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ORIGINAL PAPER

Breast cancer risk factor associations differ for pure versus invasive carcinoma with an in situ component in case–control and case–case analyses

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Abstract

Purpose Invasive ductal carcinoma (IDC) is diagnosed with or without a ductal carcinoma in situ (DCIS) component. Previous analyses have found significant differences in tumor characteristics between pure IDC lacking DCIS and mixed IDC with DCIS. We will test our hypothesis that pure IDC represents a form of breast cancer with etiology and risk factors distinct from mixed IDC/DCIS.

Methods We compared reproductive risk factors for breast cancer risk, as well as family and smoking history between 831 women with mixed IDC/DCIS ($n = 650$) or pure IDC ($n = 181$), and 1,620 controls, in the context of the Women's Circle of Health Study (WCHS), a case–control study of breast cancer in African-American and European-American women. Data on reproductive and lifestyle factors were collected during interviews, and tumor characteristics were abstracted from pathology reports. Case–control and case–case analyses were conducted using unconditional logistic regression.

Results Most risk factors were similarly associated with pure IDC and mixed IDC/DCIS. However, among postmenopausal women, risk of pure IDC was lower in women with body mass index (BMI) 25 to <30 [odds ratio (OR) 0.66; 95 % confidence interval (CI) 0.35–1.23] and BMI ≥ 30 (OR 0.33; 95 % CI 0.18–0.67) compared to women with BMI < 25, with no associations with mixed

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IDC/DCIS. In case–case analyses, women who breastfed up to 12 months (OR 0.55; 95 % CI 0.32–0.94) or longer (OR 0.47; 95 % CI 0.26–0.87) showed decreased odds of pure IDC than mixed IDC/DCIS compared to those who did not breastfeed.

Conclusions Associations with some breast cancer risk factors differed between mixed IDC/DCIS and pure IDC, potentially suggesting differential developmental pathways. These findings, if confirmed in a larger study, will provide a better understanding of the developmental patterns of breast cancer and the influence of modifiable risk factors, which in turn could lead to better preventive measures for pure IDC, which have worse disease prognosis compared to mixed IDC/DCIS.

Keywords Breast cancer · Ductal carcinoma in situ component · Risk factors · Cancer etiology · Cancer pathology

Abbreviations

IDC	Invasive ductal carcinoma
DCIS	Ductal carcinoma in situ
AA	African-American
WCHS	Women's Circle of Health Study
EA	European-American
BMI	Body mass index
OR	Odds ratio
CI	Confidence interval
ER	Estrogen receptor
HER2	Human epidermal growth factor 2
LN	Lymph node
RPCI	Roswell Park Cancer Institute
CINJ	Rutgers Cancer Institute of New Jersey
ISMMSS	Icahn School of Medicine at Mount Sinai School
OC	Oral contraceptive
MHT	Menopausal hormone therapy
HAMLET	Human milk complex of alpha-lactalbumin and oleic acid

Background

Breast cancer develops as a result of multiple genetic changes in epithelial cells lining the mammary duct concurrent with changes in the surrounding stroma [1–3]. Invasive carcinoma is thought to develop through a linear succession of morphological changes from normal cells to atypical hyperplasia, to carcinoma in situ, and then becoming invasive as the lesion breaks through the basement membrane of the duct. However, breast cancer is a heterogeneous disease, and it is unlikely that all invasive breast tumors progress through the same course of development. Evidence suggests that for a proportion of carcinomas, progression is accelerated, resulting in the development of pure invasive ductal carcinoma (IDC) that arise either de novo or without an extended period of containment, often occurring between regular mammography screenings as interval tumors [4, 5]. Previous evidence suggests that IDC with accompanying DCIS may represent a distinct clinical and biological entity from pure IDC [6]. Pure invasive carcinoma, in comparison with mixed invasive carcinoma with DCIS, is larger, of higher grade, has higher Ki-67 expression and fewer calcifications, and is more frequently negative for expression of estrogen receptor (ER) and human epidermal growth receptor 2 (HER2) [6–12]. Castro and colleagues found a substantial number of differentially expressed genes in pure DCIS compared with those expressed in mixed IDC/DCIS [13], and some studies suggest that the presence of a DCIS component is associated with cell-mediated immune changes in the microenvironment and neoplastic epithelial cells surrounding the DCIS, leading to differences in tumor progression and improved prognosis [6, 9, 10, 14–16]. Pure IDC has also been associated with younger age [7, 9, 10] and worse survival outcomes [7, 9, 17, 18], although inconsistencies among studies for these factors exist [7–10, 17, 18]. In addition, significant differences in the levels of matrix metalloproteinase expression have been observed between the tumor and stromal cells of mixed IDC/DCIS and pure IDC in histological studies [19, 20]. In sum, these differences in tumor characteristics and protein expression

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suggest potential differences in etiologic risk factors for mixed IDC/DCIS and pure IDC. Common risk factors for breast cancer, such as older age at menarche, nulliparity, older age at first birth, breast cancer in a first-degree relative, and higher postmenopausal body mass index (BMI), are consistently associated with increased overall risk of invasive breast cancer [21–25]; however, the impact of these factors on the presence or absence of concomitant DCIS remains largely unknown.

In this study, we evaluated potential risk factors associated with mixed IDC/DCIS and pure IDC in women in the Women's Circle of Health Study (WCHS), which was specifically designed to evaluate risk factors for early and aggressive breast cancer in African-American (AA) compared to European-American (EA) women [26–29]. We additionally examined screening practices and ER status to control for the possibility of an association between lack of screening and pure IDC, and the possibility that the absence of a DCIS component is simply characteristic of ER-negative tumors. Differences in risk factor profiles would provide evidence that mixed IDC/DCIS and pure IDC are biologically distinct diseases with potentially different etiologic pathways. A better understanding of the developmental patterns of breast cancer may offer more effective preventive measures and treatment options.

Methods

Study population and data

These analyses are based on the WCHS, a multicenter case–control study of breast cancer in AA and EA women, conducted in metropolitan New York City (NYC) from 2002 through 2008 and seven counties in New Jersey (NJ) from 2003 through 2012, which has been described in detail elsewhere [26–28]. Breast cancer cases in NYC were ascertained through 12 targeted hospitals, and cases from NJ were identified through the NJ State Cancer Registry of the Department of Health through rapid case ascertainment. Eligible cases included English-speaking women who self-identified as AA or EA, 20–75 years of age, with a primary, newly diagnosed, histologically confirmed breast cancer. Controls without a history of any cancer diagnosis other than non-melanoma skin cancer were identified through random digit dialing (RDD) of residential telephone numbers and frequency-matched by telephone prefixes of cases, a commonly accepted method for selecting controls in targeted areas to assemble a population comparable to cases [26–28]. The majority of cases were interviewed within 6 months of diagnosis, but were asked about behaviors prior to breast cancer diagnosis. In addition to recruitment by RDD, controls in NJ were also recruited through community-based efforts, mainly through churches and health events, with the help of community partners and advocates [28]. Community controls were on average less educated, had lower income, and were more likely to have Medicaid or Medicare as a form of insurance compared to RDD controls. Using data obtained by the American Community Survey of the United States Census Bureau, we showed within our study sample that a combination of controls recruited by RDD and from the community were more representative of the general AA community in New Jersey regarding education, income, marital status, and level of obesity, as an indicator of lifestyle factors, than RDD controls alone [28], and were a better comparison group to population-based cases recruited in NJ. Controls identified by RDD and community-based controls were frequency-matched to cases by self-reported race and 5-year age categories. In-person interviews were conducted to query participants on potential breast cancer risk factors and socioeconomic factors, including type of medical insurance and screening habits, and detailed anthropometric measurements were taken [28]. A signed release to obtain pathology data and tumor blocks was part of the informed consent process for cases, and data on hormone receptors, histology, grade, and stage were abstracted from pathology reports by trained study staff. Protocols for agreement to participate and informed consent were approved by the institutional review boards at Roswell Park Cancer Institute (RPCI), Rutgers Cancer Institute of New Jersey (CINJ), Icahn School of Medicine at Mount Sinai School (ISMMSS, formerly the Mount Sinai School of Medicine), and the participating hospitals in NYC in compliance with the Declaration of Helsinki.

