original contributions

Survival in the Real World: A National Analysis of Patients Treated for Early-Stage Breast Cancer

Risha Gidwani, DrPH[1]; Jeffrey A. Franks, MSPH[2]; Ene M. Enogela, MPH[2]; Nicole E. Caston, MPH[2]; Courtney P. Williams, DrPH[2]; Monica S. Aswani, DrPH[3]; Andres Azuero, PhD, MBA[4]; and Gabrielle B. Rocque, MD, MSPH, FASCO[2,5]

QUESTION ASKED: Among patients with early-stage breast cancer (EBC), are there differences in patients' survival for those under- and unrepresented in clinical trials compared with those well-represented in clinical trials?

SUMMARY ANSWER: Patients with EBC who were unrepresented in clinical trials compared with those who were well-represented saw an increased risk of 5-year mortality. Specifically, patients who were ≥ 70 years old and had comorbidities or concurrent cancer saw increased risks of 5-year mortality.

WHAT WE DID: Using CancerLinQ Discovery's national data set, we identified women diagnosed with EBC between 2005 and 2015. Patients were then categorized on the basis of their characteristics into clinical trial representation groups. Patients with comorbidities or concurrent cancers were considered unrepresented. Patients who were Black, Indigenous, or People of Color and/or aged < 45 or ≥ 70 years were considered under-represented. Finally, patients who were White, aged between 45 and 69 years, and without comorbidities were considered well-represented. We then compared the 5-year mortality of the unrepresented and under-represented patients with that of the well-represented patients.

WHAT WE FOUND: Patients who were considered unrepresented in clinical trials had nearly three times the hazard of 5-year mortality (adjusted hazard ratio [aHR] 2.71; 95% CI, 2.08 to 3.52) when compared with the patients considered well-represented. Patients who were considered under-represented when compared with those who were well-represented saw no significant increase in the hazard of 5-year mortality. However, among individual patient characteristics, those aged < 45 years had a lower hazard of 5-year mortality (aHR, 0.63; 95% CI, 0.48 to 0.84) and those aged ≥ 70 years had a higher hazard of 5-year mortality (aHR, 2.21; 95% CI, 1.76 to 2.77) compared with those aged 45-69 years.

BIAS, CONFOUNDING FACTORS, DRAWBACKS: We attempted to control for known confounders; however, unmeasured confounders, such as treatment adherence, might have remained. We used the laboratory results to determine comorbidities; therefore, patient comorbidities may not be complete. Among patients with concurrent cancers, we were unable to determine the patient's additional cancer stage.

REAL-LIFE IMPLICATIONS: Treatments for EBC are used across all patient characteristics; however, the majority of these patients are not being represented in clinical trials. The patients who are poorly represented are experiencing poorer survival than their well-represented counterparts. There is a need to expand clinical trial inclusion criteria and report on clinical trial outcomes by clinical and demographic characteristics to support evidence-based decision making.

ASSOCIATED CONTENT

Appendix

Author affiliations and disclosures are available with the complete article at ascopubs.org/journal/op.

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CARE DELIVERY

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abstract

PURPOSE Many patient population groups are not proportionally represented in clinical trials, including patients of color, at age extremes, or with comorbidities. It is therefore unclear how treatment outcomes may differ for these patients compared with those who are well-represented in trials.

METHODS This retrospective cohort study included women diagnosed with stage I-III breast cancer between 2005 and 2015 in the national CancerLinQ Discovery electronic medical record–based data set. Patients with comorbidities or concurrent cancer were considered *unrepresented* in clinical trials. Non-White patients and/or those age <45 or ≥ 70 years were considered *under-represented*. Patients who were White, age 45-69 years, and without comorbidities were considered *well-represented*. Cox proportional hazards models were used to evaluate 5-year mortality by representation group and patient characteristics, adjusting for cancer stage, subtype, chemotherapy, and diagnosis year.

RESULTS Of 11,770 included patients, 48% were considered well-represented in trials, 45% under-represented, and 7% unrepresented. Compared with well-represented patients, unrepresented patients had almost three times the hazard of 5-year mortality (adjusted hazard ratio [aHR], 2.71; 95% CI, 2.08 to 3.52). There were no significant differences in the hazard of 5-year mortality for under-represented patients compared with well-represented patients (aHR, 1.19; 95% CI, 0.98 to 1.45). However, among under-represented patients, those age <45 years had a lower hazard of 5-year mortality (aHR, 0.63; 95% CI, 0.48 to 0.84) and those age ≥ 70 years had a higher hazard of 5-year mortality (aHR, 2.21; 95% CI, 1.76 to 2.77) compared with those age 45-69 years.

CONCLUSION More than half of the patients were under-represented or unrepresented in clinical trials, because of age, comorbidity, or race. Some of these groups experienced poorer survival compared with those well-represented in trials. Trialists should ensure that study participants reflect the disease population to support evidence-based decision making for all individuals with cancer.

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INTRODUCTION

Efficacy data from clinical trials provide the basis for US Food and Drug Administration (FDA) approval and inclusion within clinical practice guidelines, which are subsequently applied to all patients regardless of sociodemographic characteristics or comorbidities. However, clinical trial inclusion and exclusion criteria for cancer therapies are highly selective and often do not represent the patient population who receive the therapies post-trial.[1,2] Due to concern for potential adverse events, clinical trials are commonly limited to younger, medically fit patients without significant comorbidities.[2,3] Certain racial and ethnic groups are also poorly represented in clinical trials because of systemic issues surrounding recruitment and retention.[4,5]

Understanding the generalizability of clinical trial results is crucial for the practice of evidence-based treatment for any illness but is particularly important for early-stage breast cancer (EBC), the most common female cancer. In the more than 240,000 Americans annually diagnosed with EBC,[6] 24% are Black, Indigenous, or People of Color.[7] However, fewer than 3% of patients enrolled in clinical trials are Black.[1] Additionally, 39% of patients with EBC are younger than 45 years or older than 70 years[7] and 32% have concurrent comorbidities.[1] Poor representation in clinical trials by race, age, or comorbidity status results in a knowledge gap regarding treatment outcomes for a substantial number of patients treated in real-world settings.

