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## Racial disparities in risk of second breast tumors after ductal carcinoma in situ

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### Abstract

The purpose of the study was to examine the impact of race/ethnicity on second breast tumors among women with ductal carcinoma in situ (DCIS). We identified 102,489 women diagnosed with primary DCIS between 1988 and 2009 from the 18 NCI-SEER Registries. Cox proportional hazard regression was used to estimate race/ethnicity-associated relative risks (RRs) and their 95 % confidence intervals (CI) of ipsilateral breast tumors (IBT; defined as DCIS or invasive carcinoma in the ipsilateral breast) and contralateral breast tumors (CBT; defined as DCIS or invasive carcinoma in the contralateral breast). Overall, 2,925 women had IBT and 3,723 had CBT. Compared with white women, black (RR 1.46; 95 % CI 1.29–1.65), and Hispanic (RR 1.18; 95 % CI 1.03–1.36) women had higher IBT risk, which was similar for invasive IBT and

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**Conflict of interest**

None.

ipsilateral DCIS. A significant increase in IBT risk among black women persisted, regardless of age at diagnosis, treatment, tumor grade, tumor size, and histology. The CBT risk was significantly increased among black (RR 1.21; 95 % CI 1.08–1.36) and Asian/PI (RR 1.16; 95 % CI 1.02–1.31) women compared with white women. The association was stronger for invasive CBT among black women and for contralateral DCIS among Asian/PI women ( $P_{\text{heterogeneity}} < 0.0001$ ). The black race-associated CBT risk was more pronounced among women  $\geq 50$  years at diagnosis and those with comedo DCIS; in contrast, a significant increase in risk among Asian/PI women was restricted to those  $< 50$  years and those with noncomedo DCIS. Racial/ethnic differences in risks of second breast tumors after DCIS could not be explained by pathologic features and treatment.

## Keywords

Ductal carcinoma in situ; Breast cancer; Race; Second breast tumors

The diagnosis of ductal carcinoma in situ (DCIS) has increased considerably since the 1980s, largely due to widespread use of screening mammography [1]. Approximately, 45,900 new DCIS cases were diagnosed in the United States in 2010 [2]; the age-adjusted incidence was 32 per 100,000 persons in white women and 21–30 per 100,000 persons in nonwhite women [3]. Although 10-year breast cancer mortality is less than 2 % [4], 10–24 % of DCIS patients experience second breast tumors 10 or more years after treatment [5]. Black women with invasive breast cancer are more likely than their white counterparts to present with more aggressive pathologic features and have higher breast cancer-specific mortality [6–8]. However, the impact of race/ethnicity on DCIS outcomes has not been well defined. Only a few population-based [9–12] and small institution-based studies [13–17] have compared DCIS outcomes between black and white women. The information on DCIS outcomes in women of other races is sparser [9–11, 13, 15].

Prior analyses of the Surveillance, Epidemiology, and End Results (SEER) data through 2001 that were adjusted for demographic factors and treatment reported statistically significant differences in ipsilateral and contralateral invasive breast cancers in racial/ethnic minority groups [9, 11]. There was no significant difference in risk of second breast tumors after adjustment for histopathologic factors by race/ethnicity [13, 16, 18]. However, these studies had limited power to detect racial/ethnic differences in outcomes due to small numbers of minority patients and few second breast events.

Therefore, we examined racial disparities in second breast tumors in a large cohort of women with DCIS diagnosed between 1988 and 2009 in the 18 SEER registries, controlling for age at diagnosis, treatment patterns, and histopathologic features. Further, we assessed effect modification of patient and tumor characteristics on this relationship.

## Methods

### Patient population

From the SEER 18 Registries Database (November 2011 submission), we identified women diagnosed with primary unilateral DCIS [11] between January 1988 and June 2009 with no

cancer history who were followed through December 31, 2009 ( $n = 109,938$ ); these registries cover approximately 28 % of the population. De-identified SEER data were used, exempting the study from review by our Institutional Review Board. We excluded patients younger than 20 years or older than 84 years ( $n = 1,949$ ) and those with bilateral mastectomy ( $n = 4,263$ ). White, black, and Asian/Pacific Islander women comprised 98.7 % of eligible cases, therefore, women of other races or unknown race ( $n = 1,237$ ) were excluded if they were non-Hispanic. Thus, 102,489 women with DCIS were included in the analysis. Since women undergoing mastectomy experience extremely low risk of ipsilateral breast tumors (IBTs) [5], we excluded 27,680 women treated with mastectomy for their first DCIS and thus included 74,809 in the analysis of IBTs.

Race/ethnicity was classified into mutually exclusive categories of non-Hispanic white (hereafter referred to as white), non-Hispanic black (black), non-Hispanic Asian/Pacific Islander (Asian/PI), and Hispanic. Whites accounted for 95.8 % of Hispanics. Since the exclusion of Hispanic nonwhites and Pacific Islanders did not significantly influence the result, we combined all Hispanics as a single group and non-Hispanic Asians and Pacific Islanders as a single group.