Out of a total of 1,513 women with breast cancer in the WCHS, women were excluded if they were diagnosed with pure DCIS ($n = 258$), invasive carcinomas of other types ($n = 141$), or cancers with unknown histology ($n = 283$, 53 cases of which were excluded because the presence or absence of DCIS with IDC could not be determined). Records of pure IDC patients were included only when medical reports clearly stated that there was no DCIS component, or included detailed descriptions of hyperplasia without mention of DCIS. In addition, slides of tumor samples from cases were reviewed by two breast pathologists to verify the presence or absence of DCIS. Included in the final study were 831 women with IDC (recognized as *ductal carcinoma of no special type* in accordance with World Health Organization terminology) or mixed IDC/invasive lobular carcinoma and 1,620 controls.

Statistical analyses

Differences between controls and cases with pure IDC or mixed IDC/DCIS were compared using Student's t test for continuous variables and Chi-squared tests for categorical

variables. Odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) and p values were calculated to estimate associations between risk factors and mixed IDC/DCIS or pure IDC in case–control multivariable models using unconditional logistic regression. Analyses were conducted for AA and EA women combined, which included adjustments for self-reported race. Potential interactions by race were also assessed by introducing cross product terms (race × exposure) into the logistic regression model for all women combined. Case–case analyses, using unconditional logistic regression, were performed to determine whether risk factors were differentially associated with odds of being diagnosed with pure IDC ("case") compared to odds of being diagnosed with mixed IDC/DCIS ("control"). Since AA women are more likely to be diagnosed with more aggressive breast cancers compared to EA women and risk factors for breast cancer may have differential effects in EA and AA women [29–31], case–case findings were also stratified by self-reported race to determine whether observed associations are modified by race. Wald's Chi-square test was used to calculate p values for categorical variables. p trends were calculated using median values for each category or quantile.

Risk factors evaluated included family history, defined as having a first-degree relative with breast cancer, age at menarche, parity, oral contraceptive (OC) use, menopausal hormone therapy (MHT) use, current BMI, smoking, age at first birth, age at last birth, number of births, and total breastfeeding duration. Categories for duration of OC use (1–72 months and >72 months) were defined by months of use associated with increased breast cancer risk in this and previous studies [32]. Categories of age at first and last birth were created using cutoffs from previous literature [29, 30] that allowed for adequate sample sizes within both AA and EA groups, since AA women were more likely to have earlier age at first birth as well as earlier age at last birth. ORs estimating associations with age at first birth, age at last birth, number of births, and breastfeeding were calculated among parous women only. BMI was calculated as kg/m^2, using weight and height measurements collected during home interviews. Categories of <25, 25 to <30, and ≥30 kg/m^2 were chosen for BMI, corresponding to normal and underweight, overweight, and obesity, respectively. Underweight women were included in the analyses, but were not considered as a separate category due to their small number. Data were stratified by menopausal status for examination of BMI due to differential effects of BMI on pre- and postmenopausal breast cancer risk in previous studies [28]. Women were considered premenopausal if they had either periods within the last year or at least one remaining ovary and were under the age of 50, the median age for natural menopause in the WCHS. Otherwise, women without periods within the last year were considered postmenopausal. Multivariable analyses were performed to account for potential confounding factors selected a priori. Models were adjusted for age, race, birthplace, family history, education, OC use, age at menarche, parity, and menopausal status (unless they were the main variable of interest), given their known associations with breast cancer risk and/or reproductive history. Place of birth was included in our models because women born outside of the USA tended to have more children, were more likely to have breastfed, and were more likely to be diagnosed with more aggressive disease compared to women born in the USA. Because less frequent screening may lead to the detection of more advanced lesions and because the identification of a DCIS component may be inversely associated with later-stage disease, we also adjusted for screening history using a composite screening score. The score was based on responses to three questions: whether the participant (1) had ever had a physician breast examination, (2) had self-examined breasts for lumps, or (3) had ever received a mammogram. Each screening measure was assigned 1 point, for a score of 3 for a woman who reported ever using all three screening measures. Age at first birth was included when factors associated with reproduction were assessed, and self-reported race was included when AA and EA women were combined. In case–case analyses between pure IDC and mixed IDC/DCIS, a third model with additional adjustments for ER status is shown since pure IDC was strongly associated with ER-negative cancers in our study population.

Additional case–case analyses comparing tumor characteristics of pure IDC and mixed IDC/DCIS were conducted using unconditional logistic regression. Variables describing tumor characteristics included age, tumor size, tumor grade, stage, lymph node (LN) status, lymphovascular invasion (LVI), ER status, progesterone (PR) status, HER2 status, and method of breast cancer discovery. Models were adjusted as described above for case–control analyses.

Breast cancer subtypes were approximated from ER, PR, and HER2 status. Tumors with positive ER or PR status were categorized as luminal A or B, depending on negative or positive HER2 status, respectively. Tumors with a negative ER and PR status were categorized as triple-negative or HER2-overexpressing breast cancer, depending on negative or positive HER2 status, respectively.

Sensitivity analyses were conducted to examine proportions of pure IDC and mixed IDC/DCIS across different hospitals to determine whether reporting of pure IDC and mixed IDC/DCIS varied between institutions. The potential impact of heterogeneity across institutions on risk estimates was assessed by removing cases from each specific hospital, in turn, to determine whether associations were affected. All analyses were performed using SAS 9.2.

Results

Characteristics of women with breast cancer according to pure IDC and mixed IDC/DCIS, as well as controls, are given in Table 1, along with unadjusted odds ratios (ORs) and 95 % confidence intervals (CIs) for developing pure IDC and mixed IDC/DCIS. Women with pure IDC constituted 21.8 % of women with invasive breast cancer. Sixty-three percent of women with pure IDC were AA, compared to 53.5 % of women with mixed IDC/DCIS ($p = 0.05$). Women with pure IDC were more likely to have a high school education or less (43 % pure IDC vs 33 % mixed IDC/DCIS, $p = 0.02$).