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Previous studies of outcomes in clinical trial participants compared with real-world patient populations demonstrate mixed findings. Clinical trial participants had improved survival outcomes compared with patients captured in the SEER-Medicare database.[3] However, a meta-analysis found insufficient evidence for differences in patient outcomes when comparing trial and real-world populations, due in part to inadequate control of confounding.[8,9] Furthermore, a majority of previous studies compare Medicare enrollees with clinical trial participants, yet the Medicare population is older and study findings may not adequately generalize to all individuals with cancer. This study therefore compares survival outcomes for real-world patients with EBC treated with common chemotherapy regimens who are under-represented or unrepresented in clinical trials because of age, race, and/or comorbidities with those patients who are well-represented in such trials. These data are crucial for understanding population-level outcomes for patients to whom trial results may not generalize.

METHODS

Study Sample and Design

This retrospective cohort study included women with EBC identified in the American Society of Clinical Oncology (ASCO) CancerLinQ Discovery data set between January 2005 and June 2020. CancerLinQ is a longitudinal, electronic medical record–aggregated database derived from more than 60 oncology practices across the United States representing more than 1.4 million people with a primary cancer diagnosis nationwide.[10] Patients included in our survival analysis were female, age $\geq$ 18 years, diagnosed with EBC between 2005 and 2015, and received one of the seven chemotherapy regimens of interest (see below) and at least two health care encounters after their EBC diagnosis. EBC diagnosis was identified through International Classification of Diseases (ICD)-9/10 codes (ICD-9: 174.x; ICD-10: C50.x). Patients with ICD-9/10 codes for secondary metastases (excluding breast and lymph node metastases) before EBC diagnosis were excluded because of probable distant metastases. Additional exclusion criteria included having less than 1 year of post-diagnosis data and initiation of chemotherapy $>$ 180 days post-diagnosis. Patients who received chemotherapy more than 90 days before initiation of their EBC chemotherapy regimen were included in our regimen of interest group only if they had concurrent cancer. This study was approved by the University of Alabama at Birmingham Institutional Review Board.

Outcome: 5-Year Mortality

The primary outcome for this study was 5-year overall mortality. Death was recorded in CancerLinQ Discovery after being harmonized from two data sources: third-party death data and EMR data.[11] Ten-year overall mortality was examined as a sensitivity analysis; we considered this an exploratory analysis because of the reduced sample size with a 10-year follow-up.

Exposure: Clinical Trial Representation Status

Three groups were created to evaluate the association between clinical trial representation and overall survival; group membership was based on review of clinical trial protocols and published literature on trial-based patient demographics.[12] Patients considered *unrepresented* in clinical trials had a concurrent cancer or comorbidity commonly exclusionary from trial eligibility reported on ClinicalTrials.gov using the I-SPY laboratory criteria (liver disease, renal insufficiency, thrombocytopenia, leukopenia, anemia, or uncontrolled diabetes; Appendix Table A1, online only).[13] Patients considered *under-represented* in clinical trials were Black, Indigenous, or People of Color and/or were age $<$ 45 years (Center for Disease Control and Prevention definition of young woman)[14] or $\geq$ 70 years (International Society for Geriatric Oncology definition of elderly).[15] Patients considered *well-represented* in clinical trials were White and age 45 to 69 years, with no comorbidities or concurrent cancers.

Other Variables

Cancer characteristics. Patients were identified as having stage I, II, or III EBC from staging variables present in the CancerLinQ Discovery data set according to the American Joint Committee on Cancer, 8th edition.[16] Cancer subtype was determined through hormone receptor (HR; estrogen receptor and progesterone receptor) and human epidermal growth factor receptor-2 (HER2) biomarker tests recorded in the 90-day period pre- or post-diagnosis. Patients were considered positive for a biomarker if any test was positive. Subtypes were then grouped as HR $\pm$ HER2+, HR+ HER−, and HR− HER2−. If a patient had no biomarker tests, the appropriate subtype was determined using the patient's chemotherapy regimen. Patients receiving HER2-targeted therapy were considered HER2+, whereas patients receiving any hormone therapy were considered HR+.

Patient characteristics. Patient race or ethnicity was categorized as White, Black, Hispanic or Latino, or Other. Other race included Asian, American Indian, Alaskan Natives, and Pacific Islanders; these races were combined because of small sample sizes in the data set. The age at cancer diagnosis was categorized as $<$ 45, 45-69, or $\geq$ 70 years. Laboratory result data determining common exclusionary comorbidities in clinical trials (described above) were evaluated. The closest laboratory within 1 year prechemotherapy initiation was selected. If no labs before diagnosis were available, the closest laboratory within 7 days post-chemotherapy initiation was captured.[13] Because of low prevalence of individual comorbidities, the survival model included a binary variable indicating any or no comorbidities. Concurrent cancer was defined as any cancer (excluding non-melanoma skin cancer) occurring

any time pre-EBC diagnosis or within 7 days post-EBC diagnosis using ICD-9/10 codes.

Chemotherapy. Patients were categorized as receiving one of the seven common chemotherapy treatment regimens. Additional analysis included patients receiving another chemotherapy regimen, hormone therapy alone, or no hormone therapy nor chemotherapy. Regimens of interest were categorized as high- or low-intensity. In survival models, chemotherapies of interest were grouped by

TABLE 1. Demographic and Clinical Characteristics Overall and Stratified by Early-Stage Breast Cancer Subtype in Patients Diagnosed in 2005-2015 (n = 11,770)

