ethnicity, American Joint Committee on Cancer (AJCC) stage, tumor size, lymph node involvement, surgery, receipt of neoadjuvant or adjuvant radiotherapy chemotherapy, and endocrine therapy and were identified from SEER registry records. Pre-existing comorbidities were defined by the presence of relevant diagnosis or procedure codes in the Medicare inpatient and outpatient claims and summarized using National Cancer Institute (NCI) Charlson Comorbidity Index (CCI) [19]. Chemotherapy class exposures over the year following cancer diagnosis (treatment period) were identified defined as at least two administrations of the same agent on different dates during the 365-day period following cancer diagnosis. Treatment with chemotherapy was also categorized as neoadjuvant if administered prior to the cancer-directed surgery date and adjuvant if administered after surgery and within the 12 months post-diagnosis. Use of adjuvant endocrine therapy was defined according to Medicare Part D pharmacy dispensing data for aromatase inhibitors or tamoxifen post-BC diagnosis.

2.5. Subgroups

Analyses were conducted for pre-specified subgroups based on clinically meaningful treatment characteristics including age, race/ethnicity, frailty status, AJCC stage, nodal status, tumor size, neoadjuvant treatment, and high-risk groups based on combinations of clinicopathologic characteristics [20]. Frailty status was determined using a claims-validated algorithm based on pre-cancer Medicare administrative health claims [21] and categorized women according to previously defined cutpoints associated with mortality as robust, pre-frail or frail at the time of BC diagnosis [22–24]. High-risk groupings were identified using modified clinical-pathologic scoring system incorporating estrogen receptor-negative disease and nuclear grade 3 tumor pathology (CPS + EG) scores calculated from information available for clinical or pathological stage, estrogen receptor status, and tumor grade (see appendix).

2.6. Statistical analysis

In time-to-event analyses, cumulative incidence functions were estimated for the outcome of recurrence [25]. Equality of cumulative incidence functions in the presence of competing risks was compared using Gray's test [26].

Associations between recurrence of BC and patient and tumor characteristics were evaluated using Fine and Gray competing risk regression models, accounting for death without recurrence as a competing event [27]. Subdistribution hazard ratios (SHR) and 95 % confidence intervals (CI) were estimated for covariates including age at BC diagnosis (65–69, 70–74, 75–79, 80+), race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, non-Hispanic Asian/Pacific Islander, non-Hispanic American Indian/Alaskan Native, other/unknown), AJCC stage (I, IIA, IIB, IIIA, IIIB, IIIC), lymph node status (negative, positive, 1–3, 4+ nodes, unknown), tumor size, (<2, 2–5, >5 cm), and frailty index at diagnosis (robust [≤ 0.2], pre-frail [0.2 to 0.35], frail [≥ 0.35]) in the same model with further adjustment for year of diagnosis (categorical), type of surgery (breast-conserving, mastectomy), receipt of radiotherapy (yes/no), treatment with neoadjuvant chemotherapy, (yes/no) and treatment with adjuvant chemotherapy (yes/no). All statistical tests were two-sided, and all analyses were performed using SAS (version 9.4,
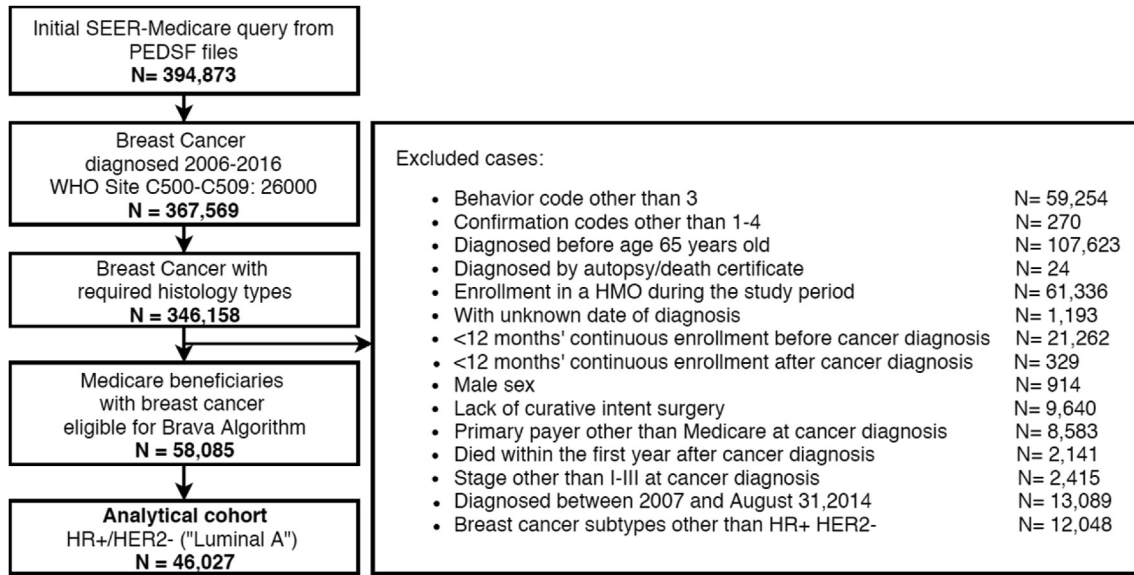
Fig. 1. CONSORT diagram for study cohort selection.

Cary, NC). P values less than 0.05 were considered statistically significant.