Case–control associations with breast cancer risk factors

Case–control comparisons are given for pure IDC and mixed IDC/DCIS in Table 2. Overall, women with a family history of breast cancer had greater odds of being diagnosed with pure IDC (OR 1.54; 95 % CI 1.02–2.34) or mixed IDC/DCIS (OR 1.44; 95 % CI 1.12–1.85) compared to those without a family history. OC use was associated with increased odds of mixed IDC/DCIS compared to nonusers (OR 1.30; 95 % CI 1.02–1.66 for over 72 months of OC use; p trend $= 0.03$), with a similar, but nonsignificant associations and trend for pure IDC (OR 1.36; 95 % CI 0.91–2.05 for over 72 months of OC use; p trend $= 0.16$). Postmenopausal women with BMI ≥ 30 compared to those with BMI < 25 kg/m^2 had a reduced risk of pure IDC (OR 0.35; 95 % CI 0.18–0.67; p trend $= 0.02$), but no associations were observed with mixed IDC/DCIS (p trend $= 0.58$). Women with last birth later than age 33 also had reduced risk of pure IDC (OR 0.59; 95 % CI 0.37–0.93; p trend $= 0.04$), but not mixed IDC/DCIS (OR 0.85; 95 % CI 0.65–1.10), compared to women who had their last birth by age 22. There was some indication that women who had breastfed 12 months or longer were less likely to be diagnosed with pure IDC compared to women

Table 1 Characteristics of breast cancer cases and controls in the WCHS, ($n = 2{,}451$)

Characteristics	Controls $n = 1{,}620$ n (%)	Pure IDC $n = 181$ (21.8 %) n (%)	Unadjusted OR (95 % CI) for developing pure IDC	Mixed IDC/DCIS $n = 650$ (78.2 %) n (%)	Unadjusted OR (95 % CI) for developing mixed IDC/DCIS	Unadjusted case–case OR (95 % CI) for developing pure IDC versus mixed IDC/DCIS
Age (mean, SD)	49.7 (9.4)	50.6 (9.9)		51.3 (10.5)[b]		
Menopausal status (n, %)						
Pre	867 (53.5)	101 (55.8)	1.00	338 (52.0)	1.00	1.00
Post	753 (46.5)	80 (44.2)	0.91 (0.67, 1.24)	312 (48.0)	1.06 (0.89, 1.27)	0.86 (0.62, 1.20)
Race (n, %)						
AA	905 (55.9)	114 (63.0)	1.00	348 (53.5)	1.00	1.00[c]
EA	715 (44.1)	67 (37.0)	0.75 (0.54, 1.02)	302 (46.5)	1.10 (0.92, 1.32)	0.68 (0.48, 0.95)
Education (n, %)						
≤High school	432 (26.7)	78 (43.1)	1.00[a]	211 (32.5)	1.00[b]	1.00[c]
Some college	394 (24.3)	43 (23.8)	0.61 (0.41, 0.90)	154 (23.7)	0.80 (0.63, 1.03)	0.76 (0.49, 1.16)
College graduate	794 (49.0)	60 (33.1)	0.42 (0.29, 0.60)	285 (43.8)	0.74 (0.59, 0.91)	0.57 (0.39, 0.83)
Birthplace (n, %)						
US born	1,352 (83.5)	130 (71.8)	1.00[a]	497 (76.7)	1.00[b]	1.00
Caribbean	133 (8.2)	33 (18.2)	2.58 (1.69, 2.34)	86 (13.3)	1.75 (1.31, 2.34)	1.47 (0.94, 2.30)
Other	135 (8.3)	18 (9.9)	1.39 (0.82, 2.34)	65 (10.0)	1.30 (0.95, 1.78)	1.06 (0.61, 1.86)
Composite screening score (n, %)						
0 + 1	110 (6.8)	25 (13.8)	1.00[a]	60 (9.2)	1.00	1.00
2	535 (33.0)	56 (30.9)	0.46 (0.28, 0.77)	194 (29.9)	0.67 (0.47, 0.95)	0.69 (0.40, 1.20)
3	975 (60.2)	100 (55.3)	0.45 (0.28, 0.73)	395 (60.9)	0.74 (0.53, 1.04)	0.61 (0.36, 1.02)

p values from Student's t test for continuous variables and from Chi-squared tests for categorical variables

WCHS Women's Circle of Health Study, *IDC* invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *OR* odds ratio, *CI* confidence interval, *SD* standard deviation, *AA* African-American, *EA* European-American

[a] $p \leq 0.05$ for comparison of pure IDC versus controls

[b] $p \leq 0.05$ for comparison of mixed IDC versus controls

[c] $p \leq 0.05$ for comparison of pure IDC versus mixed IDC/DCIS

Table 2 Associations between breast cancer risk factors and pure IDC and mixed IDC/DCIS in the WCHS ($n = 2,451$)

	Controls $n = 1,620$ n (%)	Pure IDC/DCIS $n = 181$ n (%)	OR (95 % CI)[a]	Mixed IDC/DCIS $n = 650$ n (%)	OR (95 % CI)[a]
Family history					
No	1,395 (86.2)	147 (81.2)	1.00	526 (80.9)	1.00
Yes	224 (13.8)	34 (18.8)	1.54 (1.02, 2.34)	124 (19.1)	1.44 (1.12, 1.85)
			$p = 0.04$		$p = 0.004$
Age at menarche (years)					
≥14	420 (26.0)	45 (24.9)	1.00	180 (28.0)	1.00
12–13	784 (48.7)	80 (44.2)	1.03 (0.70, 1.53)	316 (49.2)	1.12 (0.89, 1.42)
<12	407 (25.3)	56 (30.9)	1.39 (0.90, 2.13)	146 (22.8)	1.23 (0.95, 1.60)
			p trend = 0.13		p trend = 0.12
OC use (months)					
0	604 (37.3)	74 (40.9)	1.00	242 (37.3)	1.00
1–72	608 (37.6)	58 (32.0)	1.00 (0.69, 1.46)	232 (35.7)	1.12 (0.89, 1.40)
>72	407 (25.1)	49 (27.0)	1.36 (0.91, 2.05)	175 (27.0)	1.30 (1.02, 1.66)
			p trend = 0.16		p trend = 0.03
Postmenopausal MHT use					
No	516 (68.5)	51 (63.8)	1.00	212 (67.9)	1.00
Yes	237 (31.5)	29 (36.2)	1.37 (0.80, 2.35)	100 (32.1)	0.99 (0.73, 1.35)
			$p = 0.25$		$p = 0.94$
Current BMI (kg/m^2), *premenopausal*					
<25	297 (34.6)	31 (31.0)	1.00	115 (34.8)	1.00
25 to <30	231 (26.9)	24 (24.0)	0.77 (0.43, 1.39)	100 (30.3)	1.12 (0.80, 1.57)
≥30	331 (38.5)	45 (45.0)	0.99 (0.58, 1.69)	115 (34.8)	0.90 (0.64, 1.27)
			p trend = 0.68		p trend = 0.77
Current BMI (kg/m^2), *postmenopausal*					
<25	184 (25.0)	27 (36.5)	1.00	71 (23.3)	1.00
25 to <30	216 (29.3)	23 (31.1)	0.66 (0.35, 1.23)	86 (28.2)	1.08 (0.73, 1.60)
≥30	337 (45.7)	24 (32.4)	0.35 (0.18, 0.67)	148 (48.5)	1.08 (0.75, 1.57)
			p trend = 0.02		p trend = 0.58
Smoking					
No	909 (56.1)	113 (62.4)	1.00	365 (56.1)	1.00
Current/former	711 (43.9)	68 (37.6)	0.76 (0.54, 1.07)	285 (43.9)	1.01 (0.83, 1.23)
			$p = 0.11$		$p = 0.91$
Parity					
0	348 (21.6)	38 (21.0)	1.00	150 (23.4)	1.00
1	343 (21.3)	31 (17.1)	0.70 (0.42, 1.17)	132 (20.6)	0.86 (0.64, 1.14)
2	469 (29.1)	60 (33.2)	0.98 (0.63, 1.52)	185 (28.9)	0.83 (0.64, 1.08)
≥3	450 (28.0)	52 (28.7)	0.67 (0.41, 1.07)	174 (27.2)	0.72 (0.55, 0.96)
			p trend = 0.25		p trend = 0.03
Age at first birth (years)[b]					
≤22	558 (44.0)	68 (47.5)	1.00	225 (45.2)	1.00
>22 to ≤30	409 (32.3)	54 (37.8)	1.58 (1.02, 2.44)	175 (35.1)	1.14 (0.87, 1.50)
>30	301 (23.7)	21 (14.7)	0.93 (0.52, 1.65)	98 (19.7)	0.92 (0.66, 1.28)
			p trend = 0.84		p trend = 0.66
Age at last birth (years)[c]					
≤28	454 (35.8)	66 (46.1)	1.00	189 (38.0)	1.00
>28 to ≤33	356 (28.1)	41 (28.7)	0.89 (0.57, 1.37)	146 (29.3)	0.98 (0.74, 1.28)

