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Race and Risk of Subsequent Aggressive Breast Cancer Following Ductal Carcinoma in Situ

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Abstract

Background—General populations of black women have a higher risk of developing breast cancer negative for both estrogen receptor (ER) and progesterone receptor (PR) compared with white counterparts. It remains unknown about racial differences in risk of developing aggressive invasive breast cancer, characterized by both ER and PR negativity (ER-PR-) or higher 21-gene recurrence scores, following DCIS.

Methods—We identified 163,892 women (10.5% black, 9.8% Asian, and 8.6% Hispanic) with incident DCIS between 1990 and 2015 from the Surveillance, Epidemiology, and End Results datasets. Cox proportional hazards regression was used to estimate relative risks (RRs) of subsequent invasive breast cancer classified by hormone receptor status and 21-gene recurrence scores.

Results—During a median 90-month follow-up, 8,333 women developed invasive breast cancer. Compared with white women, adjusted-RRs of subsequent ER-PR- breast cancer was 1.86 (95% CI 1.57–2.20) in black women (absolute 10-year difference=2.2%) and 1.40 (95% CI 1.14–1.71) in Asian women (absolute 10-year difference=0.4%), which was stronger than the associations for

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ER+ and/or PR+ subtypes ($P_{heterogeneity}$=0.0004). 21-gene recurrence scores of subsequent ER+ early invasive breast cancers varied by race/ethnicity ($P_{heterogeneity}$=0.057); black women were more likely than white women to have a recurrence score of 26 and above (RR=1.38, 95% CI 1.00–1.92). We observed no significant difference in risks of subsequent invasive breast cancer subtypes for Hispanic women.

Conclusions—Black and Asian women with DCIS had higher risks of developing biologically aggressive invasive breast cancer compared with white counterparts. This should be considered in treatment decisions for black and Asian DCIS patients.

Precis for use in the Table of Contents:

Black and Asian women with DCIS had higher risks of developing biologically aggressive invasive breast cancer compared with white counterparts. This should be considered in treatment decisions for black and Asian DCIS patients.

Keywords

Breast cancer; ductal carcinoma in situ; race; recurrence

Ductal carcinoma in situ (DCIS), a non-obligate precursor to invasive breast cancer (IBC)[1], currently comprises 20–30% of mammographically detected breast tumors[2, 3]. Approximately 64,000 new DCIS cases were expected to be diagnosed in the United States in 2018[2]. Although the 10-year survival is higher than 98%[4], more than 10% of DCIS patients develop a second breast tumor within 10 years of diagnosis, and half of these are invasive[3].

We and others have demonstrated a significant variation by race and ethnicity in the risk of developing breast cancer following DCIS. Compared with white women, black women are more likely to have second tumors (invasive and non-invasive) in either breast and die from IBC after DCIS[5–11]. An increased risk of ipsilateral breast tumors has been observed in Hispanic women with DCIS[5, 12], and an increased risk of contralateral breast tumors has been identified in Asian women with DCIS[5].

In addition, our prior studies showed a higher proportion of estrogen receptor (ER)-positive DCIS subtypes in black women than in white women[5, 6]. However, black women with IBC who have no prior history of DCIS are far more likely than white counterparts to present with biologically aggressive features, including lack of ER, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression and high RNA expression-based recurrence scores[13–15]. It remains unknown whether black (compared with white) race is associated with a higher risk of subsequently developing biologically aggressive breast cancer in DCIS patients. In a large racially diverse population of women with DCIS, we examined the risks of subsequent IBC subtypes, characterized by hormone receptor status and 21-gene recurrence scores, by race and ethnicity.

METHODS

Patient Population

Women with unilateral DCIS diagnosed between January 1990 and June 2015 (n=211,439) were identified from the 17 Surveillance, Epidemiology, and End Results (SEER) Registries[12]. The Alaska Native Tumor Registry was excluded due to the small number of Alaskan Native patients. A Data-Use Agreement Form was required prior to access to the de-identified dataset. Since the de-identified data were used, approval from the Institutional Review Board of Washington University in St. Louis and patients' informed consent were not required.