	Overall	HER2+	HR+ HER2−	HR− HER2−
Characteristic	**n = 11,770, No. (%)**	**n = 2,906, No. (%)**	**n = 6,553, No. (%)**	**n = 2,311, No. (%)**
Clinical trial representation				
Unrepresented	879 (7)	221 (8)	469 (7)	189 (8)
Under-represented	5,267 (45)	1,356 (47)	2,748 (42)	1,163 (50)
Well-represented	5,624 (48)	1,329 (45)	3,336 (51)	959 (42)
Age at cancer diagnosis, years				
< 45	2,244 (19)	585 (20)	1,204 (18)	455 (20)
45-69	8,347 (71)	2,000 (69)	4,751 (73)	1,596 (69)
≥ 70	1,179 (10)	321 (11)	598 (9)	260 (11)
Race or ethnicity				
Black	1,750 (15)	401 (14)	805 (12)	544 (24)
Hispanic or Latino	520 (4)	133 (5)	302 (5)	85 (4)
Other race	1,025 (9)	309 (11)	556 (8)	160 (7)
White	8,475 (72)	2,063 (70)	4,890 (75)	1,522 (66)
Stage				
I	3,310 (28)	942 (32)	1,543 (24)	825 (36)
II	5,961 (51)	1,356 (47)	3,490 (53)	1,115 (48)
III	2,499 (21)	608 (21)	1,520 (23)	371 (16)
Regimen				
High intensity	7,502 (64)	2,650 (91)	3,434 (52)	1,418 (61)
TCH	1,503 (13)	1,503 (52)	—	—
AC-TH	741 (6)	741 (26)	—	—
TCHP	406 (3)	406 (14)	—	—
ACT	4,852 (41)	—	3,434 (52)	1,418 (61)
Low intensity	4,268 (36)	256 (9)	3,119 (48)	893 (39)
TH	256 (2)	256 (9)	—	—
AC	680 (6)	—	492 (8)	188 (8)
TC	3,332 (28)	—	2,627 (40)	705 (31)
Any laboratory-based comorbidity	684 (6)	178 (6)	362 (6)	144 (6)
Liver disease	101 (1)	26 (1)	50 (1)	25 (1)
Renal insufficiency	41 (0.4)	12 (0.4)	16 (0.2)	13 (0.6)
Thrombocytopenia	30 (0.3)	8 (0.3)	12 (0.2)	10 (0.4)
Leukopenia	23 (0.2)	7 (0.2)	13 (0.2)	3 (0.1)
Anemia	44 (0.4)	10 (0.3)	21 (0.3)	13 (0.6)
Uncontrolled diabetes	471 (4)	124 (4)	258 (4)	89 (4)
Concurrent cancer	211 (2)	46 (2)	116 (2)	49 (2)

Abbreviations: AC, doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, and a taxane; AC-TH, doxorubicin and cyclophosphamide followed by a taxane; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; TC, taxane and cyclophosphamide; TCH, taxane (paclitaxel or docetaxel), carboplatin, and trastuzumab; TCHP, taxane, carboplatin, trastuzumab, and pertuzumab; TH, taxane and trastuzumab.

intensity rather than individual regimens because of perfect collinearity between chemotherapy and cancer subtype for HER2+ patients. High-intensity chemotherapies included (1) a taxane (paclitaxel or docetaxel), carboplatin, and trastuzumab; (2) doxorubicin and cyclophosphamide followed by a taxane; (3) a taxane, carboplatin, trastuzumab, and pertuzumab; and (4) doxorubicin, cyclophosphamide, and a taxane. Low-intensity chemotherapies included (5) a taxane and trastuzumab, (6) doxorubicin and cyclophosphamide, and (7) a taxane and cyclophosphamide. We included patients with concurrent hormone therapy.

Supplemental analyses. In additional analyses, we evaluated the proportion of patients with EBC receiving chemotherapy, hormone therapy, a combination, or neither.

Statistical Analysis

Among our regimen of interest cohort, patient demographic and clinical characteristics were compared overall and by representation group. Adjusted hazard ratios (aHRs) and corresponding 95% CI from Cox proportional hazard models evaluated 5-year mortality by clinical trial representation group and, in a separate model, by the individual patient characteristics composing the representation groups. Mortality was analyzed for all EBC subtypes in the overall model and in models stratified by EBC subtype. The overall models were adjusted for cancer stage, subtype, chemotherapy intensity, and year of EBC diagnosis. Stratified models were adjusted for cancer stage, individual treatment regimen, and year of EBC diagnosis. Adequacy of the proportional hazards assumption was assessed using interaction effects and information criteria.[17] Supplemental analysis includes the full cohort and consisted of descriptive analysis. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Sample Characteristics

Of 11,770 included patients (Appendix Fig A1, online only), most were age 45-69 years (71%), White (72%), and diagnosed with stage II EBC (51%) or HR+ HER2− subtype (56%; Table 1). Few patients had comorbidities (6%), and even fewer had a concurrent cancer (2%). Patients considered unrepresented (7%) were categorized as such because of comorbidities alone (76%), concurrent cancer (22%), or both (2%, Fig 1). Most patients considered under-represented (45%) were categorized as such on the basis of age (44%), on the basis of race or ethnicity (39%), and on the basis of both age and race or ethnicity (17%). The remaining 48% were considered well-represented.

Regimen Intensity

Most patients received a high-intensity chemotherapy regimen, including 64% of the entire cohort and 58%, 66%, and 63% among those unrepresented, under-

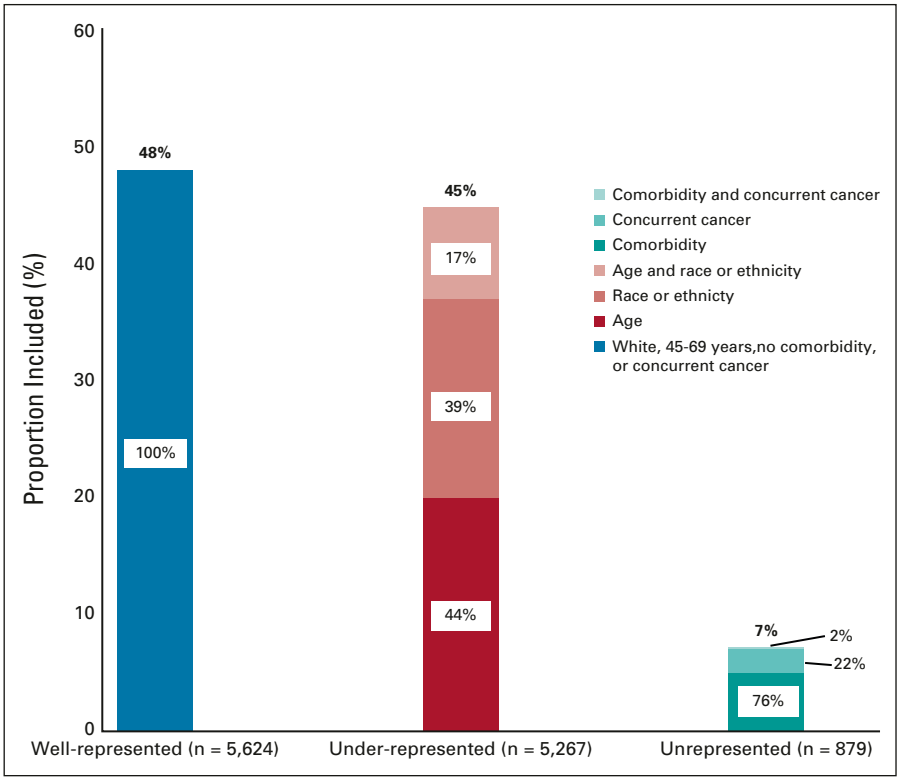

FIG 1. Reason for categorization into clinical trial representation group (n = 11,770). Proportion of patients within each representation status group and the reasoning for their inclusion in that group.