Table 2 continued

	Controls $n = 1{,}620$ n (%)	Pure IDC/DCIS $n = 181$ n (%)	OR (95 % CI)[a]	Mixed IDC/DCIS $n = 650$ n (%)	OR (95 % CI)[a]
>33	458 (36.1)	36 (25.2)	0.59 (0.37, 0.93)	163 (32.7)	0.85 (0.65, 1.10)
			p trend = 0.04		p trend = 0.15
Breastfeeding (months)[c]					
None	547 (43.1)	75 (52.4)	1.00	213 (42.7)	1.00
>0–12	402 (31.6)	40 (28.0)	0.76 (0.49, 1.19)	171 (34.3)	1.15 (0.88, 1.50)
>12	321 (25.3)	28 (19.6)	0.61 (0.37, 1.02)	115 (23.0)	0.94 (0.70, 1.27)
			p trend = 0.07		p trend = 0.49

IDC invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *WCHS* Women's Circle of Health Study, *OR* odds ratio, *CI* confidence interval, *AA* African-American, *EA* European-American, *OC* oral contraceptive, *MHT* menstrual hormone therapy, *BMI* body mass index

[a] Unconditional logistic regression models were used to estimate ORs and 95 % CIs. All models were adjusted for age, race, birthplace, family history, composite screening score, education, OC use, age at menarche, parity, and menopausal status. All associations were adjusted for covariates listed above unless the covariate was the main exposure of interest or was used as a stratification variable (menopausal status for BMI and MHT use)

[b] Among 1,912 parous women only

[c] Among 1,912 parous women only, with an additional adjustment for age at first birth

who did not breastfeed (p trend = 0.07). No associations, however, were observed between breastfeeding and risk of being diagnosed with mixed IDC/DCIS (p trend = 0.49). There was some indication that risk of pure IDC or mixed IDC/DCIS may differ by race for OC use, BMI among postmenopausal women, parity, and age at last birth. In fully adjusted models, risk of pure IDC was greater with OC use over 72 months among AA women (OR 1.75; 95 % CI 1.05–2.92), but not among EA women (OR 0.99; 95 % CI 0.51–1.95; p interaction = 0.18) (see Supplementary Table 1). Odds of mixed IDC/DCIS were similarly increased with longer OC use among AA women (OR 1.69; 95 % CI 1.21–2.36), but not among EA women (OR 0.96; 95 % CI 0.67–1.38; p interaction = 0.02) (see Supplementary Table 2). Among postmenopausal women, higher BMI was found to be protective for pure IDC only among AA women ($\geq$30 vs <25 kg/m^2, OR 0.22; 95 % CI 0.10–0.51; p interaction = 0.08). There was some indication that increasing parity was protective for pure IDC (OR 0.46; 95 % CI 0.21–1.01; p interaction = 0.24) and mixed IDC/DCIS (OR 0.61; 95 % CI 0.40–0.93; p interaction = 0.82) among EA women, but not among AA women, and older age at last birth was protective for pure IDC, but only among AA women (>33 vs $\leq$28 years, OR 0.48; 95 % CI 0.28–0.85; p interaction = 0.24).

Case–case associations with breast cancer risk factors

Case–case analyses comparing pure IDC to mixed IDC/DCIS as the "control" group are given in Table 3. EA women were less likely to be diagnosed with pure IDC compared to mixed IDC/DCIS in the age-adjusted model (OR 0.72; 95 % CI 0.52–1.01); however, this association was null in the fully adjusted model, largely attributable to additional adjustment for ER status (OR 1.07; 95 % CI 0.67–1.72, Model 3). Postmenopausal women with BMI $\geq$ 30 kg/m^2 were less likely to be diagnosed with pure IDC than mixed IDC/DCIS (OR 0.38; 95 % CI 0.19–0.79; p trend = 0.01) compared to women with BMI < 25 kg/m^2. Women who were current or former smokers were less likely to be diagnosed with pure IDC than mixed IDC/DCIS (OR 0.68; 95 % CI 0.45–1.01); however, this association was only of borderline significance. Women who breastfed up to 12 months (OR 0.55; 95 % CI 0.32–0.94) or longer (OR 0.47; 95 % CI 0.36–0.87) were approximately 50 % less likely to be diagnosed with pure IDC than with mixed IDC/DCIS (p trend = 0.18) compared to women who did not breastfeed.