## Outcomes

Second primary breast tumor was defined as an invasive breast cancer (including all histologic types) or DCIS diagnosed at least 6 months after the first DCIS. The outcomes included IBTs (defined as local recurrence of DCIS or invasive carcinoma in the ipsilateral breast), invasive IBTs, ipsilateral DCIS, contralateral breast tumors (CBTs; defined as DCIS or invasive carcinoma in the contralateral breast), invasive CBTs, and contralateral DCIS. Person-years were calculated from 6 months after the first DCIS until the date of second primary breast tumors, death, or December 31, 2009, whichever occurred first.

## Statistical analysis

The  $\chi^2$  test and analysis of variance were used, respectively, to compare baseline categorical and continuous variables across racial/ethnic groups. Kaplan–Meier estimates of 5-year probabilities of IBTs and CBTs were calculated for each group, with  $P$  values given by the log-rank test. We used Cox proportional hazards models to compute race-associated relative risk (RR) and 95 % confidence interval (CI). Assumption of proportionality for Cox models were confirmed using scaled Schoenfeld residuals. The models were controlled for age (20–39, 40–49, 50–59, 60–69, or 70–84 years) and year of the first DCIS diagnosis (1988–1989, 1990–1994, 1995–1999, 2000–2004, or 2005–2009), registry, treatment for the first DCIS (no surgical treatment, breast-conserving surgery (BCS) alone, BCS plus radiotherapy, mastectomy, or unknown) and histopathological features including tumor size (<2 cm, 2–5 cm, 5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), and histology (comedo, papillary, cribriform, solid, or NOS). The analyses were stratified by age at diagnosis of the first DCIS, treatment, and histopathologic features. Interactions between race/ethnicity and characteristics of DCIS were assessed by entering cross-product terms in multivariable-adjusted models. The statistical significance of an interaction term was evaluated by the likelihood ratio test. To determine whether race/ethnicity is differentially associated with types of second breast

tumors (invasive cancer vs DCIS), the Cox proportional hazards model was used with types of second breast tumors treated as competing risks [19]. Specifically, we estimated RRs of different types of second breast tumors using the approach described by Lunn and McNeil [20, 21] and used the likelihood ratio test for heterogeneity. All statistical analyses were performed by SAS (version 9.3; SAS Institute, Cary, NC). Statistical significance was assessed as two-sided  $P < 0.05$ .

## Results

Among 102,489 women with DCIS, 75,431 (73.6 %) were white, 9,921 (9.7 %) were black, 9,246 (9.0 %) were Asian/PI, and 7,891 (7.7 %) were Hispanic. Mean age was 58.5 years (range 20–84). Most (88.7 %) were diagnosed after 1995. The patient population was characterized pathologically by 45.5 % with poorly differentiated tumors, 22.9 % with tumors  $\leq 2$  cm, and 14.7 % with comedocarcinoma. Information on estrogen receptor (ER) status was available for 41.6 % patients, of which 77.8 % were reported after 2003 and 82.0 % were positive. Overall, 2.2 % of patients received no surgical treatment for their first DCIS, 27.5 % were treated with mastectomy, 26.5 % received BCS alone, and 43.8 % received BCS and radiotherapy.

Compared with white women, racial/ethnic minority women were significantly younger at the diagnosis of first DCIS and were more likely to have large, well or moderately differentiated, and noncomedo lesions (each  $P < 0.0001$ ) (Table 1). ER positivity was reported in 85.0 % of black women with available ER data, which was significantly higher than the other racial/ethnic groups (white 81.6 %, Asian/PI 81.7 %, and Hispanic 81.9 %;  $P < 0.0001$ ). A larger proportion of black and Asian/PI patients underwent mastectomy for their first DCIS ( $P < 0.0001$ ). Among 72,232 patients treated with BCS, radiotherapy was received more often in Asian/PI patients (64.8 %) than other racial/ethnic groups (white 62.3 %, black 61.9 %, and Hispanic 60.4 %;  $P < 0.0001$ ).

## IBTs

Among 74,809 women treated with BCS or with no surgical treatment, 2,925 (3.9 %) experienced IBTs during a median follow-up of 66 months (range 6–263). Of these IBTs, 824 (28.2 %) were DCIS and 2,101 (71.8 %) were invasive cancer. There was a statistically significant difference in the cumulative incidence of IBTs by race/ethnicity; the 5-year rate was 3.3 % in blacks and 3.1 % in Hispanics compared to 2.5 % in whites and 2.8 % in Asians/Pis (Fig. 1a,  $P < 0.0001$ ).

The multivariable-adjusted analysis showed that black (RR 1.46; 95 % CI 1.29–1.65) and Hispanic women (RR 1.18; 95 % CI 1.03–1.36) had significantly higher IBT risk compared with white women. There was no significant difference in risk between white and Asian/PI (Table 2) or individual Asian groups (Supplement Table 1). We restricted the analysis to 32,016 women (white 24,587, black 2,841, Asian/PI 2,373, and Hispanic 2,215) with available ER data. The RR was 1.29 (95 % CI 1.00–1.68;  $P = 0.06$ ) for blacks, 1.27 (95 % CI 0.93–1.74) for Asians/Pis, and 1.25 (95 % CI 0.94–1.65) for Hispanics.

We determined whether race/ethnicity is differentially associated with types of IBTs (Table 2). Among black women, the RR was 1.48 (95 % CI 1.18–1.86) for ipsilateral DCIS and 1.45 (95 % CI 1.25–1.67) for invasive IBT. Hispanic ethnicity was associated with ipsilateral DCIS (RR 1.33; 95 % CI 1.02–1.72), but not with invasive IBT (RR 1.13; 95 % CI 0.96–1.34). However, this difference was not statistically significant.