represented, and well-represented groups, respectively (Appendix Table A2, online only). The most common high-intensity treatment regimen was doxorubicin, cyclophosphamide, and a taxane, received by 35% of unrepresented, 43% of under-represented, and 41% of well-represented patients in our sample. The most common low-intensity treatment regimen was taxane and cyclophosphamide, received by 37% of unrepresented, 26% of under-represented, and 29% of well-represented patients in our sample.

Mortality

Overall. In adjusted Cox proportional hazards models, 5-year mortality post-EBC diagnosis was estimated at 90% for unrepresented patients (95% CI, 88 to 92), 95% for under-represented patients (95% CI, 94 to 96), and 96% for well-represented patients (95% CI, 95 to 97; Fig 2, Appendix Tables A3 and A4, online only). Unrepresented patients had almost three times the hazard of 5-year mortality when compared with well-represented patients (aHR, 2.71; 95% CI, 2.08 to 3.52; Table 2). Under-represented patients did not significantly differ in hazard of 5-year mortality compared with those well-represented patients (aHR, 1.19; 95% CI, 0.98 to 1.45).

Cancer subtype. In all three cancer subtypes, unrepresented patients had a higher hazard of 5-year mortality compared with those well-represented (*HER2+* [*any HR status*], aHR, 2.50; 95% CI, 1.39 to 4.48; HR+ HER2−, aHR, 2.54; 95% CI, 1.75 to 3.68; HR− HER2−, aHR, 2.75; 95% CI, 1.68 to 4.50). Mortality for under-represented versus well-represented patients differed by subtype. Under-represented patients with HR + HER2− subtype had a 38% increased hazard of 5-year mortality compared with their well-represented counterparts (aHR, 1.38; 95% CI, 1.06 to 1.78). However, there were no significant differences in 5-year mortality for under-represented versus well-represented patients with HER2+ or HR-HER2− subtype (Table 2, Fig 2, Appendix Tables A3 and A4). Similar results were seen for 10-year survival in both the overall and subtype stratified models, with under-represented patients and unrepresented patients having higher overall mortality than well-represented