We excluded patients with a prior cancer history (n=41,912) and those under 20 years (n=19). Approximately 97% of eligible cases were white, black, Asian (not including Pacific Islanders), or Hispanic, thus women of other races or unknown race (n=5,616) were excluded if they were non-Hispanic. The final sample size was 163,892. In the analysis of ipsilateral breast cancer, we also excluded patients treated with mastectomy for DCIS and those whose surgical treatment was unknown (n=47,253). Women treated with prophylactic mastectomy at initial DCIS (n=9,638) were also excluded from the analysis of contralateral breast cancer. Race and ethnicity were classified into non-Hispanic white (white), non-Hispanic black (black), non-Hispanic Asian (Asian), and Hispanic. Filipino, Chinese, and Japanese were three largest Asian subgroups and accounted for 63.4% of Asian patients. The majority (95.5%) of Hispanics were white, and thus Hispanic whites and Hispanic non-whites were combined as a single group.

Covariates

Demographic factors included age (20–39, 40–49, 50–59, 60–69, or 70–84 years) and year of DCIS diagnosis (1990–1999, 2000–2009, or 2010–2015), and Registries. Histopathological features of DCIS included tumor size (<2cm, 2–5cm, ≥5cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), and histologic pattern (comedo, papillary, cribriform, solid, or NOS). Tumor size was also categoried using the cutoffs of 1cm and 5cm, and the results were similar (Supplementary Table 1). Consistent with the literature[16], tumors were considered to be ER-positive if the immunohistochemistry results of ER were positive or borderline. PR-positive DCIS was similarly defined. Tumors positive for ER and/or PR were classified as hormone receptor-positive (ER+/PR+), and tumors negative for both ER and PR were classified as hormone receptor-negative (ER-PR-). Treatment for DCIS was categorized as no surgical treatment, breast-conserving surgery (BCS) alone, BCS plus radiation therapy, mastectomy, or unknown.

Outcomes

Subsequent breast cancer included IBC (reported to SEER registries) in either breast or metastatic breast cancer diagnosed at least six months after initial DCIS. Ipsilateral IBCs were further classified to invasive recurrences arising in the same quadrant as the original DCIS and IBCs developing elsewhere in that same breast[17]. Theoretically, the latter has the same incidence and characteristics as IBC developing in the contralateral breast. Thus, IBC

arising in the ipsilateral breast away from the original DCIS and in the contralateral breast were combined. IBC subtypes were similarly defined by both ER and PR. For IBC cases diagnosed between 2004 and 2015, SEER data were linked to 21-gene recurrence score assay results from Genomic Health, Inc (Redwood City, CA) by Information Management Services (IMS, Inc., Calverton, MD, USA)[18]. Recurrence scores of IBC were categorized as "low risk" (scores<18), "intermediate risk" (scores 18–30), and "high risk" (scores≥31)[13–15]. Due to a small number of racial minority patients who had 21-gene recurrence scores, we combined intermediate and high risk scores. A prospective trial (TAILORx) has demonstrated that chemotherapy did not benefit patients with early hormone receptor-positive invasive breast cancer whose 21-gene recurrence scores were less than 26[19]. We also dichotomized recurrence scores using a cutoff of 26.

Statistical Analysis

Baseline characteristics across racial/ethnic groups were compared using the Pearson chi-square tests for categorical variables and the ANOVA for continuous variables. Cox proportional hazards regression was used to compute race-associated hazard ratios (HRs) and 95% confidence intervals (CIs) of subsequent IBC subtypes, adjusted for receptor status in initial DCIS and the aforementioned covariates. Person-years were calculated from six months after initial DCIS until the date of subsequent breast cancer, death, or December 31, 2015, whichever occurred first. Missing ER and PR status of subsequent IBC was considered for censoring. Assumption of proportionality for Cox models was confirmed using scaled Schoenfeld residuals. To determine whether race/ethnicity was differentially associated with IBC subtypes, an extension of the Cox proportional hazards regression models was used to estimate the separate associations of race/ethnicity with the relative hazard of each subtype. Specifically, we used the approach proposed by Lunn and McNeil[20, 21], in which each patient had a separate observation for each type of outcomes and the analysis was stratified on outcome types. The initial full model assumed different associations of race/ethnicity and covariates with IBC subtypes. In a reduced model, race/ethnicity was constrained to have a single estimate across cancer subtypes and the effects of covariates were allowed to be different. Likelihood ratio tests for heterogeneity were used to determine statistically significant differences in the associations of race/ethnicity with cancer subtypes. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). Statistical significance was assessed as two-sided $P<0.05$.

