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Reproductive and Hormonal Risk Factors for Ductal Carcinoma *in situ* of the Breast

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Abstract

One-fifth of all newly diagnosed breast cancer cases are ductal carcinoma *in* situ (DCIS), but little is known about DCIS risk factors. Recent studies suggest that some subtypes of DCIS (high grade, or comedo) share histopathologic and epidemiologic characteristics with invasive disease, while others (medium or low grade, or non-comedo) show different patterns. To investigate whether reproductive and hormonal risk factors differ among comedo and non-comedo types of DCIS and invasive breast cancer, we used a population-based case-control study of 1808 invasive and 446 DCIS breast cancer cases and their age and race frequency-matched controls (1564 invasive and 458 DCIS). Three or more full-term pregnancies showed a strong inverse association with comedo-type DCIS (odds ratio (OR) = 0.53, 95% confidence interval (CI) = 0.30, 0.95) and a weaker inverse association for non-comedo DCIS (OR = 0.73, 95% CI = 0.42, 1.27). Several risk factors (age at first full-term pregnancy, breastfeeding, and age at menopause) demonstrated similar associations for comedo-type DCIS and invasive breast cancer, but different associations for non-comedo DCIS. Ten or more years of oral contraceptive showed a positive association with comedo-type DCIS (OR = 1.31, 05% CI 0.70, 2.47) and invasive breast cancer (OR = 2.33, 95% CI 1.06, 5.09), but an inverse association for noncomedo DCIS (OR = 0.51, 95% CI 0.25-1.04). Our results support the theory that comedo-type DCIS may share hormonal and reproductive risk factors with invasive breast cancer, while the etiology of non-comedo DCIS deserves further investigation.

Keywords

ductal carcinoma in situ; risk factors; breast cancer; epidemiology; reproductive

INTRODUCTION

Carcinoma *in situ* (CIS) of the breast, a classification for malignant cells that have not moved beyond the epithelium to invade the basal membrane, is further categorized as either

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lobular (LCIS) or ductal (DCIS), depending on its location (1). In addition, DCIS can be classified into comedo (high grade) and non-comedo (medium or low grade) subtypes based on histopathologic characteristics such as pattern of necrosis and maximum nuclear diameter. Both biologic and epidemiologic evidence suggest that some DCIS develops into invasive disease while other forms of DCIS may not progress to invasive breast cancer (IBC) (2-7).

Age-adjusted incidence rates for DCIS increased from 2.3 per 100,000 females in 1973 (8) to 15.8 per 100,000 in 1992 (9). The most dramatic increases have occurred since 1983, with a 17.5% annual increase in incidence rates between 1983 and 1992 compared with increases of 3.9% annually from 1973 to 1983 (9). Separate studies in Detroit (10), Connecticut (11), Vaud, Switzerland (12), and Florence, Italy (13) have shown that most of this increase was due to the introduction of screening mammography in the early 1980s and subsequent increases in its use in women age 40 and over. However, since 1992, the proportional change in incidence rates for DCIS has slowed, especially for comedo DCIS (14). In addition, 80% of all DCIS diagnosed in the US since 1980 were non-comedo type.

Whether or not DCIS lesions found through increased detection will progress to invasive disease is unknown. It is generally believed that comedo-type DCIS is more similar histologically to invasive disease than is the non-comedo-type. Studies of women diagnosed with concomitant DCIS and invasive breast cancer or with IBC following a DCIS diagnosis have reported that higher grade DCIS is associated with higher grade IBC (15-20). Estimated DCIS prevalence rates based on autopsy studies of women who died from causes other than breast cancer range from 0.2% to 14.7%, compared with 0-1.8% for invasive breast cancer (21). Therefore, some *in situ* lesions may take much longer to develop invasive characteristics or may never become invasive during a woman's lifespan. Because of the uncertainties regarding DCIS progression, most lesions are treated aggressively. Understanding the differences in risk factor profiles, if any, between DCIS subtypes is a first step toward identifying which lesions may be more likely to progress to invasive disease.