We further analyzed the impact of race/ethnicity on IBTs according to pathologic features and treatment for the first DCIS (Table 3). The risk was significantly and consistently increased among black compared to white women treated with BCS, regardless of age at diagnosis, receipt of radiotherapy, tumor grade, size, and architectural patterns. There was no statistically significant difference in the risk associated with Hispanic ethnicity according to tumor characteristics and treatment.

### CBTs

A total of 3,723 (3.6 %) patients developed CBTs among 102,489 patients with a median follow-up of 70 months (range 6–263), of which 1,145 (30.8 %) were DCIS and 2,578 (69.2 %) were invasive cancer. A statistically significant difference in the incidence of CBTs was observed across races/ethnicities, with a 5-year rate of 2.7 % in whites and blacks, 3.2 % in Asians/PIs, and 2.1 % in Hispanics (Fig. 1b,  $P < 0.001$ ).

The multivariable-adjusted CBT risk was significantly increased among black (RR 1.21; 95 % CI 1.08–1.36) and Asian/PI, especially Filipino (Supplement Table 2), women (RR 1.16; 95 % CI 1.02–1.31) compared to their white counterparts. This association depended on types of CBTs ( $P_{\text{heterogeneity}} < 0.0001$ ). The elevated risk among blacks was stronger for invasive CBT (RR 1.25; 95 % CI 1.09–1.43) than contralateral DCIS (RR 1.12; 95 % CI 0.91–1.39). In contrast, Asian/PI patients had significantly higher risk for contralateral DCIS (RR 1.59; 95 % CI 1.30–1.95) but not for invasive CBT (RR 0.96; 95 % CI 0.82–1.13) (Table 4).

Racial differences in CBTs varied by age ( $P_{\text{interaction}} = 0.01$ ) and architectural patterns of first DCIS ( $P_{\text{interaction}} = 0.049$ ) (Table 5). The black race-associated risk was much higher among women  $\geq 50$  years at diagnosis of first DCIS and those with comedo DCIS. Among Asian/PI women, a statistically significant increase in risk was found among those  $< 50$  years at diagnosis and those with noncomedo DCIS.

### Discussion

This large, multiethnic cohort of women with DCIS allowed adequately powered detection of racial/ethnic disparities in second breast tumors according to types of second breast events and characteristics of the first DCIS. The risk for second breast tumors was significantly and consistently increased in black compared to white women, regardless of whether the outcome was ipsilateral DCIS or subsequent invasive cancer in the ipsilateral or contralateral breast. More importantly, the significantly elevated IBT risk in blacks persisted despite the presence of established prognostic factors (e.g., younger age at diagnosis, aggressive pathology). The black race-associated increase in CBT risk was more obvious among women  $\geq 50$  years at diagnosis and those with comedo DCIS. Compared with white

women, Hispanic women were more likely to experience IBTs and Asian/PI women were more likely to develop CBT, particularly presented as DCIS. The positive association between Asian/PI race and CBT risk was stronger among those <50 years at diagnosis and those with noncomedo DCIS.

Invasive breast cancer is pathologically and biologically more aggressive in black compared to white women [22, 23], largely contributing to worse prognosis for blacks [7]. However, the impact of black race on pathologic features and clinical outcomes of DCIS remains unclear. In this analysis, black women were younger at diagnosis of DCIS and had larger lesions than white women. However, DCIS lesions from blacks were more likely than those from whites to be well differentiated and noncomedo subtypes, both related to favorable prognosis [24]. Institution-based studies reported that black DCIS patients presented large-size lesions more frequently than white patients despite no difference in tumor grade or architectural patterns [13, 17].

Prior analyses of SEER data through 2001 showed significantly higher incidences of invasive IBTs and invasive CBTs among black compared to white women with DCIS after adjusting for age, year, registry, and treatment, but not pathologic factors [9, 11]. This difference was no longer statistically significant after adjustment for pathologic variables [13, 16, 18]. Thus, the worse outcome among black DCIS patients may be attributable to more aggressive tumor pathology [24]. However, these studies included small numbers of black patients and thus had limited power to detect a moderate increase in risk of second breast tumors. In the current study, black race was associated with 46 % increased risk for IBTs and 21 % increased risk for CBTs after adjustment for pathologic factors, age and year of diagnosis of first DCIS, registry, and treatment. The elevated IBT risk in blacks was maintained across tumor size, grade, and architectural patterns. Future research should focus on identifying molecular markers of DCIS that may explain outcome disparities.

Notably, DCIS lesions from black women were more likely than white women to be ER<sup>+</sup>, and controlling for ER slightly reduced racial differences in IBTs. In a multiethnic cohort of 1,902 women with DCIS, blacks accounted for 11.3 % and exhibited the highest rate of ER<sup>+</sup> lesions among all racial groups [13]. Using immunohistochemical markers (ER, PR, HER2, and Ki67), Sharaf Aldeen et al. [25] classified 94 DCIS cases into five subtypes and found a similar distribution of molecular subtypes between black and white women. In addition, the basal-like DCIS defined by ER, PR, HER2, CK5/6, and EGFR displayed a comparable risk of IBTs to the other molecular subtypes [26]. Future efforts should focus on the clinical relevance of these findings and novel molecular markers that mediate poorer DCIS outcomes in black women.