HER2 data were collected for breast cancers diagnosed after 2009. A secondary analysis was performed to compare the risks of subsequent IBC classified by ER, PR, and HER2. Subsequent breast cancers occurring before 2010 were analyzed as censoring.

RESULTS

Among 163,892 women with DCIS, 71.0% were non-Hispanic white, 10.5% were non-Hispanic black, 9.8% were non-Hispanic Asian, and 8.6% were Hispanic. Compared with white women, racial/ethnic minority women were younger at initial DCIS and were more likely to have large, well-to-moderately differentiated, and noncomedo lesions (each $P<0.0001$; Table 1). Black and Asian women underwent mastectomy more frequently than

white and Hispanic women (P<0.0001). ER and PR status in initial DCIS were available for 60.3% and 56.8% of cases, respectively. The frequency of ER-PR- DCIS was lower in the black group (11.4%) than in other racial groups (White: 14.2%; Asian: 13.8%; Hispanic: 13.4%; P<0.0001; Table 1).

During a median follow-up of 90 months, 8,333 women developed IBC in either breast or metastatic breast cancer, of which 7,746 (93.0%) had ER and/or PR status available for their IBC. Compared with white women, the overall risk of subsequent IBC was significantly increased in black women (HR=1.42, 95% CI 1.32–1.52; absolute 10-year risk difference=2.2%, 95% CI 1.7%−2.7%), but not in Asian (HR=1.08, 95% CI 0.99–1.17; absolute 10-year risk difference=0.4%, 95% CI (−0.1%) - 0.8%) and Hispanic (HR=1.09, 95% CI 1.00–1.18; absolute 10-year risk difference=0.5%, 95% CI 0%−1.0%) women. The associations were much stronger for ER-PR- subtypes than ER+/PR+ subtypes ($P_{heterogeneity}$=0.0004; Table 2). Compared with White women, the multivariable-adjusted HR of ER-PR- IBC was 1.86 (95% CI 1.57–2.20) in black women, 1.40 (95% CI 1.14–1.71) in Asian women, and 1.24 (95% CI 1.00–1.54) in Hispanic women. Black women also had a significantly higher risk of subsequent triple-negative (negative for ER, PR, and HER2) breast cancer (HR=1.99, 95% CI 1.44–2.75) and Asian women had a significantly higher risk of subsequent HER2+ breast cancer (HR=1.85, 95% CI 1.21–2.84) (Supplementary Table 2).

We further examined the risks separately for ipsilateral and contralateral IBC by race/ethnicity (Table 2). Compared with white women, the risk of ipsilateral IBC was significantly higher in black (HR=1.65, 95% CI 1.49–1.83; absolute 10-year risk difference=2.1%, 95% CI 1.6%−2.6%), Asian (HR=1.23, 95% CI 1.09–1.38; absolute 10-year risk difference=0.7%, 95% CI 0.3%−1.2%), and Hispanic (HR=1.19, 95% CI 1.05–1.35; absolute 10-year risk difference=0.6%, 95 CI 0.2%−1.1%) women. There was no significant heterogeneity in the associations for risks of ipsilateral cancer subtypes ($P_{heterogeneity}$=0.57; Table 2). The multivariable-adjusted HR of ipsilateral ER-PR- subtypes was 1.83 (95% CI 1.43–2.35) in black women, 1.34 (95% CI 0.99–1.81) in Asian women, and 1.40 (95% CI 1.05–1.87) in Hispanic women.

Compared with white women, the risk of contralateral IBC was significantly increased in black women (HR=1.18, 95% CI 1.07–1.31; absolute 10-year risk difference=0.6%, 95% CI 0.2%−0.9%). This association was much stronger for ER-PR- subtypes (HR=1.97, 95% CI 1.55–2.52) than ER+/PR+ subtypes (HR=1.07, 95% CI 0.95–1.20; $P_{heterogeneity}$<.0001). Although the risk of overall contralateral IBC was similar between Asian and white women (HR=0.97, 95% CI 0.86–1.10; absolute 10-year risk difference=0.1%, 95% CI (−0.4%) - 0.3%), Asian women had a significantly higher risk of ER-PR- subtypes (HR=1.61, 95% CI 1.20–2.16). The risks of overall contralateral breast cancer and subtypes were all comparable between Hispanic and white women.