We additionally compared case–case associations stratified by race to see whether risk factors were similarly associated in both AA and EA populations (Table 4). Among AAs, postmenopausal women with BMI > 30 kg/m^2 showed significantly reduced odds of pure IDC (OR 0.33; 95 % CI 0.13–0.86) compared to those with BMI $\leq$ 25 kg/m^2; no differences were observed among EA women. ORs below unity were also observed among EA women who breastfed up to 12 months (OR 0.34; 95 % CI 0.14–0.84) or longer (OR 0.37; 95 % CI 0.14–1.03) compared to women who did not breastfeed (p trend = 0.25), with similar, but nonsignificant findings among AA women. Race-stratified analyses were limited by small sample size, particularly among EA women, with only 67

Table 3 Case–case comparison of risk factors for pure IDC versus mixed IDC/DCIS in the WCHS ($n = 831$)

	Pure IDC $n = 181$ n (%)	Mixed IDC/DCIS $n = 650$ n (%)	Model 1 Age-adjusted OR (95 % CI) [a]	Model 2 Fully adjusted OR (95 % CI)[a]	Model 3 Fully adjusted OR (95 % CI)[a]
Race					
AA	114 (63.0)	348 (53.5)	1.00	1.00	1.00
EA	67 (37.0)	302 (46.5)	0.72 (0.52, 1.01)	0.82 (0.55, 1.20)	1.07 (0.67, 1.72)
			$p = 0.05$	$p = 0.30$	$p = 0.78$
Family history					
No	147 (81.2)	526 (80.9)	1.00	1.00	1.00
Yes	34 (18.8)	124 (19.1)	0.99 (0.65, 1.51)	1.04 (0.67, 1.60)	1.07 (0.67, 1.72)
			$p = 0.70$	$p = 0.87$	$p = 0.78$
Age at menarche (years)					
≥14	56 (30.9)	180 (28.0)	1.00	1.00	1.00
12–13	80 (44.2)	316 (49.2)	0.82 (0.54, 1.24)	0.90 (0.59, 1.38)	0.92 (0.57, 1.47)
<12	45 (24.9)	146 (22.7)	1.01 (0.64, 1.58)	1.06 (0.67, 1.67)	1.18 (0.71, 1.97)
			p trend = 0.90	p trend = 0.77	p trend = 0.46
OC use (months)					
0	74 (40.9)	242 (37.3)	1.00	1.00	1.00
1–72	58 (32.0)	232 (35.8)	0.79 (0.54, 1.18)	0.86 (0.58, 1.29)	0.89 (0.57, 1.37)
>72	49 (27.1)	175 (27.0)	0.87 (0.57, 1.33)	0.98 (0.63, 1.51)	0.88 (0.54, 1.43)
			p trend = 0.46	p trend = 0.58	p trend = 0.88
Postmenopausal MHT use					
No	51 (63.8)	212 (68.0)	1.00	1.00	1.00
Yes	29 (36.3)	100 (32.1)	1.21 (0.72, 2.03)	1.38 (0.80, 2.38)	1.41 (0.78, 2.56)
			$p = 0.64$	$p = 0.25$	$p = 0.26$
Current BMI (kg/m^2), *premenopausal*					
<25	31 (31.0)	115 (34.9)	1.00	1.00	1.00
25 to <30	24 (24.0)	100 (30.3)	0.89 (0.49, 1.62)	0.73 (0.39, 1.37)	0.59 (0.29, 1.20)
≥30	45 (45.0)	115 (34.9)	1.45 (0.85, 2.46)	1.01 (0.54, 1.89)	0.89 (0.45, 1.78)
			p trend = 0.10	p trend = 0.76	p trend = 0.58
Current BMI (kg/m^2), *postmenopausal*					
<25	27 (36.5)	71 (23.3)	1.00	1.00	1.00
25 to <30	23 (31.1)	86 (28.2)	0.70 (0.37, 1.33)	0.65 (0.33, 1.27)	0.73 (0.35, 1.51)
≥30	24 (32.4)	148 (48.5)	0.42 (0.23, 0.79)	0.36 (0.19, 0.70)	0.38 (0.19, 0.79)
			p trend = 0.03	p trend = 0.003	p trend = 0.01
Smoking					
No	113 (62.4)	365 (53.2)	1.00	1.00	1.00
Current/former	68 (37.6)	285 (43.9)	0.78 (0.56, 1.10)	0.77 (0.53, 1.11)	0.68 (0.45, 1.01)
			$p = 0.16$	$p = 0.15$	$p = 0.06$
Parity					
0	38 (21.0)	151 (23.2)	1.00	1.00	1.00
1	31 (17.1)	133 (20.5)	0.93 (0.55, 1.57)	0.82 (0.48, 1.40)	0.80 (0.43, 1.46)
2	60 (33.2)	190 (29.2)	1.27 (0.80, 2.01)	1.17 (0.73, 1.88)	1.11 (0.66, 1.87)
≥3	52 (28.7)	176 (27.1)	1.21 (0.75, 1.94)	0.92 (0.56, 1.53)	0.74 (0.42, 1.31)
			p trend = 0.26	p trend = 0.88	p trend = 0.56
Age at first birth (years)[b]					
≤22	68 (47.5)	225 (45.2)	1.00	1.00	1.00
>22 to ≤30	54 (37.8)	175 (35.1)	1.01 (0.67, 1.53)	1.37 (0.86, 2.16)	1.43 (0.86, 2.36)
>30	21 (14.7)	98 (19.7)	0.69 (0.40, 1.19)	1.11 (0.59, 2.08)	1.33 (0.65, 2.70)
			p trend = 0.23	p trend = 0.56	p trend = 0.66

Table 3 continued

	Pure IDC $n = 181$ n (%)	Mixed IDC/DCIS $n = 650$ n (%)	Model 1 Age-adjusted OR (95 % CI) [a]	Model 2 Fully adjusted OR (95 % CI)[a]	Model 3 Fully adjusted OR (95 % CI)[a]
Age at last birth (years)[c]					
≤28	66 (46.1)	189 (38.0)	1.00	1.00	1.00
>28 to ≤33	41 (28.7)	146 (29.3)	0.80 (0.51, 1.24)	0.81 (0.49, 1.32)	0.77 (0.45, 1.31)
>33	36 (25.2)	163 (32.7)	0.63 (0.40, 1.00)	0.63 (0.36, 1.10)	0.75 (0.44, 1.27)
			p trend = 0.04	p trend = 0.10	p trend = 0.28
Breastfeeding (months)[c]					
None	75 (52.4)	213 (42.7)	1.00	1.00	1.00
>0–12	40 (28.0)	171 (34.3)	0.63 (0.40, 0.97)	0.62 (0.39, 1.01)	0.55 (0.32, 0.94)
>12	28 (19.6)	115 (23.0)	0.64 (0.39, 1.05)	0.58 (0.34, 1.01)	0.47 (0.36, 0.87)
			p trend = 0.14	p trend = 0.11	p trend = 0.18

Model 1 was adjusted for age only

Model 2 was adjusted for age, race, birthplace, family history, composite screening score, education, OC use, age at menarche, parity, and menopausal status

Model 3 was adjusted for all variables in Model 2 with the addition of ER status

All associations were adjusted for covariates listed above unless the covariate was the main exposure of interest or was used as a stratification variable (menopausal status for BMI and MHT use)

IDC invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *WCHS* Women's Circle of Health Study, *OR* odds ratio, *CI* confidence interval, *AA* African-American, *EA* European-American, *OC* oral contraceptive, *MHT* menstrual hormone therapy, *BMI* body mass index

[a] Unconditional logistic regression models were used to estimate ORs and 95 % CIs

[b] Among 642 parous women only

[c] Among 642 parous women only, with an additional adjustment for age at first birth

cases of pure IDC. Interactions with race were not observed in case–case analyses.