Many of the accepted risk factors for invasive breast cancer involve hormonal exposures, particularly to estrogen, whether directly through exogenous use (oral contraceptives, hormone replacement therapy) or indirectly through reproductive events such as timing of menarche and menopause, pregnancy, and lactation. Previous studies have found nulliparity, late age at first pregnancy, early menarche, late menopause, no lactation, and exogenous hormone use associated with invasive breast cancer (22). The connection between estrogen and *in situ* breast cancer is less clear.

We examined known hormonal and reproductive risk factors for invasive breast cancer to determine whether they are risk factors for DCIS, and to determine whether risk factors differ for comedo and non-comedo DCIS subtypes. Odds ratios for DCIS as well as for DCIS subtypes (comedo, non-comedo) were compared directly with those of invasive breast cancer in the same North Carolina study population.

MATERIALS AND METHODS

Study design

The Carolina Breast Cancer Study (CBCS) is a population-based case-control study of *in situ* and invasive breast cancer in African-American (AA) and Caucasian women (23). Eligible study participants were residents of 24 contiguous counties of eastern and central North Carolina who were aged 20 to 74 at time of diagnosis (cases) or selection (controls). Women with first breast cancer diagnoses (*in situ* or invasive) were identified through a rapid-ascertainment system in conjunction with the North Carolina Central Cancer Registry

(24), and controls were located via computerized lists from the Department of Motor Vehicles (under age 65) and the Health Care Finance Administration (age 65 and over). Controls were frequency-matched to cases on race and 5-year age intervals.

Invasive cases were enrolled in two phases, between 1993 and 1996 (Phase 1) and from 1996 through 2001 (Phase 2), and were over-sampled for African-Americans and younger age (20-49 years). Specifically, a process of randomized recruitment using predetermined probabilities (25) was used to balance four groups based on age and race: younger African Americans, older African-Americans, younger non-African Americans, and older non-African Americans, described in detail elsewhere (23).

In situ case enrollment occurred between 1996 and 2001 and included pure DCIS, DCIS with microinvasion to a depth of 2mm, and LCIS. All *in situ* cases matching the age and geographic constraints mentioned above were eligible for the study, with no oversampling on race or age.

Study population

A total of 705 carcinoma *in situ* (CIS) cases were identified during the enrollment period. Of these, 50 were ineligible or deceased, leaving 655 eligible cases. Five cases could not be contacted, physicians refused participation for 51 cases, and 58 declined to participate. Therefore, 541 CIS cases participated resulting in an overall response rate (participants / eligible cases) of 82.6%. Thirty-eight participants were excluded from the current analysis because they completed only a mini questionnaire that did not include hormonal or reproductive questions, along with 28 cases of pure LCIS and 29 cases of DCIS with microinvasion, leaving 446 pure DCIS cases. Of the 940 DCIS controls sampled, 122 were ineligible or deceased, 88 could not be located, and 197 refused participation. A total of 458 DCIS controls completed the full questionnaire, resulting in an overall response rate among eligible controls of 65.2%.

Risk factor distributions were similar for invasive breast cancer cases enrolled in both phases of data collection, so data for all IBC cases from Phase 1 and Phase 2 were combined to maximize statistical power, for a total of 2704 identified cases. Of those, 201 were ineligible or deceased, 64 could not be contacted, physicians refused participation for 175, and 361 declined to participate, resulting in an overall response rate among eligible cases of 76.0%. In addition, 95 invasive breast cancer cases were excluded because they completed only the mini questionnaire, leaving 1808 IBC cases for the current analysis. A total of 3600 controls for invasive breast cancer cases were identified, of which 427 were ineligible or deceased, 689 could not be located, and 739 declined participation, resulting in an overall response rate for eligible controls of 55.0%. Controls who did not complete the full questionnaire were excluded (n=175), leaving 1564 controls for the IBC study analyses.