Subsequent breast cancers were also categorized based on both laterality and locations of original DCIS and subsequent IBC (Table 3). Among 3,010 cases with known locations for both original DCIS and subsequent ipsilateral IBC, 21.4% developed IBC in the same quadrant of the same breast as the original DCIS. Compared with white women, black

women had significantly higher risks of developing IBC in the same quadrant of the same breast as the original DCIS (HR=1.51, 95% CI 1.18–1.93; absolute 10-year risk difference=0.3%, 95% CI 0.1%−0.5%) and IBC in the ipsilateral breast away from the original DCIS and in the contralateral breast (HR=1.34, 95% CI 1.24–1.45; absolute 10-year risk difference=1.5%, 95% CI 1.1%−2.0%). The increased risk of IBC in the ipsilateral breast away from the original DCIS and in the contralateral breast was much stronger for ER-PR- subtypes (HR=1.93, 95% CI 1.60–2.40) than for ER+/PR+ subtypes (ER+/PR+: HR=1.24, 95% CI 1.13–1.36) in black women ($P_{heterogeneity}<.0001$). Compared with white women, the risk was significantly increased for ER-PR- IBC developing in the ipsilateral breast away from the original DCIS and in the contralateral breast in Asian women (HR=1.45, 95% CI 1.15–1.82), but not for ER+/PR+ subtypes (HR=0.99, 95% CI 0.89–1.10). There was no significant difference in the risk of developing IBC in the same quadrant of the same breast as the original DCIS, in the different quadrant of the same breast, or in the contralateral breast between Hispanic and white women.

Among 5,045 DCIS patients who subsequently developed ER+, early stage (I, II, and IIIa) IBC between 2004 and 2015, 1,184 (23.5%) had 21-gene recurrence scores. There was no significant racial difference in the use of 21-gene assays (Supplementary Table 3). Recurrence scores varied by race/ethnicity ($P_{heterogeneity}$=0.046–0.057; Table 4). Compared with white women, the risk of subsequent ER+ IBC with a recurrence score of 26 or higher was increased in black women (HR=1.38, 95% CI 1.00–1.92). Using the developed cutoffs for intermediate and high recurrence risk, we observed a similar result for black women (HR=1.29, 95% CI 1.00–1.67). There was no significant difference in Asian and Hispanic compared to white women in the risk of developing aggressive ER+ IBC defined by recurrence scores.

DISCUSSION

Our prior analysis of the 1990–2009 SEER data demonstrated a significantly higher risk of subsequently developing IBC in black women with DCIS than in white counterparts[5]. Using immunohistochemically assessed tissue markers and 21-gene recurrence scores, the current study extends this finding to biologically aggressive IBC in a population-based racially diverse group of DCIS patients. Compared with white women, black women had a higher risk of developing IBC, characterized by ER-PR- subtypes and higher recurrence scores in ER+ tumors, following DCIS. This is consistent with the higher risk of developing ER-PR- IBC in the general population of black women[13, 22, 23]. Asian women were more likely than white women to develop ER-PR- IBC. To our knowledge, this is the only study to date examining racial differences in subsequent IBC subtypes following DCIS.

Our finding of higher risk of developing aggressive breast cancer in black women with DCIS compared to white counterparts may have clinical relevance. Black women with DCIS are more likely than White counterparts to die from breast cancer[11]. In the setting of IBC, basal-like tumors disproportionately affect African American women[13, 22, 23]. Basal-like tumors overlap largely with triple-negative tumors that have poor prognosis. Most (73%) of ER-PR- breast cancers are negative for HER2[16]. We observed that the risk of triple-negative breast cancer was nearly doubled following DCIS in black compared with white women.

Therefore, a higher risk of developing ER-PR- IBC in black women with DCIS may contribute to their worse survival.