3. Results

A total of 46,027 women aged 65 years and older diagnosed with stages I-III HR+/HER2- BC between 2007 and 2015 were identified (Table 1). Over a median follow up of 7.0 years, 6531 women experienced a BC recurrence and 1918 women died during the study period without recurrence. The median age at BC diagnosis in the overall cohort was 74 years and the majority of women were non-Hispanic white (85 %), diagnosed at AJCC stage I (62 %), node-negative (69 %), had tumor size <2 cm (67 %), had modified CPS + EG scores of 0 or 1 (88 %) and were classified as robust at BC diagnosis (56 %). Multiple comorbidities were highly prevalent at the time of BC diagnosis; 39 % of women had NCI−CCI scores of 6 or greater. Compared to women who did not experience a BC recurrence during follow up, women who had a BC recurrence were similar with respect to age but were more likely to have been diagnosed with AJCC stage III BC (16 % vs. 6 %), have higher nodal involvement (4+: 13 % vs. 4 %), tumor size >5 cm (8 % vs. 4 %), modified CPS + EG scores of ≥2 (19 % vs. 9 %) and be pre-frail or frail at diagnosis (47 % vs. 43 %).

Women who experienced a BC recurrence had similar mastectomy rates compared to women who did not (20 % each) but were more likely to have received radiotherapy (57 % vs. 51 %) and been treated with neoadjuvant or adjuvant chemotherapy (13 % vs. 8 %) (Table 2). The proportion of women initiating adjuvant endocrine therapy within the first-year post-diagnosis was similar between those that did and did not experience a BC recurrence during follow up (61 % and 60 %).

The 3-year and 5-year cumulative incidences of BC recurrence in the overall cohort were 10.2 % (95 % CI: 9.9–10.5) and 16.4 % (95 % CI: 16.0–16.8), respectively, with an overall cumulative incidence of BC recurrence of 24.0 % (95 % CI: 23.1–24.9) over a median follow up of 7 years (range: 1–9) (Table 3).

No differences were observed between the cumulative incidence functions by age group (Fig. 2A, P = 0.628), whereas differences in cumulative incidence functions across groups stratified by race/ethnicity, AJCC stage, lymph node status, tumor size and frailty

status were statistically significant (Fig. 2B–E, all p-values <0.001). Five-year cumulative incidence of BC recurrence was highest among Black (21.2 %, 95 % CI 19.4, 23.1), Hispanic (19.5 %, 95 % CI 17.4, 21.6) and American Indian/Alaskan Native women (25.6 %, 95 % CI 17.5, 34.4) compared to white (16.1 %, 95 % CI 15.7, 16.5), and Asian/Pacific Islander women (13.2 %, 95 % CI 11.4, 15.1) (Table 3). BC recurrence rates also differed substantially across tumor characteristics with 5-year cumulative incidence of 13.4 % (95 % CI 12.9, 13.8) among node-negative women and 37.3 % (95 % CI 35.1, 39.5) among women with 4+ nodes involved (Table 3); women with tumors sizes of <2 cm had a 5-year cumulative incidence of 13.9 % (95 % CI 13.4, 14.3) where as women with tumors >5 cm had a 5-year cumulative incidence of 28.1 % (95 % CI 25.8, 30.3). Women that were pre-frail (17.6 %, 95 % CI: 16.9−18.3) or frail (19.7 % 95 % CI 18.1, 21.4) at BC diagnosis had higher 5-year cumulative incidences of BC recurrence compared to women that were classified as robust patients (15.3 %, 95 % CI 14.7, 15.8). Similar trends in cumulative incidence rates among women that received neoadjuvant chemotherapy by age, stage, lymph node status and tumor size (Supplemental Table 1).

Adjusted estimates from multivariable Fine and Gray competing risk regression models found that women with 4+ nodes involved had a 2.6-fold (95 % CI: 2.15−3.10) higher recurrence risk compared to those with node negative BC whereas women with 1−3 nodes had 1.5-fold at greater risk (95 % CI: 1.36−1.64), after adjusting for year of diagnosis and therapy; tumor size >5 cm was associated with a 1.6-fold (95 % CI: 1.44−1.88) higher recurrence risk compared to tumors <2 cm (Fig. 3). Independent of other clinical characteristics and treatment differences, Black (SHR 1.27, 95 % CI 1.15−1.40) and American Indian/Alaskan Native women (SHR 1.85, 95 %: CI: 1.29−1.67) had a significantly increased BC recurrence risk compared to white women. Compared to women who were robust at diagnosis, women categorized as pre-frail (SHR 1.13, 95 % CI: 1.07−1.19) and frail (SHR 1.28, 95 % CI 1.15−1.42) had significantly higher BC recurrence risk. Results stratified by treatment and CPS + EG are reported in the supplemental material.

4. Discussion

This population-based study of older women with HR+/HER2-

Table 1

Descriptive characteristics of women diagnosed with HR-positive, HER2-negative early breast cancer in the Surveillance, Epidemiology and End Results Medicare Linked Database, 2007 to 2015.