Also, studies have suggested that socioeconomic disadvantages account for the disproportionately elevated mortality risk in black women with invasive breast cancer [27–30]. However, a meta-analysis of 20 studies evaluating survival of black and white breast cancer patients demonstrated that blacks maintained statistically significant excess risk of mortality after adjusting for socioeconomic status [6]. Future studies to disentangle the impacts of race and socioeconomic status on DCIS outcomes are warranted.

Two prior studies of DCIS outcomes reported that black race was differentially associated with types of IBTs. Collins et al. [15] evaluated IBTs among 2,995 DCIS patients treated with BCS, of which 9.6 % were black, and reported an 80 % increased risk of ipsilateral DCIS and a 30 % increased risk of invasive IBTs among black compared with white women. In contrast, the analysis of California Cancer Registry data showed that the risk for invasive IBTs was significantly increased among black DCIS patients but not for ipsilateral DCIS [9]. We instead found that black race was similarly associated with risks for ipsilateral DCIS and invasive IBTs after DCIS. Therefore, racial differences in local DCIS recurrence and the progression to invasive cancer in the ipsilateral breast may be mediated by common biological pathways.

Few studies have compared DCIS outcomes between Asian/PI, Hispanic, and white women [9–11, 13], with the majority reporting no difference [9, 10, 13]. However, risk of advanced invasive IBT was 130 % higher in Hispanic than white women with DCIS [11]. The current study with more racial minority women found that Hispanic ethnicity was associated with significantly increased risk for IBTs but not for CBTs. Yet, Asian/PI women had increased risk for CBTs, largely driven by a significant increase in contralateral DCIS, but not for IBTs. Whether the elevated risk of contralateral DCIS among Asian/PI women resulted from their greater use of surveillance mammography is unknown. Among breast cancer patients with equal access to health care, Asians/PIs were more likely than whites to undergo surveillance mammography [31]. However, lower use of mammography was found among older Asians/PIs compared to their white counterparts [32].

We found that black and Hispanic women treated with BCS alone had a higher risk of IBTs than white women. Given that radiotherapy following BCS reduces IBTs by 50 % after DCIS [33, 34], adding radiation after surgical excision may be appropriate for black and Hispanic patients who are at high IBT risk. The increased IBT risk persisted in blacks treated with BCS and radiotherapy, indicating the need for more intensive follow-up to improve outcomes. Many DCIS cases are over-diagnosed because more than half of DCIS patients would not develop invasive breast cancer if left untreated [35–37]. A challenge in DCIS management is the identification of DCIS patients who are most likely to go on to cancer, which should integrate routine clinicopathological factors and novel molecular markers and take into account race/ethnicity and other patient-related factors.

Our study has limitations. Variables that could influence DCIS outcomes were unavailable in the SEER database. Positive surgical margins are consistently associated with increased IBT risk after DCIS [24]. Five-year tamoxifen use could reduce the risk of ipsilateral and contralateral breast tumors among DCIS patients treated with BCS and radiation by 35 % and 41 %, respectively [38]. Prompt initiation and completion of adjuvant therapy are also important for breast cancer patients with BCS to lower their risks of local recurrence and mortality [39–41]. Studies reported no racial difference in surgical margins or receipt of hormone therapy in DCIS patients [13, 14, 16, 42, 43]. However, black race was associated with longer waiting time for and lower probabilities of completing radiotherapy following BCS [40, 41]. Hispanics and Chinese with hormone receptor-positive breast cancer were less likely than other groups to initiate adjuvant hormone therapy within a year after

diagnosis [44]. Of those who initiated adjuvant hormone therapy, blacks were more likely to be nonadherent to therapy and Asians/Pis were more likely to continue therapy [45].

Evidence suggests the associations of obesity and alcohol consumption with increased risk of second breast tumors in DCIS survivors [10, 46, 47]. Compared with white patients, the odds of being overweight or obese were higher in black and Hispanic DCIS patients and lower in Asian/PI DCIS patients [48]. Alcohol intake was less prevalent in black and Asian/PI than white and Hispanic women with breast cancer [49]. Due to the lack of lifestyle information, we could not assess the contribution of lifestyles to racial disparities in DCIS prognosis.

Additionally, data on tumor size and grade were unavailable for approximately 30 % of DCIS cases. Missing indicators were created for the current analysis. However, the associations between black race and risks of IBTs (RR 1.54; 95 % CI 1.27–1.88) and CBTs (RR 1.33; 95 % CI 1.11–1.59) remained statistically significant in the sensitivity analysis of complete cases.