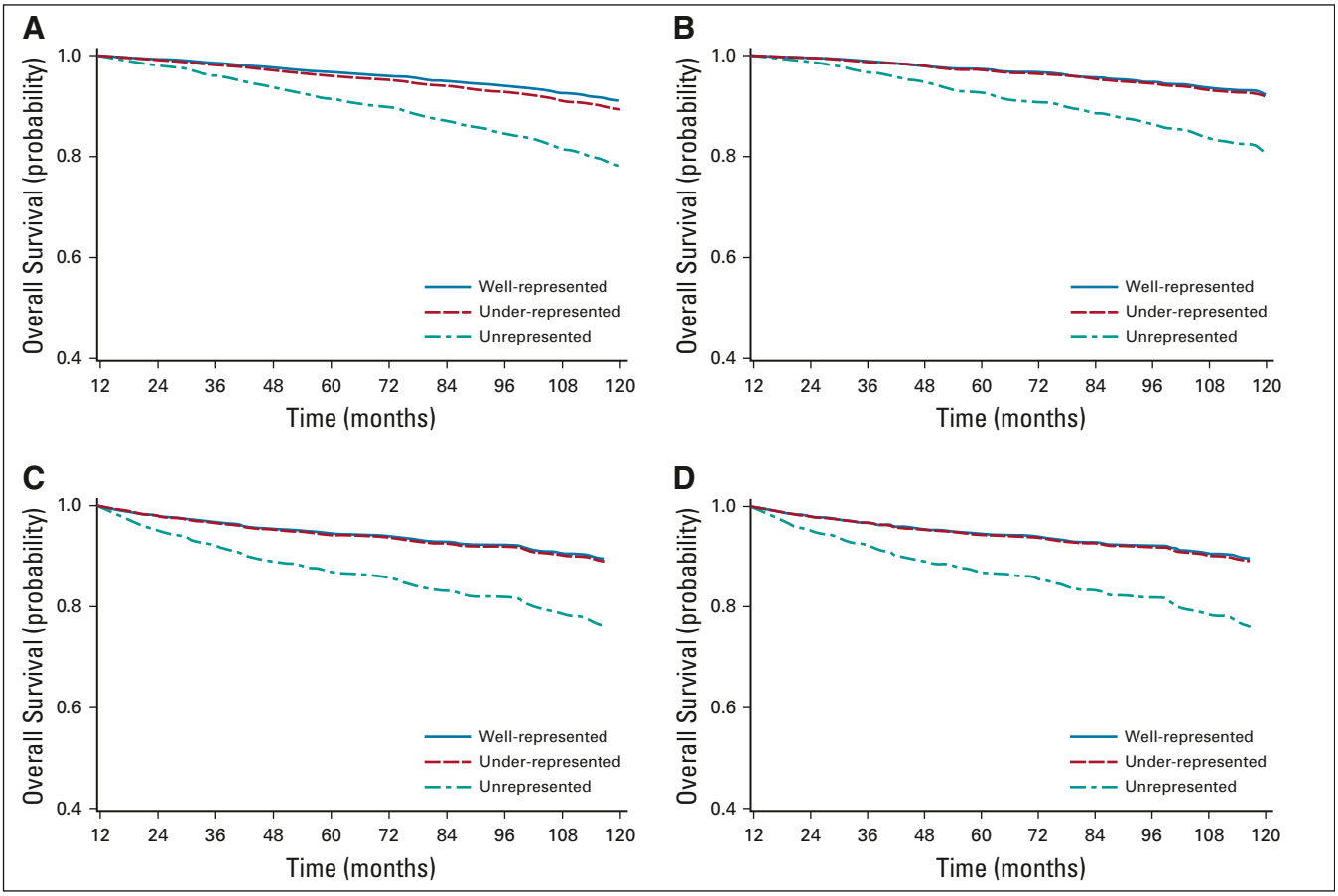

FIG 2. Cox proportional hazard survival curves of 5-year survival overall and by cancer subtype by clinical representation status in patients diagnosed with early-stage breast cancer between 2005 and 2015. (A) Survival curve across all patients (n = 11,770). (B) Survival curve for patients with a HER2+ subtype (n = 2,906). (C) Survival curve for patients with a HR+ HER2−subtype (n = 6,553). (D) Survival curve for patients with a HR−HER2−subtype (n = 2,311). Overall model: adjusted for stage, regimen intensity, subtype, and year of diagnosis. Stratified model: adjusted for stage, regimen, and year of diagnosis. ER, estrogen receptor; HER2, human epidermal growth factor receptor-2.

TABLE 2. Cox Proportional Hazard Model Results by Estimating the Association Between Clinical Trial Representation Status and 5-Year Survival Overall and by Cancer Subtype in Patients Diagnosed With Early-Stage Breast Cancer in 2005-2015 (n = 11,770)

	Overall		HER2+		HR+ HER2−		HR− HER2−	
Representation	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
Well-represented	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Under-represented	1.19	0.98 to 1.45	1.01	0.65 to 1.57	1.38	1.06 to 1.78	0.93	0.63 to 1.36
Unrepresented	2.71	2.08 to 3.52	2.50	1.39 to 4.48	2.54	1.75 to 3.68	2.75	1.68 to 4.50

NOTE. Overall model: adjusted for stage, regimen intensity, subtype, and year of diagnosis. Stratified model: adjusted for stage, regimen, and year of diagnosis.

Abbreviations: aHR, adjusted hazard ratio; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; ref, reference.

patients (aHR, 1.16; 95% CI, 1.00 to 1.35; aHR, 2.45; 95% CI, 1.97 to 3.05, Appendix Table A5, online only).

Individual patient characteristics. When evaluating associations between mortality and individual patient characteristics, we found significant differences in 5-year mortality on the basis of age and comorbidity in the overall model. Patients with any comorbidity had 2.5 times the hazard of 5-year mortality (aHR, 2.49; 95% CI, 1.91 to 3.24; Table 3) compared with those without comorbidities. Those with a concurrent cancer had a 67% increased hazard of 5-year mortality compared with those without a concurrent cancer (aHR, 1.67; 95% CI, 1.01 to 2.75). Patients age < 45 years had a 37% decreased hazard of death (aHR, 0.63; 95% CI, 0.48 to 0.84) compared with those age 45-69 years, and patients age ≥ 70 years had more than two times the hazard of 5-year mortality (aHR, 2.21; 95% CI, 1.76 to 2.77) compared with patients age 45-69 years. Similar results were seen when stratifying the individual characteristics by subtype. In the overall model, there were no significant differences in 5-year hazard of death among patients of different races or ethnicities. However, in models stratified by subtype, Black patients with HR-HER2- cancer had a 49% increased hazard of death compared with those who were White (aHR, 1.49; 95% CI, 1.02 to 2.18). Similar results were found in models evaluating 10-year survival (Appendix Table A6, online only). In supplemental analyses of all patients with early-stage breast cancer (n = 38,640), we found that the majority of patients received hormone monotherapy (48%) and that 17% of patients received no therapy (hormone therapy nor chemotherapy). However, there were no differences in the proportion of patients receiving no hormone therapy nor chemotherapy across patient characteristics. Modest differences were observed for other treatment categories, except for patients ≥ 70 years having higher rates of hormone therapy alone than younger patients (Appendix Table A7, online only).

DISCUSSION

More than half of patients with EBC in this electronic medical record–based cohort study would not be well-represented in conventional clinical trials on the basis of demographic and clinical characteristics. These characteristics, specifically age, comorbidity status, concurrent cancer, and to a lesser degree, race/ethnicity, were associated with differences in survival outcomes. For example, in adjusted analyses, we found that patients who are traditionally unrepresented in clinical trials because of comorbidities or concurrent cancer had an almost threefold higher hazard of 5-year mortality compared with those well-represented. Comorbidities may be present in a third of individuals with EBC[1]; thus, clinical trial results may overestimate survival for this large segment of the patient population. Our finding on reduced survival in patients with comorbidities is particularly noteworthy; 5-year hazard of death has a lower bound 95% CI of 2.08; even this conservative estimate indicates a large mortality difference among patients with and without comorbidities.

For patients unrepresented in clinical trials, the FDA approval process may unintentionally result in differing outcomes for trial-based and real-world patient populations. In most cases, FDA approval is contingent upon the safety and efficacy of a drug tested via randomized clinical trial. Once FDA approval is granted, the drug may be legally prescribed to any patient with the clinical condition, regardless of factors such as age or comorbid status. Our analysis shows that these populations do receive common treatment regimens at a similar rate to the general population. By excluding patients with differing clinical conditions from trials but including them in the population to which drugs can be disseminated, one runs the risk of inadvertently causing injury. For example, observational data indicate that cancer patients with baseline anemia and renal dysfunction have higher likelihood of chemotherapy-related toxicity.[18] Patients with diagnoses of peripheral vascular disease, dementia, chronic pulmonary disease, liver, and renal diseases have higher cancer-related mortality.[19] Although the FDA recommends increasing diversity of enrollment, no requirement exists to reinforce these recommendations.[20] Our results suggest that such a requirement may be advisable.