	All women (N = 46,027)		No recurrence (n = 39,496)		Recurrence (n = 6531)	
	n	(%)	n	(%)	n	(%)
Age at diagnosis, years						
Mean (SD)	74.9	(6.8)	74.9	(6.8)	74.9	(6.7)
Median (IQR)	74	(69−80)	74	(69−80)	74	(69−80)
65-69	12,278	(26.7)	10,548	(26.7)	1730	(26.5)
70-74	12,582	(27.3)	10,800	(27.3)	1782	(27.3)
75-79	9529	(20.7)	8179	(20.7)	1350	(20.7)
80+	11,638	(25.3)	9969	(25.2)	1669	(25.6)
Race/ethnicity[a]						
Non-Hispanic white	38,951	(84.6)	33,498	(84.8)	5453	(83.5)
Non-Hispanic Black	2763	(6.0)	2267	(5.7)	496	(7.6)
Hispanic	2092	(4.5)	1757	(4.4)	335	(5.1)
Non-Hispanic Asian/Pacific Islander	1918	(4.2)	1707	(4.3)	211	(3.2)
Non-Hispanic American Indian/Alaskan Native	153	(0.3)	121	(0.3)	32	(0.5)
AJCC stage						
I	28,306	(61.5)	25,050	(63.4)	3256	(49.9)
II	14,239	(30.9)	11,977	(30.3)	2262	(34.6)
IIA	10,452	(22.7)	8927	(22.6)	1525	(23.4)
IIB	3787	(8.2)	3050	(7.7)	737	(11.3)
III	3482	(7.6)	2469	(6.3)	1013	(15.5)
IIIA	1933	(4.2)	1437	(3.6)	496	(7.6)
IIIB	662	(1.4)	−	−	−	−
IIIC	858	(1.9)	536	(1.4)	322	(4.9)
Stage III NOS	29	(0.1)	−	−	−	−
Lymph node status						
Negative	31,678	(68.8)	27,993	(70.9)	3685	(56.4)
Positive	9748	(21.2)	7631	(19.3)	2117	(32.4)
1-3	7156	(15.5)	5877	(14.9)	1279	(19.6)
4+	2592	(5.6)	1754	(4.4)	838	(12.8)
Unknown	4601	(10.0)	3872	(9.8)	729	(11.2)
Tumor size, cm						
<2	30,643	(66.6)	26,922	(68.2)	3721	(57.0)
2-5	13,193	(28.7)	10,914	(27.6)	2279	(34.9)
>5	2104	(4.6)	1601	(4.1)	503	(7.7)
Unknown	87	(0.2)	59	(0.1)	28	(0.4)
Frailty index						
Robust	25,837	(56.1)	22,378	(56.7)	3459	(53.0)
Pre-frail	16,914	(36.7)	14,357	(36.4)	2557	(39.2)
Frail	3276	(7.1)	2761	(7.0)	515	(7.9)
NCI−CCI score						
3	7326	(15.9)	6456	(16.3)	870	(13.3)
4	11,160	(24.2)	9584	(24.3)	1576	(24.1)
5	9790	(21.3)	8339	(21.1)	1451	(22.2)
6+	17,751	(38.6)	15,117	(38.3)	2634	(40.3)
Comorbidities at diagnosis						
Diabetes	15,904	(34.6)	13,508	(34.2)	2396	(36.7)
Hypertension	34,024	(73.9)	29,111	(73.7)	4913	(75.2)
Dyslipidemia	30,609	(66.5)	26,300	(66.6)	4309	(66.0)
COPD	9124	(19.8)	7702	(19.5)	1422	(21.8)
Chronic kidney disease	3634	(7.9)	3123	(7.9)	511	(7.8)
Coronary heart failure	3773	(8.2)	3139	(7.9)	634	(9.7)
Chronic liver disease	400	(0.9)	339	(0.9)	61	(0.9)
Stroke or transient ischemic attack	4882	(10.6)	4128	(10.5)	754	(11.5)
CPS + EG score						
0	25,815	(56.1)	22,903	(58.0)	2912	(44.6)
1	14,840	(32.2)	12,524	(31.7)	2316	(35.5)
2	4439	(9.6)	3371	(8.5)	1068	(16.4)
3+	449	(1.0)	286	(0.7)	163	(2.5)
Unknown	484	(1.1)	412	(1.0)	72	(1.1)

Abbreviations: AJCC, American Joint Committee on Cancer staging system; COPD, chronic obstructive pulmonary disease; CPS + EG, clinical-pathologic scoring system incorporating estrogen receptor-negative disease and nuclear grade 3 tumor pathology; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; NCI−CCI, National Cancer Institute-Charlson Comorbidity Index score; SD, standard deviation.

[a] A total of 150 (0.3 %) patients lack race/ethnic information.

early BC described the cumulative incidence of recurrence across multiple clinical subgroups—age, race/ethnicity, stage, tumor size, lymph node status, and frailty status at diagnosis. Although HR+/HER2- BC generally has favorable 5-year survival due to early detection and treatment advancements, we identified older women with high-risk features among whom BC recurrence rates were two-fold higher. Independent of other clinical risk factors and treatment differences, a diagnosis of node-positive BC with a primary tumor size >2 cm increases the recurrence risk for patients with HR+/HER2-early BC, especially for those with stage III disease, 4+ nodes, and a tumor size >5 cm. Frailty among older women was significantly associated with higher BC recurrence risk, and we

Table 2
Summary of primary breast cancer treatment with type of surgery, radiotherapy, chemotherapy and endocrine therapy for HR-positive, HER2-negative early breast cancer.