Our study provides a more comprehensive examination of racial/ethnic differences in DCIS outcomes than previous studies. Black women with DCIS experienced disproportionately higher risks for second breast tumors, even when uniformly treated with BCS and radiotherapy. They may then need more intensive post-treatment followup. Hispanic DCIS patients had a greater IBT risk if treated with BCS alone and might be appropriate candidates for additional treatment. Differences in tumor pathology and treatment could not account for elevated risk for second breast tumors in racial minority women. Further studies are needed to determine whether biological and nonbiological (e.g., socioeconomic status) characteristics of DCIS are different across racial groups and whether these contribute to outcome disparities. Detailed treatment and followup information is needed to understand the contributions of healthcare quality and surveillance mammography use to racial disparities in DCIS outcomes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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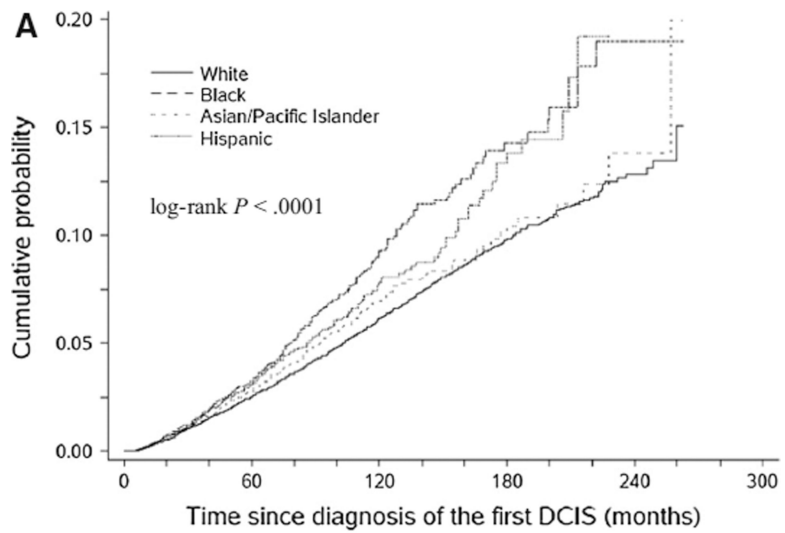
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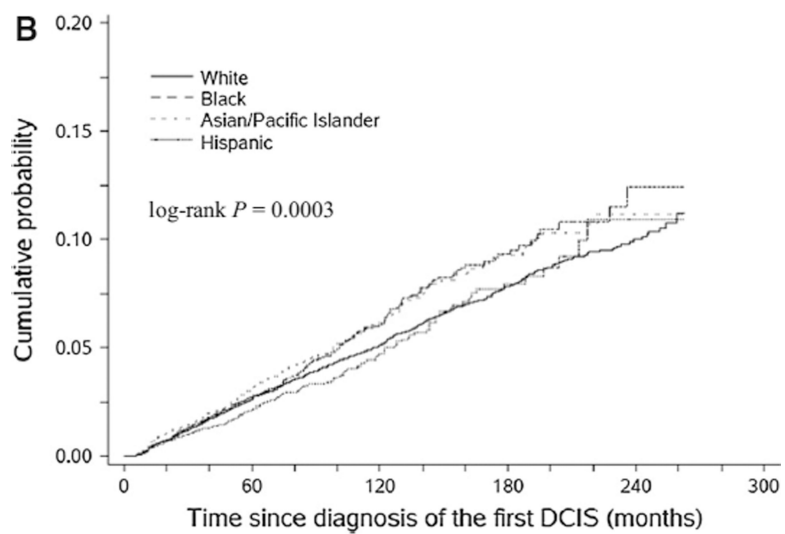
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No. at risk					
White	55504	31219	9934	2986	408
Black	7006	3447	963	226	38
Asian/PI	6418	3361	1148	283	39
Hispanic	5881	2629	710	176	11



No. at risk					
White	75431	44557	16256	5806	985
Black	9921	5122	1588	471	81
Asian/PI	9246	5203	1893	570	95
Hispanic	7891	3898	1167	351	43

**Fig. 1.** Cumulative incidences of second breast tumors in the ipsilateral breast (a) and contralateral breast (b) among four racial/ethnic groups of women with DCIS

**Table 1**  
 Characteristics of women with unilateral ductal carcinoma in situ (DCIS) in the SEER 18 Cancer Registries, 1988–2009, stratified by race and ethnicity<sup>a</sup>  
 (n = 102,489)

	No. of patients (%)					P <sup>b</sup>
	White	Black	Asian/PI	Hispanic		
Total	75,431 (73.6)	9,921 (9.7)	9,246 (9.0)	7,891 (7.7)		–
Age at diagnosis, y						
Mean (SD)	59.1 (12.1)	57.6 (12.0)	56.0 (11.6)	56.0 (11.7)		<0.0001
20–39	2,505 (3.3)	512 (5.2)	457 (4.9)	378 (4.8)		–
40–49	16,182 (21.5)	2,267 (22.9)	2,598 (28.1)	2,262 (28.7)		–
50–59	21,165 (28.1)	2,881 (29.0)	2,787 (30.1)	2,320 (29.4)		–
60–69	18,181 (24.1)	2,384 (24.0)	2,001 (21.6)	1,733 (22.0)		–
70	17,398 (23.1)	1,877 (18.9)	1,403 (15.2)	1,198 (15.2)		<0.0001
Length of follow-up, months						
Mean (range)	82.6 (6,263)	72.2 (6,263)	77.4 (6,263)	69.8 (6,263)		<0.0001
6–11	3,743 (5.0)	625 (6.3)	560 (6.1)	556 (7.1)		–
12–59	27,131 (36.0)	4,174 (42.1)	3,663 (39.6)	3,437 (43.6)		–
60–119	28,301 (37.5)	3,534 (35.6)	3,130 (33.9)	2,731 (34.6)		–
120	16,256 (21.6)	1,588 (16.0)	1,893 (20.5)	1,167 (14.8)		<0.0001
Year of the first DCIS diagnosis <sup>c</sup>						
1988–1989	1,915 (2.5)	179 (1.8)	157 (1.7)	75 (1.0)		–
1990–1994	7,374 (9.8)	720 (7.3)	721 (7.8)	488 (6.2)		–
1995–1999	11,946 (15.8)	1,411 (14.2)	1,545 (16.7)	1,004 (12.7)		–
2000–2004	28,284 (37.5)	3,589 (36.2)	3,173 (34.2)	2,847 (36.1)		–
2005–2009	25,912 (34.4)	4,022 (40.5)	3,650 (39.5)	3,477 (44.1)		<0.0001
Histological subtype						
Not otherwise specified	50,510 (67.0)	6,795 (68.5)	6,319 (68.3)	5,394 (68.4)		–
Comedo	11,523 (15.3)	1,293 (13.0)	1,174 (12.7)	1,025 (13.0)		–
Papillary	4,397 (5.8)	820 (8.3)	545 (5.9)	509 (6.5)		–
Cribriform	5,616 (7.5)	662 (6.7)	814 (8.8)	657 (8.3)		–
Solid	3,385 (4.5)	351 (3.5)	394 (4.3)	306 (3.9)		<0.0001