Two distinct types of ipsilateral breast cancer recurrence have been proposed: true local recurrences and new ipsilateral primary tumors[17, 24, 25]. They are generally distinguished from each other based on both histopathology and location[17, 26, 27]. True recurrence has similar histopathology to primary tumors and is close to the primary tumor bed. True recurrence may reflect regrowth of clonogenic cells that have not been completely removed by local treatment. New primary IBCs are independent of the original breast cancer and have different clinical features and prognosis from true recurrence[17, 26, 27]. Development of new primary IBC has been considered a result of genetic predisposition to breast cancer and associated with higher occurrences of contralateral IBC[28]. We observed that the risk of developing IBC in the ipsilateral breast away from the original DCIS and contralateral breasts, particularly hormone receptor-negative subtypes, was significantly increased in black women. This indicates underlying genetic susceptibility to breast cancer, early-life behavioral exposures, and/or their interactions in black women. Prior studies demonstrated that patients with true local recurrence had worse survival than those with new ipsilateral primary IBC[26, 27]. Our finding of higher risk of developing ipsilateral IBC in the same quadrant of breast in black patients may contribute to their worse survival. Molecular assays (e.g., loss of heterozygosity) are more reliable approaches to show clonal relationships between original tumors and ipsilateral IBCs and to distinguish genetically related recurrence from genetically distinct new primaries[24, 25]. Racial differences in the distinct types of ipsilateral IBC need to be confirmed using molecular methods.

The 21-gene recurrence score is an RT-PCR based assay that is currently applied to early ER-positive IBC to assess prognosis and likely benefit from chemotherapy in addition to endocrine therapy[29]. Using the TAILORx defined cutoff value of 26[19], we observed that black DCIS patients were more likely than white counterparts to subsequently develop aggressive ER+ IBC. Using commonly used definitions of intermediate (18–30) and high (≥31) recurrence risks generated a similar result. This finding was consistent with the racial difference in RNA expression-based recurrence scores reported for first primary IBC[13–15]. A recent analysis of TAILORx trial data (including 8189 whites, 693 blacks, 405 Asians, and 432 others) showed a similar distribution of recurrence scores across race groups in patients with early hormone receptor-positive, HER2-negative invasive breast cancer (having no prior diagnosis of DCIS), and worse survival in black patients[30]. Our finding needs to be confirmed in future studies with a larger number of black DCIS patients who had 21-gene assay results for subsequent invasive breast cancer.

Biological differences (other than intrinsic subtypes) between IBC in black women and in white women have been identified. In a comprehensive analysis of genomic, transcriptomic, and proteomic data from the Cancer Genome Atlas, Huo et al[31] found that a number of molecular features differed between black and white IBCs after adjusting for age and subtypes, including DNA copy number, gene expression, and DNA methylation. Gene expression profiling of luminal A and basal-like IBCs identified six genes that were differentially expressed between black and white patients and were also associated with survival[32]. In that study, some poor outcome-associated genes were up-regulated in cancer-

adjacent normal breast tissue from black women versus white women. Our data are consistent with the idea that black women exhibit genetic profiles in nascent tumor cells and/or surrounding normal cells that creates a race-associated biological difference. This race-associated genetic difference may occur at the earliest stages of carcinogenesis.

We observed a higher risk of developing ER-PR- IBC in Asian women with DCIS than in white counterparts. The clinical relevance of this finding remains to be determined because there was no survival differences between Asians and whites in DCIS patients from the SEER[11]. Within Asian-American women with first primary IBC, distributions of ER-PR- subtypes have been reported to vary across ethnic groups with the highest frequency in South Asians and the lowest frequency in Japanese and Chinese[33, 34]. The number of Asian DCIS patients with subsequent IBC did not allow us to examine ethnic differences within Asian women.