	All women (N = 46,027)		No recurrence (n = 39,496)		Recurrence (n = 6531)	
	n	(%)	N	(%)	N	(%)
Surgery						
Breast-conserving	37,053	(80.5)	31,802	(80.5)	5251	(80.4)
Mastectomy (including radical)	8974	(19.5)	7694	(19.5)	1280	(19.6)
Radiotherapy						
None	22,160	(48.1)	19,318	(48.9)	2842	(43.5)
Any	23,867	(51.9)	20,178	(51.1)	3689	(56.5)
Chemotherapy						
None	42,153	(91.6)	36,495	(92.4)	5658	(86.6)
Any	3874	(8.4)	3001	(7.6)	873	(13.4)
Cyclophosphamide	3598	(92.9)	2823	(94.1)	775	(88.8)
Anthracycline-including	1489	(38.4)	1117	(37.2)	372	(42.6)
Taxane-including	3283	(84.7)	2579	(85.9)	704	(80.6)
Platinum-including	121	(3.1)	72	(2.4)	49	(5.6)
Methotrexate	277	(7.2)	205	(6.8)	72	(8.2)
5-Fluorouracil	408	(10.5)	304	(10.1)	104	(11.9)
Neoadjuvant chemotherapy						
None	45,468	(98.8)	39,095	(99.0)	6373	(97.6)
Any	559	(1.2)	401	(1.0)	158	(2.4)
Cyclophosphamide	498	(89.1)	365	(91.0)	133	(84.2)
Anthracycline-including	333	(59.6)	250	(62.3)	83	(52.5)
Taxane-including	453	(81.0)	330	(82.3)	123	(77.8)
Completion of first course treatment[1]						
No	14,619	(31.8)	12,708	(32.2)	1911	(29.3)
Yes	31,408	(68.2)	26,788	(67.8)	4620	(70.7)
Endocrine therapy[2]						
None	18,250	(39.7)	15,716	(39.8)	2534	(38.8)
Any endocrine therapy	27,777	(60.3)	23,780	(60.2)	3997	(61.2)
Any aromatase inhibitors	24,948	(54.2)	21,296	(53.9)	3652	(55.9)
Anastrozole	18,484	(40.2)	15,914	(40.3)	2570	(39.4)
Exemestane	3512	(7.6)	2691	(6.8)	821	(12.6)
Letrozole	7827	(17.0)	6499	(16.5)	1328	(20.3)
Tamoxifen	6149	(13.4)	5153	(13.0)	996	(15.3)

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2.
1. Completion of first course treatment defined as mastectomy or breast-conserving surgery plus radiotherapy.
2. Use of individual endocrine therapy agents not mutually exclusive.

observed differences in recurrence rates by race/ethnicity, with higher rates among Black, Hispanic, and American Indian/Alaskan Native patients compared to their white counterparts with HR+/HER2- BC.

Detailed population-based estimates elucidating BC recurrence rates in the literature are limited, even for the most frequent subtype (i.e., HR+/HER2-early BC) and particularly among older women who are underrepresented in BC clinical trials. In a meta-analysis of randomized controlled trials conducted between 1990 and 2007 comparing mastectomy and breast-conserving surgery for stages I-II BC, 3-year locoregional recurrence rates were 1.9 % and 3.2 %, respectively; and 5-year locoregional recurrence rates were 7.1 % and 7.4 %, respectively. These recurrence rates differ from our estimated 3- and 5-year BC recurrence rates of 7.7 % and 13.2 %, respectively, for stage I and 11.5 % and 18.5 % for stage II, highlighting the importance of identifying population-based estimates outside of clinical trial settings. In a meta-analysis of 88 trials including 62,923 women with estrogen receptor-positive BC, the 5-year distant recurrence rates for women with node-negative disease, 1 to 3 nodes, and 4+ nodes involved were 6 %, 10 %, and 22 %, respectively [28], which was confirmed in a real world study from the United Kingdom [29]. In contrast, our corresponding estimates for BC recurrence at 5 years were 13 % in node-negative disease, 21 % in women with 1—3 nodes, and 37 % in women with 4+ nodes involved, which is similar to other studies using the SEER-Medicare Linked Database using our validated claims-based algorithm [17,18] although we identified all invasive recurrences versus distant recurrences only. Thus, despite lack of site-specific information of recurrence events, these detailed estimates of BC recurrence rates

fill a remaining gap in knowledge for HR+/HER2-disease in a more recent time period and in the context of contemporary BC treatment.

The prognostic significance of the tumor size and lymph node status in our multivariable analyses are similar to those of multiple other clinical trials and observational studies; although, other important biomarkers and indicators of recurrence risk are used in clinical practice. Studies from the transATAC (Anastrozole, Tamoxifen, Alone or in Combination) cohort have demonstrated the value of Oncotype DX recurrence score, the immunohistochemical score and the PAM50-based recurrence risk score in providing additional information for predicting BC recurrence beyond that of clinical variables in women with HR-positive BC [30—32]. Still, BC recurrence risk by clinical subgroups need to be described, given access to specific biomarkers or genetic expression profiles may not be routine. Our findings support the distinction in recurrence risks between older women and younger women with BC. Additionally, while radiation therapy often extends disease free survival, it has limited effect on overall mortality, and absolute clinical gain from radiotherapy should be weighed against the burden of treatment, especially for elderly and frail patients. A prospective cohort study of 3024 women aged 18—40 years in the United Kingdom (66 % ER + and 44 % HER -) found that local recurrence rates were between 3 % and 5 % at 5 years post-diagnosis [33].