	No. of patients (%)					<i>p</i> <sup>b</sup>
	White	Black	Asian/PI	Hispanic		
Grade						
Well differentiated	7,432 (14.2)	1,185 (17.2)	990 (13.9)	785 (13.1)		–
Moderately differentiated	20,688 (39.4)	2,866 (41.6)	2,978 (41.7)	2,553 (42.7)		–
Poorly differentiated	24,356 (46.4)	2,847 (41.3)	3,173 (44.4)	2,636 (44.1)		<0.0001
Missing	22,955	3,023	2,105	1,917		–
Tumor size, cm						
<2.0	39,429 (78.9)	4,519 (72.8)	5,052 (72.2)	3,838 (72.0)		–
2.0–4.9	8,326 (16.7)	1,233 (19.9)	1,592 (22.8)	1,160 (21.8)		–
5.0	2,235 (4.5)	456 (7.4)	350 (5.0)	335 (6.3)		<0.0001
Missing	25,441	3,713	2,252	2,558		–
Estrogen receptor						
Negative	5,624 (18.4)	684 (15.0)	728 (18.3)	631 (18.1)		–
Positive	25,013 (81.6)	3,882 (85.0)	3,251 (81.7)	2,855 (81.9)		<0.0001
Missing	44,794	5,355	5,267	4,405		–
Surgery for first DCIS						
None	1,599 (2.1)	277 (2.8)	121 (1.3)	212 (2.7)		–
BCS <sup>d</sup>	53,644 (71.4)	6,685 (67.7)	6,265 (68.0)	5,638 (71.7)		–
Mastectomy <sup>e</sup>	19,927 (26.5)	2,915 (29.5)	2,828 (30.7)	2,010 (25.6)		<0.0001
Missing	261	44	32	31		–
Radiation therapy for first DCIS						
No	40,506 (54.7)	5,546 (56.9)	5,053 (55.3)	4,308 (55.7)		–
Yes	33,556 (45.3)	4,200 (43.1)	4,081 (44.7)	3,425 (44.3)		0.0003
Missing	1,369	175	112	158		–
Surgery and radiation therapy for first DCIS						
No surgery	1,599 (2.2)	277 (2.8)	121 (1.3)	212 (2.7)		–
BCS <sup>d</sup> alone	19,852 (26.8)	2,506 (25.7)	2,176 (23.9)	2,183 (28.2)		–
BCS <sup>d</sup> and radiation	32,787 (44.2)	4,064 (41.6)	3,998 (43.8)	3,324 (43.0)		–
Mastectomy <sup>e</sup>	19,927 (26.9)	2,915 (29.9)	2,828 (31.0)	2,010 (26.0)		<0.0001
Missing	1,266	159	123	162		–

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*SD* standard deviation, *BCS* breast-conserving surgery

<sup>a</sup>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 or Pacific Islander (Asian/PI), and Hispanic (Hispanic)

<sup>b</sup>*P* values were calculated from a comparison across all groups except the groups with missing values

<sup>c</sup>Cases diagnosed between 1988 and 1989 were from nine registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah). Cases diagnosed between 1990 and 1999 were from 12 registries (the above nine registries, plus Los Angeles, San Jose-Monterey, and Rural Georgia). Cases diagnosed since 2000 were from 17 registries (the above 12 registries, plus Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia). Cases from the Alaska Native Tumor Registry were excluded due to the small number of Alaskan Native patients

<sup>d</sup>Breast-conserving surgery consisted of excisional biopsy, lumpectomy, nipple resection, wedge resection, quadrantectomy, segmental mastectomy, tylectomy, and partial mastectomy, NOS

<sup>e</sup>Mastectomy included total mastectomy, modified radical mastectomy, radical mastectomy, subcutaneous mastectomy and mastectomy, not otherwise specified

Risk of ipsilateral breast tumors<sup>a</sup> associated with race and ethnicity among women with unilateral ductal carcinoma in situ (DCIS) diagnosed between 1988 and 2009<sup>b</sup> (*n* = 74,809)