This study has limitations. Some variables influencing DCIS outcomes (e.g., surgical margins and endocrine therapy) were unavailable. Prior studies reported no racial difference in surgical margins or endocrine therapy in DCIS patients[6, 9, 35, 36]. Of those who initiated endocrine therapy, blacks were more likely than whites to be nonadherent to therapy and Asians were more likely to continue therapy[37]. Obesity and alcohol consumption have been associated with increased risk of subsequent breast cancer in DCIS patients[38, 39]. We were unable to assess their contributions to racial differences in DCIS outcomes. The duration of follow-up was longer in white patients than in racial minority patients. However, exclusion of patients diagnosed after 2010 did not significantly change the race-associated risks (Supplementary Table 4). Approximately 40% of DCIS cases had no hormone receptor data, and missing indicators were used in the analysis. This approach has been demonstrated to have no significant impacts on the estimated associations between exposures and cancer outcomes when missingness is less than 50%[40]. The finding of a race-associated higher risk of ER-PR- IBC in all eligible patients was consistent with a race-associated higher risk of changing hormone receptor positive to negative status observed in a subgroup of patients who had complete hormone receptor data in both DCIS and subsequent IBC (Supplementary Table 5). 21-gene recurrence scores were available for only 24% of DCIS patients who subsequently developed early ER-positive IBC. Among women with IBC who had no history of DCIS, black race has been associated with underutilization of 21-gene assays and higher recurrence scores[14, 15]. Therefore, higher risk of recurrence score-defined aggressive IBC in black women with DCIS may reflect racial differences in testing. However, there was no significant racial difference in 21-gene testing in our sample.

Overall, we provide evidence for a higher risks of subsequently developing aggressive IBC in black and Asian DCIS patients compared with white counterparts. This gives a better understanding of racial influences on the risk of IBC following diagnosis of DCIS and should be considered in the management of DCIS. While the molecular and genetic features underlying this higher risk remain undiscovered, we have now specified the biological context to study these inherent racial differences. Future work will assess its contribution to poorer survival in black women with DCIS. Better understanding of race-associated biological and non-biological differences in the progression of DCIS will help distinguish

high-risk from low-risk DCIS patients and improve personalized treatment to reduce the disproportionate burden of breast cancer in black women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Age and age-standardized characteristics of women with unilateral ductal carcinoma in situ (DCIS) in the SEER by race and ethnicity[†] (n=163,892), 1990 to 2015.

	White	Black	Asian	Hispanic	*p*[‡]
Number of cases	116431	17274	16039	14148	
Age at diagnosis, %					
Mean (SD)	59.5 (12.4)	58.3 (12.2)	56.4 (11.7)	56.2 (11.8)	<.0001
20–39	3.1	4.4	4.5	4.8	
40–49	20.9	21.5	27.5	28.1	
50–59	27.8	29.2	30.0	29.9	
60–69	24.9	25.5	22.8	21.9	
≥70	23.3	19.5	15.2	15.3	<.0001
Length of follow-up, %					
Median (range), months	95 (6–311)	79 (6–311)	83 (6–311)	75 (6–311)	<.0001
6–11 months	3.3	4.8	5.0	5.9	
12–59 months	27.0	33.8	32.0	35.1	
60–119 months	31.3	32.5	30.9	31.9	
≥120 months	38.4	28.8	32.1	27.2	<.0001
Year of the first DCIS diagnosis, %					
1990–1999	17.0	12.7	14.3	10.1	
2000–2009	53.3	49.9	48.3	49.3	
2010–2015	29.7	37.4	37.5	40.6	<.0001
Histological subtype, %					
Not otherwise specified	66.9	68.4	67.5	68.3	
Comedo	13.5	11.4	11.8	11.6	
Papillary	5.2	7.0	5.0	5.4	
Cribriform	8.5	8.2	10.0	9.4	
Solid	5.9	5.0	5.8	5.3	<.0001
Grade[§], %					
Well differentiated	13.7	16.6	14.1	14.3	
Moderately differentiated	40.0	43.3	43.3	43.6	
Poorly differentiated	46.3	40.1	42.6	42.1	<.0001
Tumor size[¶], %					
<2.0 cm	75.3	69.9	69.2	70.0	
2.0–4.9 cm	19.2	21.8	24.9	22.8	
≥5.0 cm	5.5	8.3	5.9	7.2	<.0001
Estrogen receptor[††], %					
Negative	15.9	12.9	15.5	14.9	
Positive	84.1	87.1	84.5	85.1	<.0001
Progesterone receptor[‡‡], %					
Negative	26.1	21.9	23.9	24.7	

	White	Black	Asian	Hispanic	$P^{\ddagger}$
Positive	73.9	78.1	76.1	75.3	<.0001
Hormone receptor status[§§], %					
ER- and PR-	14.2	11.4	13.8	13.4	
ER+ or PR+	85.8	88.6	86.2	86.6	<.0001
Treatment for primary DCIS[¶¶], %					
No surgery	2.2	3.4	2.1	3.0	
BCS alone	24.7	23.4	23.0	26.2	
BCS and radiation	44.3	43.6	44.0	43.7	
Mastectomy	28.9	29.5	31.0	27.1	<.0001

Abbreviations: SD, standard deviation; BCS, breast-conserving surgery; ER, estrogen receptor; PR, progesterone receptor.