Central pathology review

Initial DCIS diagnosis was assigned by the referring physician and verified for 446 cases by a pathologist employed by the CBCS based on a review of pathology reports and H&E stained slides. Less than two percent of the cases reviewed were classified as something other than DCIS based on the CBCS pathologist's evaluation. DCIS subtype classification was based on a detailed microscopic examination of an H&E stained slide for each case. Cases classified as comedo DCIS had a comedo-type pattern of necrosis and two of the following three characteristics: large or very large nuclear diameter (>2 times the diameter of a red blood cell), vesicular nuclear pleomorphism, or prominent nucleoli. All other DCIS cases were classified as non-comedo. Fifty-six DCIS cases were not subtyped, leaving a total of 393 DCIS cases (163 comedo and 230 non-comedo) for DCIS subtype analyses.

Data collection and description of variables of interest

Trained female nurses conducted in-person interviews at the woman's home or another agreed upon location using a structured questionnaire. Topics covered by the questionnaire include sociodemographic factors, menstrual and pregnancy history, medical history, hormone use, family history of cancer, physical activity and occupational history. The nurse measured height and weight at the time of the interview; all other questions were answered via self-report. Participants were given visual aids to assist with recall, such as pictures of common prescription and non-prescription drugs and calendars to pinpoint dates. Average time between diagnosis and interview was 198 days for DCIS cases and 145 days for invasive breast cancer cases.

Main hormonal and reproductive risk variables included parity (categorized for analyses as no full-term pregnancies, one, two, three or more), age at first full-term pregnancy (<26, 26+), lactation (never, ever), oral contraceptive (OC) use (never, ever) and duration of OC use (<5 years, 5 to 10 years, >10 years), use of hormone replacement therapy (HRT) (never, ever), duration of HRT use (<5 years, 5-10 years, >10 years) and recency of HRT use (never, current, former 5+ years since last use), age at menopause (<40, 40-49, 50+), and age at menarche (≤11, 12, 13, 14+). Participants who classified their race as American Indian/Eskimo, Asian or Pacific Islander, or Other (n=13 for DCIS, n=53 for invasive) were combined with Whites, resulting in two race categories: African-American and non African-American. Age at the time of interview was computed from self-reported birth date and included in all analyses as a continuous variable. Women under age 50 were considered postmenopausal if they had undergone natural menopause (menstruation cessation), bilateral oophorectomy, or irradiation of the ovaries. In women aged 50 or older, menopausal status was assigned based on menstruation cessation. Natural and surgical menopause were combined for analysis, since duration of estrogen exposure was the main focus.

Statistical analyses

The main outcome variable was ductal carcinoma *in situ*, which included all cases of pure DCIS. Differences in exposure and outcome variable distributions by case-control status and histological type were evaluated using chi-square tests generating two-sided p-values. Odds ratios and 95 percent confidence intervals were computed using unconditional logistic regression. Tests for trend were conducted by evaluating the p-value for the beta coefficient where exposure was coded as an ordinal variable. Case-control analyses were conducted for all data in order to estimate main effects for the risk factors, comparing each case group (DCIS or invasive) to frequency-matched controls. In addition to analyses for all DCIS cases combined, univariate and multivariate analyses were conducted for DCIS cases stratified on histopathologic subtype (comedo vs. non-comedo) and case-case analyses were used to identify factors with different relationships between comedo and non-comedo DCIS (26). All regression models contained an offset term to account for the sampling probabilities used to identify eligible cases and controls (25). If removal of the covariate from the model resulted in a 10 percent or larger change in stratum-specific regression coefficients, that variable was considered a confounder and remained in the final model.

All evaluations of potential effect measure modification and confounding were conducted on the *in situ* and invasive datasets separately. The resulting model included covariates that met modeling criteria for either dataset in order to facilitate direct comparisons between *in situ* and invasive model estimates. All statistical analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Distributions

A total of 904 women participated in the DCIS study, of which 18.1 percent were African-American (N=164). The mean age of all DCIS cases combined (55.16 ± 11.07 SD) and of comedo and non-comedo cases (Table 1) was slightly higher than that of controls (54.46 ± 10.26 SD), and a higher percentage of DCIS cases than controls were African-American (21.1% of all DCIS combined vs. 15.3% of controls). Comedo DCIS cases were slightly more likely to have a first degree family member with breast cancer and a college education and were more often in the highest income bracket than non-comedo cases.