Case–case associations with tumor characteristics

When associations with tumor characteristics were examined, tumors larger than 2 cm were more likely to be pure IDC than mixed IDC/DCIS (OR 1.58; 95 % CI 1.07–2.35 for tumors 2 to <5 cm; OR 2.16; 95 % CI 1.00–4.67 for tumors ≥5 cm) (Table 5). In addition to tumor size, ER-negative tumors were also associated with increased odds of pure IDC (OR 2.79; 95 % CI 1.93–4.05), while positive LN status (OR 0.55; 95 % CI 0.35–0.87) and LVI (OR 0.58; 95 % CI 0.36–0.92) were associated with reduced odds of pure IDC. Triple-negative tumors were over three times more likely to be pure IDC than mixed IDC/DCIS (OR 3.26; 95 % CI 2.08–5.12). Tumors discovered by palpation rather than mammogram were more likely to be pure IDC than mixed IDC/DCIS (OR 1.54; 95 % CI 1.02–2.32). A significant interaction between race and tumor grade in association with pure IDC was observed; EA women with higher-grade tumors were more likely to have pure IDC (OR 3.94; 95 % CI 1.32–11.7), whereas higher grade was not associated with pure IDC among AA women (OR 1.38; 95 % CI 0.81–2.37; p interaction = 0.02) (data not shown).

Case–case risk factor associations stratified by ER status

When stratified by ER status (Supplementary Table 3), reduced odds of being diagnosed with pure IDC compared to mixed IDC/DCIS were noted for ER-negative breast cancers among postmenopausal women with BMI ≥ 30 compared to women with BMI < 25. Greater time spent breastfeeding was similarly associated with lower odds of pure IDC among women with ER-positive and ER-negative breast cancers. Associations, however, were not statistically significant for EA women, likely due in part to sample size limitations. Interactions by ER status were not statistically significant.

Discussion

There are few reported studies in the literature investigating potential differences between pure IDC and mixed IDC/DCIS for invasive breast cancers [2, 6–9, 11, 17]. We hypothesized that risk factors for pure IDC may differ from those for mixed IDC/DCIS if these cancers are biologically distinct from one another [6]. Identification of a distinct risk factor profile for pure IDC could target women who should be more closely screened to prevent pure IDC

Table 4 Associations between breast cancer risk factors and odds of pure IDC compared to mixed IDC/DCIS, by AA and EA race, in the Women's Circle of Health Study, ($n = 755$)

	AA			EA		
	Pure IDC $n = 108$ *n* (%)	Mixed IDC/DCIS $n = 317$ *n* (%)	OR (95 % CI)[a]	Pure IDC $n = 67$ *n* (%)	Mixed IDC/DCIS $n = 263$ *n* (%)	OR (95 % CI)[a]
Age (years)						
<45	35 (32.4)	97 (30.6)	0.88 (0.47, 1.67)	17 (25.4)	67 (25.5)	0.93 (0.43, 2.03)
≥45	73 (67.6)	220 (69.4)	1.00	50 (74.6)	196 (74.5)	1.00
			$p = 0.70$			$p = 0.86$
Family history						
No	94 (87.0)	271 (85.5)	1.00	48 (71.6)	198 (75.3)	1.00
Yes	14 (13.0)	46 (14.5)	0.84 (0.42, 1.67)	19 (28.4)	65 (24.7)	1.17 (0.62, 2.21)
			$p = 0.62$			$p = 0.63$
Age at menarche (years)						
≥14	27 (25.0)	83 (26.2)	1.00	11 (16.4)	49 (18.6)	1.00
12–13	50 (46.3)	141 (44.5)	1.13 (0.63, 2.02)	32 (47.8)	146 (55.5)	0.84 (0.38, 1.83)
<12	31 (28.7)	93 (29.3)	1.15 (0.61, 2.17)	24 (35.8)	68 (25.9)	1.41 (0.62, 3.22)
			p trend = 0.68			p trend = 0.28
OC use (months)						
0	44 (40.7)	123 (38.9)	1.00	28 (47.8)	91 (34.6)	1.00
1–72	37 (34.3)	113 (35.8)	0.97 (0.56, 1.67)	24 (35.8)	94 (35.7)	0.83 (0.43, 1.63)
>72	27 (25.0)	80 (25.3)	0.98 (0.54, 1.81)	15 (22.4)	78 (29.7)	0.68 (0.31, 1.48)
			p trend = 0.62			p trend = 0.41
Postmenopausal MHT use						
No	33 (68.7)	121 (74.2)	1.00	16 (50.0)	72 (60.5)	1.00
Yes	15 (31.3)	42 (25.8)	1.26 (0.58, 2.74)	16 (50.0)	47 (39.5)	2.06 (0.80, 5.30)
			$p = 0.56$			$p = 0.14$
Current BMI (kg/m^2), *premenopausal*						
≤25	13 (21.7)	30 (19.7)	1.00	16 (47.1)	71 (50.7)	1.00
>25 to ≤30	14 (23.3)	48 (31.6)	0.46 (0.17, 1.23)	6 (17.6)	41 (29.3)	0.52 (0.17, 1.60)
>30	33 (55.0)	74 (48.7)	0.64 (0.26, 1.57)	12 (35.3)	28 (20.0)	1.88 (0.64, 5.53)
			p trend = 0.89			p trend = 0.68
Current BMI (kg/m^2), *postmenopausal*						
≤25	12 (26.7)	23 (14.5)	1.00	12 (38.7)	42 (36.2)	1.00
>25 to ≤30	16 (35.5)	43 (27.0)	0.62 (0.23, 1.69)	9 (29.0)	32 (27.6)	1.02 (0.33, 3.15)
>30	17 (37.8)	93 (58.5)	0.33 (0.13, 0.86)	10 (32.3)	42 (36.2)	0.70 (0.23, 2.15)
			p trend = 0.03			p trend = 0.53
Smoking						
No	72 (66.7)	193 (60.9)	1.00	36 (53.7)	137 (52.1)	1.00
Current/former	36 (33.3)	124 (39.1)	0.71 (0.41, 1.21)	31 (46.3)	126 (47.9)	0.95 (0.54, 1.70)
			$p = 0.21$			$p = 0.87$
Parity						
0	14 (12.3)	54 (15.5)	1.00	24 (35.8)	97 (32.1)	1.00
1	22 (19.3)	85 (26.6)	0.78 (0.33, 1.84)	9 (13.4)	48 (15.9)	0.80 (0.30, 2.11)
2	38 (33.3)	93 (26.7)	1.14 (0.52, 2.51)	22 (32.8)	97 (32.1)	1.06 (0.51, 2.21)
≥3	40 (35.1)	116 (33.3)	0.79 (0.35, 1.78)	12 (17.9)	60 (19.9)	0.65 (0.56, 1.65)
			p trend = 0.79			p trend = 0.58
Age at first birth (years)[b]						
≤22	54 (58.7)	168 (62.9)	1.00	10 (23.8)	38 (21.4)	1.00
>22 to ≤30	29 (31.5)	73 (27.3)	1.30 (0.72, 2.40)	20 (47.6)	83 (46.6)	0.81 (0.30, 2.16)