Supplementary table 6 shows distributions of missing values for each variable across race groups.

[†]Race and ethnicity were classified into mutually exclusive categories of non-Hispanic White (hereafter referred to as white), non-Hispanic Black (black), non-Hispanic Asian (Asian), and Hispanic (Hispanic).

[‡]*P* values were calculated from a comparison across all groups except the groups with missing values.

Table 2.

Adjusted hazard ratios of subsequent invasive breast cancer classified by laterality and hormone receptor status according to race and ethnicity in women with DCIS in the SEER, 1990 to 2015

	Person-years	All second invasive events[†]		ER+ or PR+		ER- and PR-	
		Cases	HR[††] (95% CI)	Cases	HR[††] (95% CI)	Cases	HR[††] (95% CI)
Subsequent invasive breast cancer[‡]							
White	1018475	5884	1.00	4653	1.00	821	1.00
Black	129931	1002	1.42 (1.32, 1.52)	720	1.31 (1.21, 1.43)	190	1.86 (1.57, 2.20)
Asian	128657	807	1.08 (0.99, 1.17)	620	1.01 (0.92, 1.11)	135	1.40 (1.14, 1.71)
Hispanic	102614	640	1.09 (1.00, 1.18)	505	1.09 (0.99, 1.20)	102	1.24 (1.00, 1.54)
							$P_{heterogeneity}$=0.0004
Ipsilateral invasive breast cancer[§]							
White	709275	2438	1.00	1846	1.00	393	1.00
Black	89081	478	1.65 (1.49, 1.83)	341	1.58 (1.40, 1.78)	86	1.83 (1.43, 2.35)
Asian	86294	378	1.23 (1.09, 1.38)	286	1.19 (1.03, 1.36)	61	1.34 (0.99, 1.81)
Hispanic	72785	309	1.19 (1.05, 1.35)	235	1.20 (1.04, 1.38)	59	1.40 (1.05, 1.87)
							$P_{heterogeneity}$=0.57
Contralateral invasive breast cancer[¶]							
White	971003	3134	1.00	2556	1.00	363	1.00
Black	126291	446	1.18 (1.07, 1.31)	322	1.07 (0.95, 1.20)	92	1.97 (1.55, 2.52)
Asian	125104	396	0.97 (0.86, 1.10)	306	0.89 (0.78, 1.02)	68	1.61 (1.20, 2.16)
Hispanic	98900	292	0.98 (0.87, 1.11)	234	0.97 (0.84, 1.11)	38	1.13 (0.80, 1.60)
							$P_{heterogeneity}$<.0001

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; 95% CI, 95% confidence interval.

[†]Second invasive breast cancer included those positive for ER or PR (ER+ or PR+), those negative for both ER and PR (ER-PR-), and those with no information on ER and PR.

[‡]Subsequent invasive breast cancer included ipsilateral invasive breast cancer, contralateral invasive breast cancer, and subsequent metastatic breast cancer.

[§]The analysis included the patients who had been treated with breast-conserving surgery or no surgical treatment for their primary DCIS.

[¶]Patients who had received bilateral mastectomy for their primary DCIS were excluded.

[††]Relative risks were adjusted for age (20–39, 40–49, 50–59, 60–69, or ≥70 years) and year of the primary DCIS diagnosis (1990–1999, 2000–2009, or 2010–2015), registry, treatment for primary DCIS (no surgical treatment, breast-conserving surgery alone, breast-conserving surgery followed by radiation therapy, mastectomy, or unknown), histopathological features of primary DCIS including tumor size (<2 cm, 2–5 cm, ≥5 cm or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), histology (comedo, papillary, cribriform, solid, or NOS), and hormone receptor expression (positive, negative, or unknown).

Table 3.