Table 2

	Person-years	Ipsilateral breast tumors			Ipsilateral DCIS			Ipsilateral invasive cancer		
		Cases	RR <sup>c</sup>	95 % CI <sup>c</sup>	Cases	RR <sup>c</sup>	95 % CI <sup>c</sup>	Cases	RR <sup>c</sup>	95 % CI <sup>c</sup>
White	355,850	2,104	1.00	Referent	595	1.00	Referent	1,509	1.00	Referent
Black	39,822	3,30	1.46	1.29–1.65	98	1.48	1.18–1.86	232	1.45	1.25–1.67
Asian/PI	39,132	255	1.11	0.96–1.29	62	0.94	0.70–1.27	193	1.18	0.99–1.39
Hispanic	32,118	236	1.18	1.03–1.36	69	1.33	1.02–1.72	167	1.13	0.96–1.34

*P*<sub>heterogeneity</sub> = 0.25

RR relative risk, 95 % CI 95 % confidence interval

<sup>a</sup> Ipsilateral breast tumors were defined as local recurrence of DCIS or invasive carcinoma in the ipsilateral breast that was diagnosed at least 6 months after the first DCIS

<sup>b</sup> Patients who had been treated with mastectomy for their first DCIS (*n* = 27,680) were excluded

<sup>c</sup> Relative risks were adjusted for age (20–39, 40–49, 50–59, 60–69, or 70–84 years) and year of the first DCIS diagnosis (1988–1989, 1990–1994, 1995–1999, 2000–2004, or 2005–2009), registry, treatment for the first DCIS (no surgical treatment, breast-conserving surgery alone, or breast-conserving surgery plus radiation therapy) and histopathological features including tumor size (<2 cm, 2–5 cm, 5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), and histology (comedo, papillary, cribriform, solid, or NOS)



**Table 3**

Stratified analysis of racial/ethnic differences in risk of ipsilateral breast tumors by characteristics of the first ductal carcinoma in situ (DCIS)

	Cases	Person-years	RR <sup>a</sup>	95 % CI <sup>a</sup>
Age at diagnosis <50 years				
White	696	90,678	1.00	Referent
Black	122	11,431	1.49	1.22–1.83
Asian/PI	114	13,137	1.13	0.91–1.41
Hispanic	94	10,707	1.10	0.88–1.38
Age at diagnosis ≥ 50 years				
White	1,408	265,172	1.00	Referent
Black	208	28,391	1.45	1.25–1.69
Asian/PI	141	25,995	1.09	0.90–1.33
Hispanic	142	21,411	1.24	1.03–1.48
<i>P</i> <sub>interaction</sub> = 0.45				
Breast-conserving surgery alone				
White	1,103	135,774	1.00	Referent
Black	181	15,372	1.51	1.28–1.78
Asian/PI	126	14,063	1.03	0.85–1.26
Hispanic	132	12,587	1.27	1.05–1.54
Breast-conserving surgery and radiation therapy				
White	848	202,215	1.00	Referent
Black	117	22,223	1.33	1.09–1.63
Asian/PI	108	23,808	1.21	0.96–1.53
Hispanic	86	17,502	1.19	0.95–1.51
<i>P</i> <sub>interaction</sub> = 0.40				
Well or moderately differentiated DCIS				
White	610	125,031	1.00	Referent
Black	103	15,280	1.63	1.31–2.03
Asian/PI	82	16,142	0.97	0.75–1.26
Hispanic	77	12,913	1.08	0.85–1.39
Poorly differentiated DCIS				
White	522	91,332	1.00	Referent
Black	83	9,121	1.39	1.09–1.78
Asian/PI	67	10,946	1.12	0.85–1.47
Hispanic	63	8,795	1.19	0.91–1.57
<i>P</i> <sub>interaction</sub> = 0.47				
DCIS <2 cm				
White	1,212	208,235	1.00	Referent
Black	150	20,843	1.32	1.11–1.58
Asian/PI	152	24,548	1.13	0.94–1.37
Hispanic	127	17,749	1.21	1.00–1.46

	Cases	Person-years	RR <sup>a</sup>	95 % CI <sup>a</sup>
DCIS 2 cm				
White	189	32,937	1.00	Referent
Black	52	4,688	1.86	1.34–2.58
Asian/PI	35	4,970	1.20	0.80–1.78
Hispanic	36	4,146	1.55	1.07–2.26
<i>P</i> <sub>interaction</sub> = 0.07				
Comedo type				
White	440	59,707	1.00	Referent
Black	60	5,360	1.44	1.08–1.91
Asian/PI	39	5,295	0.97	0.68–1.38
Hispanic	45	4,868	1.14	0.83–1.58
Noncomedo type				
White	1,664	296,144	1.00	Referent
Black	270	34,462	1.47	1.28–1.68
Asian/PI	216	33,837	1.14	0.97–1.34
Hispanic	191	27,250	1.19	1.01–1.39
<i>P</i> <sub>interaction</sub> = 0.40				

RR relative risk, 95 % CI 95 % confidence interval

<sup>a</sup>Relative risks were adjusted for the covariates listed in the footnote of Table 2

Risk of second breast tumors in the contralateral breast associated with race and ethnicity among women with unilateral ductal carcinoma in situ (DCIS) diagnosed between 1988 and 2009 ( $n = 102,489$ )