Invasive breast cancer cases and controls were slightly younger than their DCIS counterparts, as reflected in both mean and median ages. IBC cases and controls included larger proportions of African-Americans than corresponding DCIS cases and controls because African-Americans were over-sampled for the IBC study. Phase II IBC cases had a higher percentage of African-American participants than phase I IBC cases.

Age and race were included in all multivariate models along with the offset terms to account for probability sampling by age and race age. No other covariates met our criteria for inclusion in models as a confounder, and there was no significant odds ratio modification by any of the evaluated covariates at a 0.05 alpha level.

DCIS and invasive cases vs. controls

A first full-term birth under age 26 was inversely associated with both DCIS and invasive breast cancer. An inverse association with parity strengthened with number of full-term pregnancies in the DCIS group but remained relatively constant for IBC, regardless of number of pregnancies (Table 2). Ever having breastfed was not associated with DCIS but was inversely associated with invasive cancer.

Increasing duration of OC use was positively associated with invasive breast cancer but not DCIS. Any HRT use was not associated with DCIS in this study but was inversely associated with invasive disease, with some evidence of a stronger association for greater than 10 years of HRT use. Odds ratios were also more strongly inverse for IBC compared to DCIS for current but not former HRT use (data not shown). Younger age at menopause (<40) was inversely associated with both invasive disease and DCIS, although the strength and consistency of the relationship was more apparent for IBC. Similarly, older ages at menarche showed inverse associations with both DCIS and IBC but were more consistent for IBC. Each increase in age at menarche was associated with a decrease in odds ratio for IBC.

DCIS comedo vs. non-comedo

Experiencing at least one full-term pregnancy was inversely associated with comedo DCIS, with stronger inverse associations for increasing numbers of full-term births (Table 3). Non-comedo DCIS were inversely associated with three or more full-term births, but the association was weaker than the corresponding odds ratio for comedo DCIS. Ever breastfeeding was not significantly associated with either comedo or non-comedo DCIS, though the OR was less than 1.0 for comedo but not non-comedo DCIS. Similarly, odds ratios for ever use of hormone replacement therapy were not statistically significant for either DCIS subtype, although the association was inverse for comedo but not non-comedo DCIS. Odds ratios for recent and former HRT were more strongly inverse for comedo compared to non-comedo DCIS (data not shown). When comedo and non-comedo DCIS

cases were compared in a case-case analysis, ORs were statistically significant only for duration of OC use; however, these associations were based on small numbers of cases.

Results did not differ substantially when we adjusted for history of screening mammography (data not shown).

DISCUSSION

Using a large, population-based study of carcinoma *in situ* of the breast and invasive breast cancer, we evaluated known hormonal and reproductive risk factors for invasive breast cancer to determine whether they are also risk factors for DCIS. Parity and younger age at first full-term pregnancy, and younger age at menopause (<40) were inversely associated with both DCIS and IBC, while older age at menopause was positively associated with IBC only, and older age at menarche was inversely associated with IBC only. Ten or more years of oral contraceptive use showed a positive association with comedo-type DCIS and invasive breast cancer but an inverse association for non-comedo DCIS.

When DCIS cases in our study were separated into the two main histologic subtypes, comedo and non-comedo, comedo-type DCIS associations paralleled invasive results more frequently than non-comedo DCIS. Specifically, parity, lactation, and HRT use were inversely associated with both comedo DCIS and IBC. These results support the theory that DCIS is not a uniform disease, and similarities in risk factors between comedo DCIS and invasive breast cancer are in agreement with data showing that comedo DCIS is more closely related to invasive breast cancer (27).