Several options exist for reducing transportability and increasing generalizability of existing clinical trials for patients

TABLE 3. Cox Proportional Hazard Model Results Estimating the Association Between Patient Characteristics and 5-Year Survival Overall and by Cancer Subtype in Patients Diagnosed With Early-Stage Breast Cancer in 2005-2015 (n = 11,770)

	Overall		HER2+		HR+ HER2−		HR− HER2−	
Characteristic	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
Race or ethnicity								
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.21	0.96 to 1.52	1.14	0.66 to 1.98	0.99	0.68 to 1.42	1.49	1.02 to 2.18
Hispanic	0.73	0.43 to 1.22	1.61	0.69 to 3.74	0.63	0.31 to 1.29	0.23	0.03 to 1.63
Other race	0.96	0.69 to 1.34	0.59	0.26 to 1.37	1.07	0.70 to 1.64	0.99	0.49 to 2.00
Age, years								
45-69	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
< 45	0.63	0.48 to 0.84	0.43	0.21 to 0.88	0.65	0.44 to 0.96	0.72	0.44 to 1.18
≥ 70	2.21	1.76 to 2.77	2.05	1.26 to 3.34	2.47	1.83 to 3.35	1.66	1.00 to 2.75
Stage								
I	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
II	2.47	1.84 to 3.33	2.42	1.29 to 4.55	2.19	1.42 to 3.36	2.78	1.61 to 4.78
III	5.31	3.90 to 7.24	6.80	3.62 to 12.79	4.17	2.64 to 6.58	6.37	3.58 to 11.33
Any comorbidities								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.49	1.91 to 3.24	2.11	1.14 to 3.91	2.31	1.59 to 3.36	3.09	1.91 to 4.99
Concurrent cancer								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.67	1.01 to 2.75	3.71	1.59 to 8.63	1.14	0.51 to 2.57	1.31	0.48 to 3.60

NOTE. Overall model: adjusted for stage, regimen intensity, subtype, and year of diagnosis. Stratified model: adjusted for stage, regimen, and year of diagnosis.

Abbreviations: aHR, adjusted hazard ratio; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; ref, reference.

with comorbidities. One favored approach is careful consideration and potential removal of some exclusion criteria. ASCO and The Friends of Cancer Research developed trial inclusion recommendations in 2017, highlighting scenarios where exclusion criteria should be removed and additional monitoring should be considered.[21] Notably, if patients with comorbidities were included in clinical trials, the safety and efficacy profile of commonly used medications may be less favorable. However, given the need of clinicians to practice evidence-based medicine for the entire patient population, understanding safety and efficacy risks in a clinical trial is crucial to limit population-based harm. Another approach to identifying potential harm for unrepresented patients who will inevitably receive these treatments would be to require *systematic* post-marketing surveillance once treatments have received FDA approval.

Another key finding from this study is the difference in survival observed by age. We found that patients with EBC age ≥ 70 years had more than twice the hazard of 5-year mortality compared with patients age 45-69 years. Of the seven seminal trials for the EBC treatments we evaluate here,[22-28] only one reported hazard ratios for survival by age, evaluating patients < 50 and ≥ 50 years.[24] None specifically considered survival for older adults. Although life expectancy decreases with age,[29] the lack of outcomes reported by clinically relevant age categories means that oncologists cannot provide appropriate prognostic information for older adults and may select treatments that are not optimally matched to the patient's risk of recurrence and death. The dearth of evidence needed to make data-driven decisions regarding cancer treatment for patients at age extremes has substantial implications, including the misapplication of standard treatments. A meta-analysis of three EBC trials found that adults age > 70 years had similar benefit from chemotherapy for EBC, but experienced increased toxicity and treatment-related death when compared with younger patients. Notably, only 3% of patients within the analyzed trials were > 70 years old,[30] suggesting that relatively few patients in this age category were deemed fit and appropriate for the trials. Less fit patients may experience greater treatment-related toxicity, which could contribute to the higher hazard of death observed within our study. To address this knowledge gap and properly inform decision making, we propose both increased effort toward older adult enrollment in clinical trials and requirements to report age-based toxicities, adverse events, progression-free survival, and overall survival.

This study did not find differences in mortality by race or ethnicity in the overall EBC cohort but did find increased mortality in triple-negative disease (HR− HER2−) for Black compared with White patients. Another study also found differences in EBC survival, but for different subtypes. Warner and colleagues found that Black patients with EBC had 21% higher stage-specific hazard of mortality compared with White patients with EBC. However, in their analysis, HR+ HER2− tumors drove this difference, with no difference observed in triple-negative EBC.[31] The difference in our findings may result from our examination of treatments received in community-based rather than academic-based settings because of differences in care setting examined (largely academic versus largely community in ours) or differences might have also resulted from confounding, since their analysis did not adjust for treatment intensity. Finally, given that racial disparities are multifactorial, with contributions of biology, social, behavioral, environmental, and access-related factors,[32] unmeasured confounders might have contributed to our lack of observed difference in race/ethnicity-based survival in the overall cohort.

This study was a retrospective evaluation of observational data, meant to evaluate the real-world effectiveness of commonly used EBC treatments, and is therefore subject to limitations. Although we attempted to control for known confounders, such as cancer subtype and treatment intensity, unmeasured confounders, such as treatment adherence, functional status, or access to care, may remain. However, unmeasured confounders would have to be unequally distributed across representation groups for bias to occur in our estimates. For example, patients or physicians might have selected shorter, less-intense treatment regimens because of difficulties with access to care. Because of limited ability to capture comorbidities using diagnoses in electronic health record data and inability to assess severity of problem-based comorbidities using this database, we focused on comorbidities captured by laboratory results[33]; thus, our work does not fully capture patient comorbidities. Our proportion of exclusions because of laboratory-based comorbidities is less than the proportion of patients diagnosed with comorbidities in a breast cancer population,[1] and thus, we are likely underestimating this population. However, these problem-based comorbidities do not necessarily exclude a patient from clinical trials. Using a laboratory-based approach, patients with these comorbidities can be reasonably assumed to be ineligible. A small proportion (2%) of patients had concurrent cancer, which may be underestimated by excluding patients diagnosed with the cancers simultaneously who did not receive a regimen of interest. We had no information on the stage of patients' concurrent cancer. It is therefore possible that some died of their concurrent cancer, whereas others died of breast cancer. However, because of the small proportion of deaths, we do not believe that this significantly biased overall survival estimates.

In conclusion, most patients with EBC receiving treatment in real-world settings are not well-represented in clinical trials, yet receive treatment on the basis of the results of these trials. Our results indicate that patients unrepresented in trials have a higher hazard of 5-year mortality compared with those who are well-represented. To inform the practice of evidence-based medicine in an equitable manner, our findings support a need to both expand clinical trial inclusion criteria and report on clinical trial outcomes by clinical and demographic characteristics.