Whereas an association between frail health status and BC specific- and all-cause mortality have been documented [5], this is the first study to report on an independent association between frailty in older women and BC recurrence risk. Comorbid conditions such as diabetes, more prevalent in older patients, may influence

Table 3
Cumulative incidence of breast cancer recurrence among women with HR-positive, HER2-negative early breast cancer.

Characteristic	2-year cumulative incidence		3-year cumulative incidence		4-year cumulative incidence		5-year cumulative incidence		Overall cumulative incidence	
	Rate	(95 % CI)	Rate	(95 % CI)	Rate	(95 % CI)	Rate	(95 % CI)	Rate	(95 % CI)
All women	6.6 %	(6.4, 6.9)	10.2 %	(9.9, 10.5)	13.4 %	(13.1,13.8)	16.4 %	(16.0, 16.8)	24.0 %	(23.1, 24.9)
Age, years										
66-69	6.9 %	(6.4, 7.4)	10.5 %	(9.9, 11.1)	13.6 %	(12.9, 14.3)	16.5 %	(15.7, 17.3)	24.4 %	(22.9, 26.0)
70-74	6.7 %	(6.2, 7.2)	10.1 %	(9.6, 10.7)	13.0 %	(12.3, 13.6)	16.2 %	(15.4, 17.0)	24.6 %	(22.4, 26.9)
75-79	6.2 %	(5.7, 6.7)	9.6 %	(9.0, 10.3)	13.5 %	(12.7, 14.2)	16.2 %	(15.3, 17.1)	23.3 %	(21.9, 24.9)
80+	6.6 %	(6.2, 7.1)	10.3 %	(9.7, 10.9)	13.7 %	(13.0, 14.4)	16.8 %	(16.0, 17.6)	23.1 %	(21.7, 24.5)
Race/ethnicity										
Non-Hispanic white	6.4 %	(6.2, 6.7)	9.9 %	(9.6, 10.2)	13.1 %	(12.7, 13.5)	16.1 %	(15.7, 16.5)	23.4 %	(22.4, 24.4)
Non-Hispanic Black	9.0 %	(8.0, 10.2)	13.5 %	(12.2, 14.9)	17.8 %	(16.2, 19.4)	21.2 %	(19.4, 23.1)	29.3 %	(26.4, 32.2)
Hispanic	7.7 %	(6.6, 9.0)	12.0 %	(10.5, 13.5)	15.9 %	(14.1, 17.7)	19.5 %	(17.4, 21.6)	27.5 %	(24.1, 31.1)
Non-Hispanic Asian/Pacific Islander	5.7 %	(4.7, 6.9)	8.3 %	(7.0, 9.8)	10.8 %	(9.3, 12.5)	13.2 %	(11.4, 15.1)	24.3 %	(18.7, 30.4)
Non-Hispanic American Indian/Alaskan Native	11.6 %	(6.9, 17.7)	20.2 %	(13.5, 27.8)	22.4 %	(15.2, 30.5)	25.6 %	(17.5, 34.4)	39.1 %	(20.8, 56.9)
AJCC stage										
I	4.7 %	(4.5, 5.0)	7.7 %	(7.3, 8.0)	10.5 %	(10.1, 10.9)	13.2 %	(12.8, 13.7)	20.1 %	(19.2, 21.0)
II	7.6 %	(7.2, 8.1)	11.5 %	(11.0, 12.1)	15.1 %	(14.4, 15.8)	18.5 %	(17.8, 19.3)	27.6 %	(25.4, 29.9)
III	17.8 %	(16.5, 19.1)	25.1 %	(23.5, 26.6)	30.3 %	(28.6, 32.1)	34.1 %	(32.2, 35.9)	40.9 %	(38.4, 43.5)
Lymph node status										
Negative	4.8 %	(4.6, 5.1)	7.7 %	(7.4, 8.1)	10.6 %	(10.2, 11.0)	13.4 %	(12.9, 13.8)	20.4 %	(19.6, 21.3)
1-3	9.0 %	(8.3, 9.7)	13.2 %	(12.4, 14.1)	16.9 %	(15.9, 17.9)	20.6 %	(19.5, 21.7)	30.4 %	(26.8, 34.2)
4+	19.6 %	(18.0, 21.2)	27.2 %	(25.4, 29.1)	33.2 %	(31.2, 35.2)	37.3 %	(35.1, 39.5)	45.0 %	(41.9, 47.9)
Tumor size, cm										
<2	5.1 %	(4.9, 5.4)	8.1 %	(7.8, 8.4)	11.1 %	(10.7, 11.5)	13.9 %	(13.4, 14.3)	21.5 %	(20.3, 22.6)
2-5	8.6 %	(8.1, 9.1)	13.1 %	(12.5, 13.8)	16.9 %	(16.2, 17.6)	20.4 %	(19.6, 21.3)	28.0 %	(26.5, 29.6)
>5	15.8 %	(14.2, 17.5)	21.3 %	(19.5, 23.2)	25.6 %	(23.5, 27.7)	28.1 %	(25.8, 30.3)	35.5 %	(31.8, 39.1)
Frailty status										
Robust	6.1 %	(5.8, 6.4)	9.4 %	(9.0, 9.8)	12.5 %	(12.0, 12.9)	15.3 %	(14.7, 15.8)	22.6 %	(21.4, 23.8)
Pre-frail	7.0 %	(6.6, 7.4)	10.7 %	(10.2, 11.2)	14.1 %	(13.6, 14.7)	17.6 %	(16.9, 18.3)	25.9 %	(24.5, 27.4)
Frail	8.6 %	(7.7, 9.7)	13.4 %	(12.1, 14.7)	17.3 %	(15.8, 18.8)	19.7 %	(18.1, 21.4)	25.5 %	(22.8, 28.2)
CPS + EG score										
0	4.8 %	(4.5, 5.0)	7.6 %	(7.2, 7.9)	10.4 %	(10.0, 10.9)	13.2 %	(12.7, 13.7)	19.9 %	(19.0, 20.9)
1	7.2 %	(6.8, 7.7)	11.2 %	(10.6, 11.7)	14.6 %	(14.0, 15.3)	17.8 %	(17.1, 18.6)	26.3 %	(24.4, 28.3)
2	13.6 %	(12.6, 14.6)	19.2 %	(17.9, 20.4)	23.6 %	(22.2, 25.0)	27.6 %	(26.1, 29.2)	36.4 %	(33.9, 39.0)
3+	23.2 %	(19.3, 27.3)	34.4 %	(29.7, 39.1)	38.8 %	(33.8, 43.9)	44.1 %	(38.6, 49.6)	47.1 %	(39.9, 53.9)