Adjusted hazard ratios of developing invasive breast cancer in the same quadrant of the same breast as the original DCIS and invasive breast cancer in the ipsilateral breast away from the original DCIS or contralateral breast according to race and ethnicity in women with DCIS in the SEER, 1990 to 2015

	Person-years	All second invasive events[†]		ER+ or PR+		ER- and PR-	
		Cases	HR[‡] (95% CI)	Cases	HR[‡] (95% CI)	Cases	HR[‡] (95% CI)
Invasive breast cancer in the ipsilateral breast away from the original DCIS and in the contralateral breast.							
White	971003	4741	1.00	3776	1.00	630	1.00
Black	126291	755	1.34 (1.24, 1.45)	547	1.24 (1.13, 1.36)	149	1.93 (1.60, 2.40)
Asian	125104	648	1.06 (0.97, 1.17)	497	0.99 (0.89, 1.10)	107	1.45 (1.15, 1.82)
Hispanic	98900	489	1.05 (0.95, 1.16)	388	1.05 (0.94, 1.17)	71	1.14 (0.88, 1.47)
							$P_{heterogeneity}$<.0001
Invasive breast cancer in the same quadrant of the same breast as the original DCIS							
White	709275	431	1.00	327	1.00	62	1.00
Black	89081	83	1.51 (1.18, 1.93)	63	1.47 (1.10, 1.95)	11	1.48 (0.75, 2.90)
Asian	86294	71	1.15 (0.87, 1.52)	55	1.16 (0.84, 1.59)	13	1.49 (0.75, 2.98)
Hispanic	72785	60	1.16 (0.88, 1.54)	47	1.22 (0.89, 1.67)	12	1.63 (0.85, 3.13)
							$P_{heterogeneity}$=0.80

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

[†]Second invasive breast cancer included those positive for ER or PR (ER+ or PR+), those negative for both ER and PR (ER-PR-), and those with no information on ER and PR.

[‡]Relative risks were adjusted for age (20–39, 40–49, 50–59, 60–69, or ≥70 years) and year of the primary DCIS diagnosis (1990–1999, 2000–2009, or 2010–2015), registry, treatment for primary DCIS (no surgical treatment, breast-conserving surgery alone, breast-conserving surgery followed by radiation therapy, mastectomy, or unknown), histopathological features of primary DCIS including tumor size (<2 cm, 2–5 cm, ≥5 cm or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), histology (comedo, papillary, cribriform, solid, or NOS), and hormone receptor expression (positive, negative, or unknown).

Table 4.

Multivariable-adjusted hazard ratios of higher levels of 21-gene recurrence scores of hormone receptor-positive early invasive breast cancer among women with DCIS in the SEER, 1990 to 2015.

	Person-years	Recurrence scores							
		<18		≥18		<26		≥26	
		Cases	HR† (95% CI)	Cases	HR† (95% CI)	Cases	HR† (95% CI)	Cases	HR† (95% CI)
White	1018475	421	1.00	421	1.00	602	1.00	240	1.00
Black	129931	58	1.11 (0.84, 1.46)	68	1.29 (1.00, 1.67)	84	1.13 (0.90, 1.42)	42	1.38 (1.00, 1.92)
Asian	128657	77	1.37 (1.07, 1.75)	57	0.97 (0.73, 1.28)	97	1.19 (0.96, 1.48)	37	1.11 (0.78, 1.57)
Hispanic	102614	50	1.17 (0.87, 1.57)	32	0.71 (0.50, 1.02)	64	1.03 (0.80, 1.34)	18	0.71 (0.44, 1.14)
		$P_{heterogeneity}$=0.046				$P_{heterogeneity}$=0.057			

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

†Relative risks were adjusted for age (20–39, 40–49, 50–59, 60–69, or ≥70 years) and year (1990–1999, 2000–2009, or 2010–2015) of the primary DCIS diagnosis, treatment for primary DCIS (no surgical treatment, breast-conserving surgery alone, breast-conserving surgery followed by radiation therapy, mastectomy, or unknown), histopathological features of primary DCIS including tumor size (<2 cm, 2–5 cm, ≥5 cm or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), histology (comedo, papillary, cribriform, solid, or NOS), and hormone receptor expression (positive, negative, or unknown)