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PRIOR PRESENTATION

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Survival in the Real World: A National Analysis of Patients Treated for Early-Stage Breast Cancer

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APPENDIX

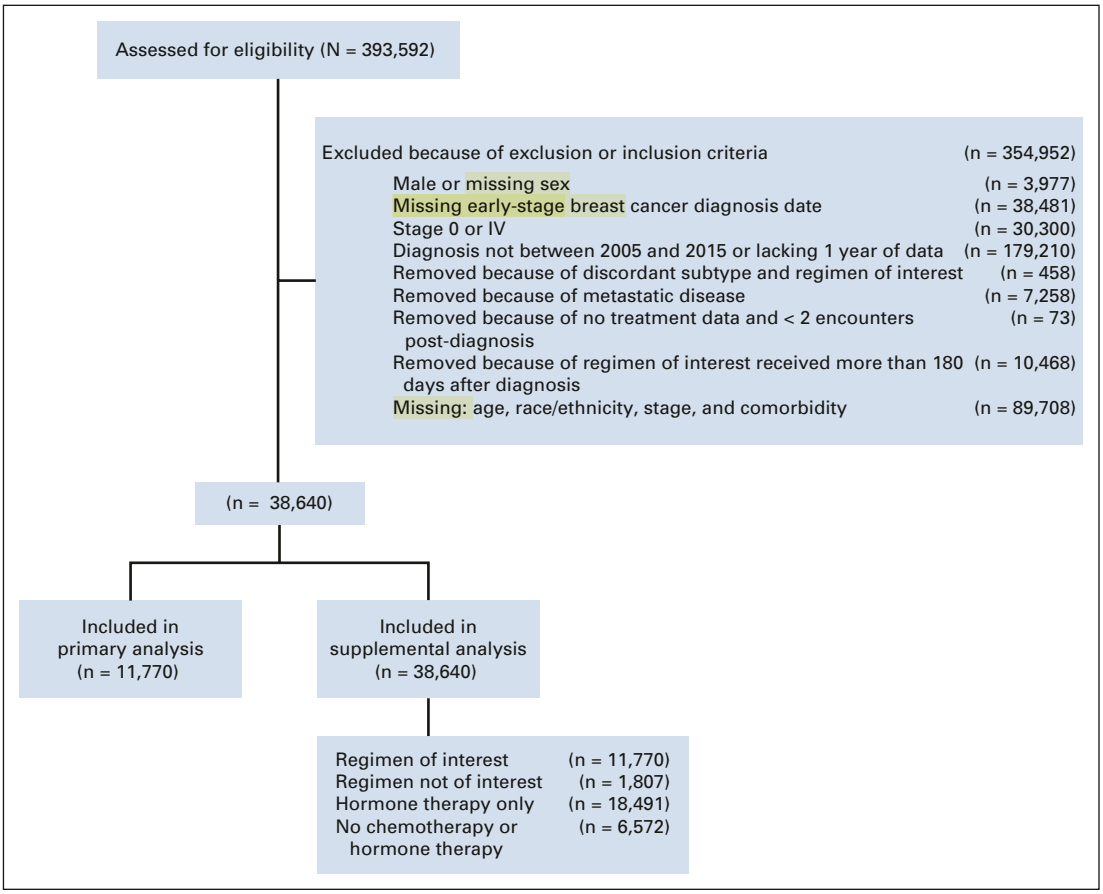

FIG A1. Exclusion cascade.

TABLE A1. Laboratory Values and Cutoffs Used to Determine Comorbidities

Comorbidities	Test Name	Laboratory Value
Liver disease (having at least one test result)	ALT	> 78 U/L
	AST	> 59 U/L
	Bilirubin	> 2.8 mg/dL
Renal insufficiency	Creatinine (serum and whole blood)	> 1.8 mg/dL
Thrombocytopenia	Platelet count	< 1,000/μL
Leukopenia (having at least one positive test result)	Leukocytes	< 3,000/μL
	Neutrophils	< 1,500/μL
Anemia	Hemoglobin	< 9 g/dL
Uncontrolled diabetes	Hemoglobin A1c (HbA1c)	> 8 HbA1c
	Glucose	> 200 mg/dL

TABLE A2. Receipt of High- and Low-Intensity Chemotherapy Treatment Regimens by Clinical Trial Representation Status in Patients Diagnosed With Early-Stage Breast Cancer in 2005-2015 (n = 11,770)

Regimen	Well-represented, n = 5,624, No. (%)	Under-represented, n = 5,267, No. (%)	Unrepresented, n = 879, No. (%)
High-intensity	3,528 (63)	3,464 (66)	510 (58)
TCH	693 (12)	662 (13)	148 (17)
AC-TH	370 (7)	349 (7)	22 (3)
TCHP	172 (3)	204 (4)	30 (3)
ACT	2,293 (41)	2,249 (43)	310 (35)
Low-intensity	2,096 (37)	1,803 (34)	369 (42)
TH	94 (2)	141 (3)	21 (2)
AC	358 (6)	295 (6)	27 (3)
TC	1,644 (29)	1,367 (26)	321 (37)

Abbreviations: AC, doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, and a taxane; AC-TH, doxorubicin and cyclophosphamide followed by a taxane; TC, taxane and cyclophosphamide; TCH, taxane (paclitaxel or docetaxel), carboplatin, and trastuzumab; TCHP, taxane, carboplatin, trastuzumab, and pertuzumab; TH, taxane and trastuzumab.

TABLE A3. No. of Patients With Early-Stage Breast Cancer at Risk per Year

Representation	12 Months	24 Months	36 Months	48 Months	60 Months
Overall					
Well-represented	5,624	5,466	5,190	4,792	4,186
Under-represented	5,267	5,053	4,772	4,353	3,757
Unrepresented	879	821	758	682	578
HER2+					
Well-represented	1,329	1,293	1,227	1,120	956
Under-represented	1,356	1,303	1,225	1,106	932
Unrepresented	221	206	187	170	143
HR+ HER2−					
Well-represented	3,336	3,264	3,104	2,889	2,545
Under-represented	2,748	2,645	2,502	2,284	1,985
Unrepresented	469	442	413	374	315
HR− HER2−					
Well-represented	959	909	859	783	685
Under-represented	1,163	1,105	1,045	963	840
Unrepresented	189	173	158	138	120

Abbreviations: HER2, human epidermal growth factor receptor-2; HR, hormone receptor.