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CI, confidence interval; AJCC, American Joint Committee on Cancer staging system; CPS + EG, clinical-pathologic scoring system incorporating estrogen receptor-negative disease and nuclear grade 3 tumor pathology; CI, confidence interval.

several biological mechanisms related to increased invasive BC and recurrence risk [7,34,35]. Another reason for an observed increased BC recurrence risk among women with a higher degree of frailty at the time of diagnosis and treatment could be the use of attenuated treatment regimens [36] or lower rates of surveillance mammography [8] when cognitive deficits and greater comorbidity are present; or where life expectancy and the long-term benefits of treatment and screening are limited [37]. While frailty is a construct that encompasses physiological decline (e.g., organ system failure or dysfunction) and accumulation of illness and ability to perform daily activities [38], it is also a measure that may indicate how and whether a patient will tolerate cancer treatment [39] and may play an important role in clinical decision-making [40].

Although BC subtypes prevalence differs by race (e.g., higher rates of triple-negative BC among Black women) [41], the greatest disparities in survival exist in HR+/HER2- BC, which carries a more favorable prognosis overall. The full extent of BC health disparities among Hispanic, American Indian, and Alaskan Native women is less known [42,43]. A recent U.S. population-based study of women aged 40—64 years diagnosed with BC between 2010 and 2016 determined that nearly half of the observed disparity in diagnosis with locally-advanced versus early-stage disease comparing Black, Hispanic, and American Indian/Alaskan Native women with their non-Hispanic white counterparts was mediated by a lack of adequate health insurance [44]. This study provides additional

evidence for a population of women ages 65 years and older with HR+/HER2- BC where racial differences persist, even among women who were continuously enrolled in Medicare and after accounting for treatment differences, reflecting a potential racial disparity in BC care.