Table 4 continued

	AA			EA		
	Pure IDC $n = 108$ n (%)	Mixed IDC/DCIS $n = 317$ n (%)	OR (95 % CI)[a]	Pure IDC $n = 67$ n (%)	Mixed IDC/DCIS $n = 263$ n (%)	OR (95 % CI)[a]
>30	9 (9.78)	26 (9.7)	1.79 (0.72, 4.45)	12 (28.6)	57 (32.0)	0.76 (0.23, 2.49)
			p trend = 0.67			p trend = 0.92
Age at last birth (years)[c]						
≤28	52 (56.5)	131 (49.1)	1.00	11 (26.2)	42 (23.6)	1.00
>28 to ≤33	20 (21.7)	63 (23.6)	0.70 (0.36, 1.36)	15 (35.7)	66 (37.1)	0.82 (0.31, 2.16)
>33	20 (21.7)	73 (27.3)	0.75 (0.40, 1.42)	16 (38.1)	70 (39.3)	0.81 (0.31, 2.11)
			p trend = 0.19			p trend = 0.88
Breastfeeding (months)[c]						
None	52 (56.5)	132 (49.3)	1.00	23 (54.8)	61 (34.3)	1.00
>0–12	25 (27.2)	78 (29.1)	0.69 (0.36, 1.33)	11 (26.2)	70 (39.3)	0.34 (0.14, 0.84)
>12	15 (16.3)	58 (21.6)	0.47 (0.22, 1.04)	8 (19.0)	47 (26.4)	0.37 (0.14, 1.03)
			p trend = 0.20			p trend = 0.25

IDC invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor, *OR* odds ratio, *CI* confidence interval, *AA* African-American, *EA* European-American, *MHT* menstrual hormone therapy, *BMI* body mass index

[a] Unconditional logistic regression was used to estimate odds of having pure IDC versus mixed IDC/DCIS, with analyses adjusted for age, birthplace, family history, composite screening score, education, OC use, age at menarche, parity, menopausal status, and ER status. Analysis of MHT use was not adjusted for menopausal status since only postmenopausal women were included in the analysis. Associations were adjusted for covariates listed above unless the covariate was the main exposure of interest or was used as a stratification variable

[b] Among 580 parous women only

tumors, which have been shown to be associated with poorer prognosis than mixed IDC/DCIS [6–11]. To our knowledge, this is the first study to examine risk factors associated with pure IDC versus mixed IDC/DCIS. In this case–control study of breast cancer in AA and EA women, we found that higher BMI among postmenopausal women, older age at last birth, and longer duration of breastfeeding among parous women were protective for pure IDC, but not for mixed IDC/DCIS.

Demographic characteristics differed between pure IDC and mixed IDC/DCIS as well. Women with more education and more extensive history of breast cancer screening were less likely to have pure IDC than mixed IDC/DCIS. This is similar to findings for women with ER-negative breast cancer compared to women with ER-positive breast cancer, who were found to have attained less education and were screened less often [33]. Likewise, Starks et al. [34] found that breast cancer patients with p53 mutations were more likely to have lower incomes, and suggested that a lifetime of exposures associated with socioeconomic status might result in different breast cancer etiologies. To reduce potential bias resulting from an association between later detection and pure IDC diagnosis, we adjusted our models for screening history and education level.

Tumor characteristics differed between pure IDC and mixed IDC/DCIS in this and previous studies [5, 6, 10]. Pure IDC cases were not only more likely to be ER negative, but women with pure IDC were also less likely to have lymph node involvement or LVI. Previous studies have found pure IDC tumors to have higher Ki-67 expression [6], fewer associated calcifications [10], and a greater likelihood of being an interval breast cancer [5]. Pure IDC may show tumor characteristics associated with a fast-growing tumor etiology, with fewer cases of lymph node involvement among women with less education and possibly lower socioeconomic status.

Postmenopausal women with normal or lower BMIs were more likely to be diagnosed with pure IDC than mixed IDC/DCIS in our study. After menopause, when estrogen is no longer produced by the ovaries, adipose tissue is the depot for conversion of androgens to estrogens through aromatase activity [36, 37]. Estrogens are known to be related to breast cancer risk, and it is thought that higher risk with greater BMI in postmenopausal women is mediated through this mechanism [38]. Most studies show a greater association between risk and BMI among women with ER-positive breast cancer [39–42], although there are studies with discrepant findings [35, 43, 44]. There were no associations observed between mixed IDC/DCIS and BMI in this study. In case–control analyses, we found that higher BMI among postmenopausal women was unexpectedly associated with decreased odds of pure IDC, which is in contrast to previous studies looking at all breast cancers combined [38], suggesting that pure IDC may

Table 5 Associations between tumor characteristics and odds of pure IDC compared to mixed IDC/DCIS in the Women's Circle of Health Study ($n = 755$)

	Pure IDC $n = 175$ n (%)	Mixed IDC/DCIS $n = 580$ n (%)	OR (95 % CI)[a]
Age (years)			
<45	52 (29.7)	164 (28.3)	1.00
≥45	123 (70.3)	416 (71.7)	1.17 (0.65, 2.11)
			$p = 0.61$
Tumor size (cm)			
<2	74 (49.7)	347 (63.7)	1.00
2 to <5	63 (42.3)	174 (31.9)	1.58 (1.07, 2.35)
≥5	12 (8.0)	24 (4.4)	2.16 (1.00, 4.67)
			p trend = 0.008
Tumor grade			
1	22 (13.6)	91 (16.2)	1.00
2	48 (29.6)	240 (42.7)	0.75 (0.43, 1.34)
3	92 (56.8)	231 (41.1)	1.49 (0.86, 2.57)
			p trend = 0.01
TNM stage			
1	45 (38.8)	233 (49.8)	1.00
2	58 (50.0)	169 (36.1)	1.63 (1.03, 2.57)
3	13 (11.2)	66 (14.1)	0.87 (0.43, 1.75)
			p trend = 0.63
Lymph nodes			
Negative	81 (68.1)	269 (58.2)	1.00
Positive	38 (31.9)	193 (41.8)	0.55 (0.35, 0.87)
			$p = 0.01$
Lymphovascular invasion			
Negative	92 (73.6)	281 (64.3)	1.00
Positive	33 (26.4)	156 (35.7)	0.58 (0.36, 0.92)
			$p = 0.02$
ER			
Positive	96 (54.9)	450 (77.6)	1.00
Negative	79 (45.1)	130 (22.4)	2.79 (1.93, 4.05)
			$p < 0.0001$
PR			
Positive	88 (50.9)	370 (66.3)	1.00
Negative	85 (49.1)	188 (33.7)	1.87 (1.30, 2.68)
			$p = 0.0008$
HER2			
Negative	136 (84.0)	415 (77.9)	1.00
Positive	26 (16.0)	118 (22.1)	0.65 (0.41, 1.05)
			$p = 0.08$
Breast cancer subtypes			
Luminal A	79 (49.1)	341 (64.2)	1.00
Luminal B	14 (8.70)	78 (14.7)	0.78 (0.41, 1.46)
Non-luminal	12 (7.45)	40 (7.53)	1.30 (0.64, 2.63)
Triple negative	56 (34.8)	72 (13.6)	3.26 (2.08, 5.12)
			$p < 0.0001$
Method of tumor discovery			
Mammogram	53 (32.5)	231 (43.7)	1.00
Palpation	110 (67.5)	298 (56.3)	1.54 (1.02, 2.32)
			$p = 0.04$