**Table 4**

	Contralateral breast tumors <sup>a</sup>			Contralateral DCIS			Contralateral invasive cancer			
	Cases	RR <sup>b</sup>	95 % CI <sup>b</sup>	Cases	RR <sup>b</sup>	95 % CI <sup>b</sup>	Cases	RR <sup>b</sup>	95 % CI <sup>b</sup>	
White	519,306	2,765	1.00	Referent	816	1.00	Referent	1,949	1.00	Referent
Black	59,670	362	1.21	1.08–1.36	102	1.12	0.91–1.39	260	1.25	1.09–1.43
Asian/PI	59,638	378	1.16	1.02–1.31	160	1.59	1.30–1.95	218	0.96	0.82–1.13
Hispanic	46,067	218	0.95	0.82–1.09	67	0.99	0.77–1.29	151	0.93	0.79–1.11
$P_{\text{heterogeneity}} < 0.0001$										

RR relative risk, 95 % CI 95 % confidence interval

<sup>a</sup>Contralateral breast tumors were defined as DCIS or invasive carcinoma developed in the contralateral breast at least 6 months after first DCIS

<sup>b</sup>Relative risks were adjusted for age (20–39, 40–49, 50–59, 60–69, or 70–84 years) and year of the first DCIS diagnosis (1988–1989, 1990–1994, 1995–1999, 2000–2004, or 2005–2009), registry, treatment for the first DCIS (no surgical treatment, breast-conserving surgery (BCS) alone, BCS plus radiation therapy, mastectomy, or unknown) and histopathological features including tumor size (<2 cm, 2–5 cm, 5 cm, or unknown), grade (well differentiated, moderately differentiated, poorly differentiated, or unknown), and histology (comedo, papillary, cribriform, solid, or NOS)

**Table 5**

Stratified analysis of racial/ethnic differences in risk of contralateral breast tumors by characteristics of the first ductal carcinoma in situ (DCIS)

	Cases	Person-years	RR <sup>a</sup>	95 % CI <sup>a</sup>
Age at diagnosis <50 years				
White	658	141,171	1.00	Referent
Black	79	18,247	1.03	0.81–1.31
Asian/PI	134	20,566	1.39	1.12–1.71
Hispanic	61	15,870	0.87	0.67–1.15
Age at diagnosis ≥ 50 years				
White	2,107	378,135	1.00	Referent
Black	283	41,423	1.34	1.15–1.56
Asian/PI	244	39,073	0.91	0.75–1.11
Hispanic	157	30,031	0.96	0.78–1.17
$P_{\text{interaction}} = 0.01$				
Breast-conserving surgery alone				
White	708	135,774	1.00	Referent
Black	82	15,372	1.01	0.80–1.28
Asian/PI	85	14,063	1.06	0.83–1.35
Hispanic	66	12,587	1.03	0.79–1.34
Breast-conserving surgery and radiation therapy				
White	1,079	202,215	1.00	Referent
Black	143	22,223	1.34	1.12–1.61
Asian/PI	144	23,808	1.18	0.96–1.46
Hispanic	79	17,502	0.91	0.72–1.16
Mastectomy				
White	906	163,455	1.00	Referent
Black	121	19,848	1.16	0.95–1.41
Asian/PI	144	20,507	1.20	0.98–1.48
Hispanic	71	13,783	1.00	0.78–1.28
$P_{\text{interaction}} = 0.13$				
Well or moderately differentiated DCIS				
White	817	159,784	1.00	Referent
Black	112	20,476	1.14	0.93–1.40
Asian/PI	122	21,842	1.07	0.86–1.33
Hispanic	82	16,882	0.98	0.77–1.24
Poorly differentiated DCIS				
White	691	134,319	1.00	Referent
Black	98	14,275	1.45	1.16–1.81
Asian/PI	103	16,957	1.11	0.88–1.39
Hispanic	51	13,218	0.75	0.56–1.01
$P_{\text{interaction}} = 0.12$				

	Cases	Person-years	RR <sup>a</sup>	95 % CI <sup>a</sup>
DCIS <2 cm				
White	1,492	278,952	1.00	Referent
Black	176	27,547	1.28	1.09–1.51
Asian/PI	204	32,930	1.10	0.92–1.31
Hispanic	116	22,690	1.03	0.85–1.26
DCIS ≥ 2 cm				
White	366	64,236	1.00	Referent
Black	56	9,606	1.09	0.81–1.46
Asian/PI	80	10,988	1.28	0.97–1.68
Hispanic	38	8,017	0.85	0.60–1.20
<i>P</i> <sub>interaction</sub> = 0.23				
Comedo type				
White	512	98,174	1.00	Referent
Black	67	9,302	1.47	1.13–1.92
Asian/PI	58	9,821	1.07	0.78–1.45
Hispanic	28	7,862	0.68	0.46–1.01
Non-comedo type				
White	2,253	421,132	1.00	Referent
Black	295	50,368	1.16	1.02–1.32
Asian/PI	320	49,817	1.18	1.02–1.35
Hispanic	190	38,038	1.01	0.87–1.18
<i>P</i> <sub>interaction</sub> = 0.049				

RR relative risk, 95 % CI 95 % confidence interval

<sup>a</sup>Relative risks were adjusted for the covariates listed in the footnote of Table 4