Several strengths of this study are worth noting. First, this study used population-based cohorts of women with BC over an eight-year span with detailed demographic and clinical characteristics. Second, frailty index was based on the healthcare administrative records of Medicare enrollees and demonstrated excellent predictive power on clinically meaningful outcomes such as death in multiple validation studies using SEER-Medicare data. Third, the algorithm used in identifying BC recurrence was developed in large hospital system electronic health records and employed a combination of both diagnosis and procedure codes. Finally, competing risk models designed to assess BC-related and recurrence risks while accounting for deaths without the events of interest as competing risks provided more accurate estimates of relative risks. Despite these strengths, our analyses could not fully rule out potential interactions among risk factors, and the recurrence rates in diverse patient groups should be interpreted with caution.
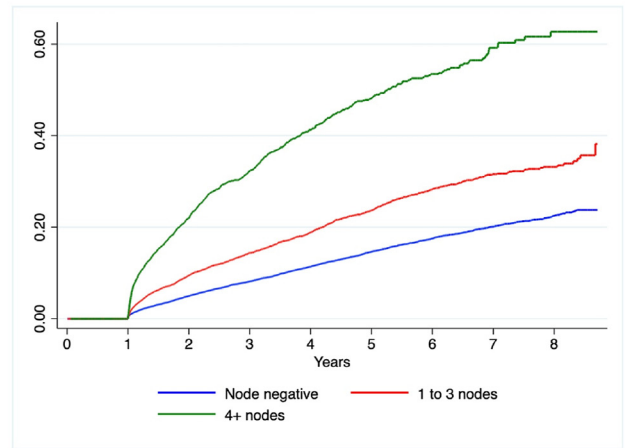
BC recurrences are not routinely collected by SEER registries; therefore, we used a claims-based algorithm validated for use with the SEER-Medicare Linked Database to determine our main outcome of interest. Although the algorithm used achieved a
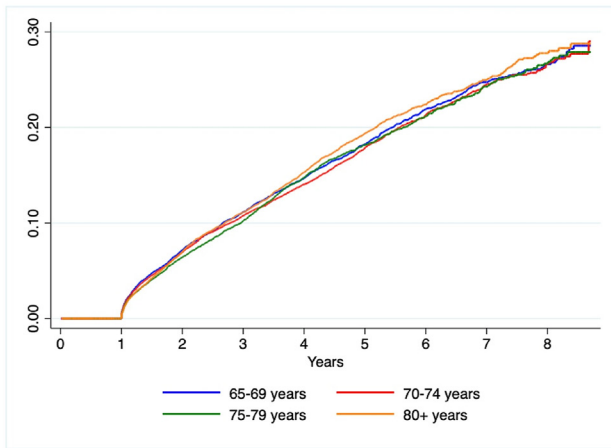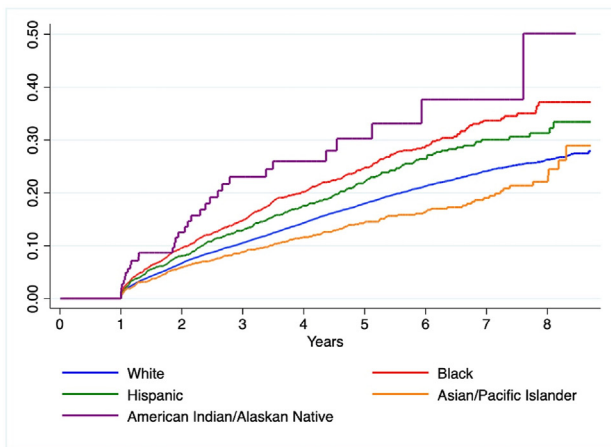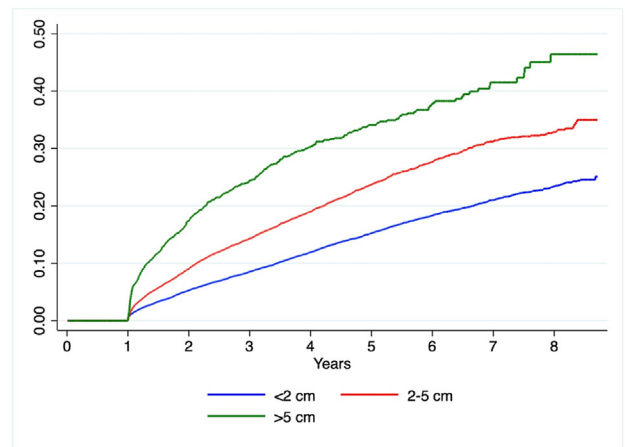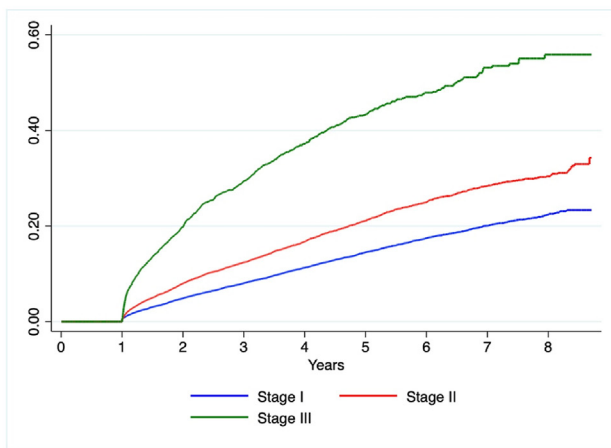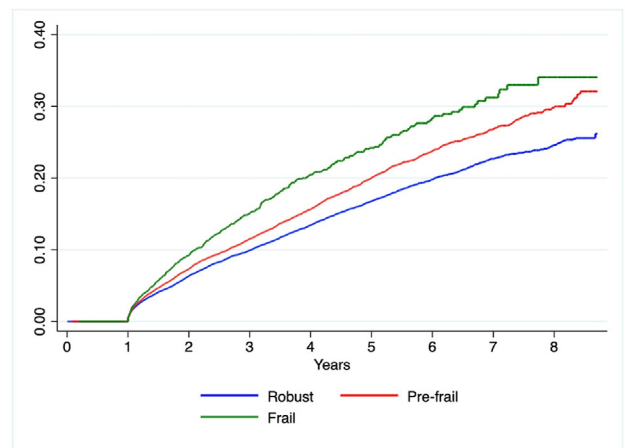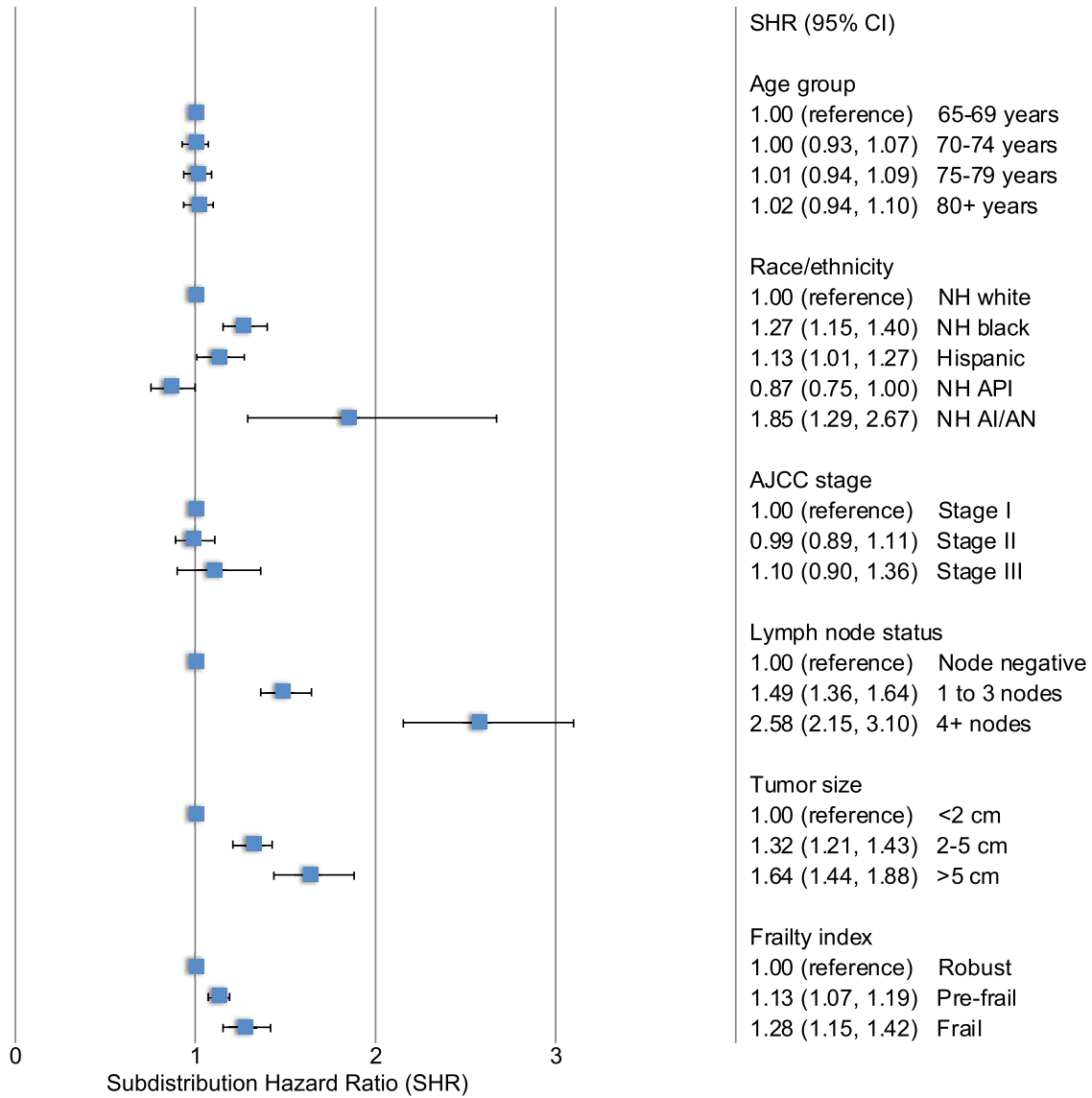
Fig. 2. Cumulative incidence functions for breast cancer recurrence by (A) age group; (B) race/ethnicity; (C) AJCC stage; (D) tumor size; (E) lymph node status; (F) frailty status.