IDC invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *OR* odds ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor 2, *OC* oral contraceptive

[a] Unconditional logistic regression models were used to estimate ORs and 95 % CIs. All models were adjusted for age, race, birthplace, family history, composite screening score, education, OC use, age at menarche, parity, and menopausal status. Associations were adjusted for covariates listed above unless the covariate was the main exposure of interest

represent a subset of breast cancer with unique risk factors. A decreased risk of overall invasive breast cancer was observed among postmenopausal AA women with BMI ≥ 25 in the Black Women's Health Study, similar to the decreased risk of pure IDC observed among postmenopausal AA women in our study [44]. It is known that BMI influences metabolic pathways [45] and subsequently may influence cancer development and progression [46]. In one follow-up study of 2,092 breast cancer survivors, women with metabolic syndrome were twice as likely to experience distant metastasis [47]. It is possible that BMI measured at baseline might have been affected by breast cancer treatment since home interviews with anthropometric measurements were conducted approximately 6 months after diagnosis. Potential bias from the effect of treatment on BMI, however, cannot explain the different estimates found between pre- and postmenopausal women.

We observed an inverse association between breastfeeding and pure IDC compared to mixed IDC/DCIS. Breastfeeding appears to be modestly protective for breast cancer [48–50], but seems to be substantially more protective against the more aggressive breast cancer subtypes, including hormone receptor-negative and basal-like cancers in most [29, 51–54], but not all studies [30, 55]. Mechanisms postulated for these effects include the reduction in ovulatory cycles, induction of breast differentiation, and the presence of human milk complex of alpha-lactalbumin and oleic acid (HAMLET) secreted in milk that causes tumor cells to undergo apoptosis [56–60]. Women with an older age at last birth also had reduced odds of pure IDC, contrary to the noted increase in breast cancer risk in women up to 10 years after pregnancy [61]. More studies are needed to examine reproductive factors associated with breast cancer in AA women compared to EA women.

Previous studies describe an association between ER-negative breast cancer and pure IDC [6, 11]. Because pure IDC tumors are more likely to be ER negative, the observed association between breastfeeding and reduced odds of pure IDC in relation to mixed IDC may be similar to previous studies showing a greater protective effect of breastfeeding against ER-negative tumors [29, 51–54]. However, despite the strong association of pure IDC with negative ER status, observations after stratification by ER status indicated that the association between longer duration of breastfeeding and reduced risk of pure IDC did not depend upon ER status and therefore unlikely to be mediated by estrogen-related pathways.

AA breast cancer patients present more often than EA patients with positive LNs and tumors that are larger, higher grade, ER negative, and later stage, i.e., characteristics associated with a poor prognosis [62–66]. Because disease characteristics associated with pure IDC are also more common in AA women, the presence or absence of a DCIS component may reflect a distinct natural history that could account for some of the differences observed between AA and EA patients. In our study, AA women with breast cancer were more likely to have pure IDC than mixed IDC/DCIS, but observed associations between breast cancer risk factors and risk of pure IDC or mixed IDC/DCIS, with the exception of OC use, BMI among postmenopausal women, parity, and age at last birth, were not found to be differential by race. Once adjustment for demographic and breast cancer risk factors was added to the model, however, the increased odds of pure IDC among AA women were attenuated, suggesting that the development of pure IDC versus mixed IDC/DCIS is related, in part, to different risk factor and demographic profiles. The higher occurrence of pure IDC due to these factors may account for some of the disparities observed in breast cancer characteristics between AA and EA women.

Strengths of this study include the large number of participants and extensive information provided by in-person interviews, pathology reports, and tumor samples available in the WCHS, allowing for the examination of several risk factors and tumor characteristics with adjustment for potential confounders. Rarer forms of breast cancer were not included and cases were limited to invasive tumors with ductal histology so that analyses could be focused on a set of tumors with more similar etiologies and prognosis. Finally, this is the first study of our knowledge that has examined the association of breast cancer risk factors and the presence or absence of an in situ component concomitant to invasive carcinoma, which could affect disease prognosis. In addition, we had the benefit of looking at associations within AA and EA women.

Several potential limitations should be noted when interpreting these data. First, missing data on the histology of breast tumors led to the exclusion of 30 % of cases from our analyses, which could have biased our findings if records between pure IDC and mixed IDC/DCIS were differentially or systematically missing from a group of women that shared similar risk factors. We compared tumor characteristics and risk factors between WCHS participants with and without missing histologies and found no significant differences. ER status, tumor size, breastfeeding, and BMI in women with missing tumor histologies were intermediate between women with pure IDC and mixed IDC/DCIS, suggesting a similar proportion of women with missing data among women with pure IDC and mixed IDC/DCIS. Secondly, lack of standardization of pathology reports collected from a number of different hospitals may have introduced misclassification, possibly attenuating associations if misclassifications were non-differential across our variables of interest. Analyses of pure IDC and mixed IDC/DCIS diagnoses at individual hospitals did not identify any significant differences in the proportion of pure IDC to mixed IDC/DCIS to indicate reporting biases stemming from pathology reports. Additionally, two breast pathologists reviewed selected slides from registered cases to verify the presence or absence of DCIS. Some hospitals did report greater numbers of women with negative ER status, which may reflect possible differences in the reporting of ER status or true underlying differences in the patient populations served. Finally, bias may have been introduced with earlier detection of mixed IDC/DCIS compared to pure IDC if women with mixed IDC/DCIS are more likely to obtain screening mammography. Women with pure IDC, who tend to be less educated, may have lower access to screening and present at a later disease stage with larger cancers, although this does not explain why women with pure IDC were less likely to have positive lymph node status. To reduce potential bias resulting from screening, we included a screening score in our models and adjusted for education, although residual confounding may still have occurred since the score only contained information on ever screening behavior rather than screening behavior close in time to the cancer diagnosis.

Conclusions

In conclusion, breast cancer has been described as a heterogeneous disease based upon a range of genetic factors, molecular profiles, and clinical manifestations. The presence or absence of a DCIS component, a tumor characteristic associated with breast cancer outcomes, may represent different etiologic pathways for breast cancer. Some risk factors varied significantly between cases with pure IDC and mixed IDC/DCIS. Although a portion of pure IDC cancers may have progressed from mixed IDC/DCIS cancers, the absence of a DCIS component may also

represent a tumor type with a distinctive developmental pathway, associated with lower BMI in postmenopausal women and shorter breastfeeding duration. These findings need to be confirmed in a larger study. Understanding of modifiable risk factors associated with reduced risk of pure IDC can potentially be applied to preventing this breast cancer subtype.

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Compliance with ethical standards WCHS protocols for agreement to participate and informed consent were approved by the institutional review boards at Roswell Park Cancer Institute (RPCI), Rutgers Cancer Institute of New Jersey (CINJ), Icahn School of Medicine at Mount Sinai School (ISMMSS, formerly the Mount Sinai School of Medicine), and the participating hospitals in NYC in compliance with the Declaration of Helsinki.

Conflict of interest The authors declare that they have no competing interests.

Informed consent Informed consent was obtained from all individual participants included in the study.

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