TABLE A4. Predicted Probability of 5-Year Survival by Patient Characteristics in Patients Diagnosed With Early-Stage Breast Cancer Between 2005 and 2015

Characteristic	Predicted Probabilities, %	95% CI
Clinical trial representation		
Unrepresented	90	88 to 92
Under-represented	95	94 to 96
Well-represented	96	95 to 97
Subtype		
HER2+	95.5	95 to 96
HR+ HER2−	96	95 to 97
HR− HER2−	93	92 to 94
Age at cancer diagnosis, years		
< 45	97	96 to 98
45-69	95	94 to 96
≥ 70	90	89 to 92
Race or ethnicity		
Black	94	93 to 96
Hispanic or Latino	96	95 to 98
Other race	95	94 to 97
White	95	94 to 96
Any laboratory-based comorbidity		
No	95.6	95 to 96
Yes	90	87 to 92
Concurrent cancer		
No	95	94 to 96
Yes	92	89 to 96

Abbreviations: HER2, human epidermal growth factor receptor-2; HR, hormone receptor.

TABLE A5. Cox Proportional Hazard Model Results Evaluating the Association Between Clinical Trial Representation Status and 10-Year Survival Overall and by Cancer Subtype in Patients Diagnosed With Early-Stage Breast Cancer Between 2005 and 2015 (n = 11,770)

	Overall		HER2+		HR+ HER2−		HR− HER2−	
Representation	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI
Well-represented	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Under-represented	1.16	1.00 to 1.35	1.08	0.76 to 1.54	1.24	1.02 to 1.51	0.97	0.69 to 1.34
Unrepresented	2.45	1.97 to 3.05	2.69	1.68 to 4.33	2.21	1.65 to 2.97	2.39	1.51 to 3.78

NOTE. Overall model: adjusted for stage, regimen intensity, subtype, and year of diagnosis. Stratified model: adjusted for stage, regimen, and year of diagnosis.

Abbreviations: aHR, adjusted hazard ratio; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; ref, reference.

TABLE A6. Cox Proportional Hazard Model Results Evaluating the Association Between Patient Characteristics and 10-Year Survival Overall and by Cancer Subtype in Patients Diagnosed With Early-Stage Breast Cancer Between 2005 and 2015 (n = 11,770)

	Overall		HER2+		HR+ HER2−		HR− HER2−	
Characteristic	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
Race or ethnicity								
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.18	0.98 to 1.42	1.37	0.90 to 2.09	1.00	0.76 to 1.31	1.37	0.98 to 1.92
Hispanic	0.66	0.43 to 1.02	1.27	0.59 to 2.74	0.52	0.29 to 0.96	0.53	0.17 to 1.69
Other races	0.88	0.66 to 1.16	0.61	0.30 to 1.26	0.99	0.71 to 1.40	0.81	0.42 to 1.56
Age, years								
45-69	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
< 45	0.57	0.45 to 0.72	0.35	0.18 to 0.65	0.65	0.48 to 0.87	0.56	0.35 to 0.91
≥ 70	2.58	2.17 to 3.07	2.57	1.75 to 3.78	2.70	2.14 to 3.40	2.17	1.45 to 3.25
Stage								
I	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
II	2.07	1.66 to 2.58	2.48	1.54 to 3.99	1.84	1.36 to 2.50	2.29	1.48 to 3.52
III	3.98	3.14 to 5.03	4.45	2.69 to 7.36	3.51	2.53 to 4.86	4.63	2.87 to 7.47
Any comorbidities								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.45	1.80 to 2.81	2.31	1.31 to 3.50	2.04	1.49 to 2.77	2.80	1.78 to 4.39
Concurrent cancer								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.72	1.16 to 2.57	3.42	1.64 to 7.14	1.52	0.87 to 2.64	0.97	0.36 to 2.63

NOTE. Overall model: adjusted for stage, regimen intensity, subtype, and year of diagnosis. Stratified model: adjusted for stage, regimen, and year of diagnosis.

Abbreviations: aHR, adjusted hazard ratio; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; ref, reference.

TABLE A7. Characteristics of Patients Diagnosed With Early-Stage Breast Cancer Who Received Treatment in 2005-2015 (n = 38,640)

	Race, No. (%)				Age, No. (%)			Any Comorbidities, No. (%)		Concurrent Cancer, No. (%)	
Treatment	**White**	**Black**	**Hispanic**	**Others**	**< 45 Years**	**45-69 Years**	**≥ 70 Years**	**Yes**	**No**	**Yes**	**No**
Regimen of interest (n = 11,770)[a]	8,475 (29)	1,750 (39)	520 (35)	1,025 (27)	2,244 (49)	8,347 (33)	1,179 (13)	684 (27)	11,086 (31)	211 (28)	11,559 (31)
Regimen not of interest (n = 1,807)	1,239 (4)	296 (7)	78 (5)	194 (5)	324 (7)	1,230 (5)	253 (3)	140 (6)	1,667 (5)	120 (16)	1,687 (5)
Hormone therapy only (n = 18,491)	14,425 (50)	1,639 (36)	621 (42)	1,805 (48)	1,180 (26)	11,576 (46)	5,735 (65)	1,202 (48)	17,289 (48)	274 (36)	18,217 (48)
No chemotherapy or hormone therapy (n = 6,572)	4,721 (16)	859 (19)	273 (18)	719 (19)	848 (19)	4,039 (16)	1,685 (19)	471 (19)	6,101 (17)	156 (21)	6,416 (17)

[a]Regimens of interest included the following: (1) a taxane (paclitaxel or docetaxel), carboplatin, and trastuzumab (TCH); (2) doxorubicin and cyclophosphamide followed by a taxane (AC-TH); (3) a taxane, carboplatin, trastuzumab, and pertuzumab (TCHP); (4) doxorubicin, cyclophosphamide, and a taxane (ACT); (5) a taxane and trastuzumab (TH); (6) doxorubicin and cyclophosphamide (AC); and (7) a taxane and cyclophosphamide (TC).