sensitivity and specificity of 69 % and 99 %, respectively, it does not differentiate the patterns of recurrence since procedures and chemotherapy are not site-specific. Additionally, the low sensitivity allowed for results to be biased towards a more conservative estimate to further emphasize which patients will benefit. However, this method required conditions on our selected cohort of continuous enrollment in Medicare and at least one year of survival (delayed entry) to sufficiently distinguish an incident recurrence from prevalent BC diagnoses. We also lacked information on other factors that could not be determined from cancer registry or Medicare claims data such as obesity and clinical biomarkers (e.g., recurrence scores, Ki67).

SHR (95% CI)

Age group
1.00 (reference)   65-69 years
1.00 (0.93, 1.07)   70-74 years
1.01 (0.94, 1.09)   75-79 years
1.02 (0.94, 1.10)   80+ years

Race/ethnicity
1.00 (reference)   NH white
1.27 (1.15, 1.40)   NH black
1.13 (1.01, 1.27)   Hispanic
0.87 (0.75, 1.00)   NH API
1.85 (1.29, 2.67)   NH AI/AN

AJCC stage
1.00 (reference)   Stage I
0.99 (0.89, 1.11)   Stage II
1.10 (0.90, 1.36)   Stage III

Lymph node status
1.00 (reference)   Node negative
1.49 (1.36, 1.64)   1 to 3 nodes
2.58 (2.15, 3.10)   4+ nodes

Tumor size
1.00 (reference)   <2 cm
1.32 (1.21, 1.43)   2-5 cm
1.64 (1.44, 1.88)   >5 cm

Frailty index
1.00 (reference)   Robust
1.13 (1.07, 1.19)   Pre-frail
1.28 (1.15, 1.42)   Frail

Fig. 3. Forest plot of multivariable-adjusted[1] subdistribution hazard ratios and robust 95 % confidence intervals for breast cancer recurrence for selected characteristics in Fine and Gray competing risk regression models.
Abbreviations: AJCC, American Joint Committee on Cancer staging system; CI, confidence interval; NH, Non-Hispanic; API, Asian and Pacific Islander; AI/AN, American Indian/Alaskan Native.
1 Estimates are mutually adjusted for listed covariates, type of surgery, radiotherapy, and chemotherapy
2.Kim et al. J Gerontol A Biol Sci Med Sci. 2018; 73 (7):980–987.

5. Conclusions

The present study demonstrates that recurrence risk for older patients with HR+/HER2-early BC increases with stage, nodal status, tumor size, frailty, and in racial/ethnic minority groups.

Declaration of competing interest

JZ, NAN, AAA, CCH and GSC are employees of UIC who were paid contractors to Pfizer for the development of the manuscript. NK is a paid consultant to Pfizer. JC, DM and EHL are shareholders and are employed by Pfizer Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.08.005.

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