Many studies examined reproductive risk factors for invasive breast cancer and DCIS, but differences in study designs, methods, and populations make comparisons of results difficult. Including both DCIS and invasive cases from the same population circumvents many of those issues, allowing for direct comparison between odds ratios. Six previous studies of reproductive or hormonal risk factors for DCIS have included invasive cases as well (28-33), and as with the current study, these studies found few differences in risk factors between DCIS and invasive disease. Two other studies examined reproductive risk factors in CIS cases only (34, 35). Parity (28-31, 33-35), young age at first full-term pregnancy (28, 29, 31-34), and older age at menarche (28, 33) were inversely associated with both outcomes, while older age at menopause and postmenopausal hormone replacement therapy use (31, 33) have been positively associated with both forms of cancer.

Only one other published study examined reproductive risk factors for comedo and noncomedo DCIS specifically, which were limited to parity and age at first full-term birth (29). In that study, the authors found no association with parity and either DCIS subtype and a positive association between comedo DCIS and age at first birth of 25 or higher (OR=1.38, 95% CI 1.02-1.88 for age 25-29, OR=1.63, 1.05-2.52 for age 30+). In contrast, parity showed a stronger inverse association with comedo DCIS than with non-comedo or all DCIS combined in our study, especially for two or more full-term pregnancies.

Evidence suggests that a woman's breasts reach full maturity after a full-term pregnancy, making the cells less vulnerable to neoplastic changes (36). In the current study, ever having a full-term pregnancy was inversely associated with invasive breast cancer. For DCIS, the protective association was limited to those with a first full-term pregnancy under age 26. Nine previous DCIS risk factor studies included parity and age at first full-term pregnancy, all of which found results similar to ours (29-31, 33-35, 37, 38).

In the current study, lactation was inversely associated with IBC but showed no overall association with DCIS. Only three other studies assessed associations with lactation and

DCIS (30, 31, 35). Two found no association between breastfeeding and either DCIS or IBC (30, 31), but in the third study, lactating for 24 months or more was associated with DCIS (OR=2.00, 95% CI 1.11-3.60) (35). These varied findings may be due to differences in lactation practices in the underlying populations. For instance, breastfeeding is more prevalent and done for longer periods of time in China, where a significant inverse association with lactation for more than 24 months was found for IBC (OR=0.46, 0.27-0.78) (39).

Estrogen levels play an important role in reproductive events. Increase in estrogen leads to menarche, and decreasing levels precipitate menopause. In addition, estrogen augmented by progesterone has been shown to promote cell division, which increases the chance of mutant cell growth (40). The current study results support this theory for both invasive breast cancer and DCIS. Other studies that examined age at menarche and menopause found mixed results. Three found no association between age at menarche and DCIS or invasive disease (30, 34, 38). Of the two others reporting an association with age at menarche, Longnecker et al used the youngest age group as the referent and found an inverse association with the oldest age group (≥14 years) for both DCIS and invasive disease (OR=0.36, 0.15-0.87 for DCIS, OR=0.61, 0.43-0.86 for invasive) (33), while Kerlikowske et al found a positive association for the youngest age at menarche group (≤12 years) compared with those over age 12 at menarche for invasive breast cancer only (OR=1.9, 1.4-2.7) (28). Menopause at age 55+ was associated with DCIS (OR=1.53, 1.07-2.18) and IBC (OR=2.85, 1.37-6.35) in the Longnecker et al study (33) but was associated with DCIS only in the study by Claus et al (2001) (OR=1.71, 1.05-2.77). Age 45+ at menopause showed an increased association with IBC only in the study by Trentham-Dietz et al (OR=1.03, 1.02-1.04 continuous per year). One other study reported no association between age at menopause and either DCIS or invasive disease (38).

The link between oral contraceptive use and breast cancer risk is less clear than with other hormonal risk factors, especially among earlier-stage cancer. OC use showed no association with DCIS or invasive disease in our study. All other studies that included both invasive and DCIS cases found OC use was positively associated with IBC but not associated with DCIS (31, 32, 41-43).

Although most other studies found that postmenopausal hormone replacement therapy was positively associated with either DCIS or invasive breast cancer (31, 33, 34, 38, 44, 45), HRT was inversely associated with IBC in our study, especially among those using HRT for longer than 10 years. While this difference is puzzling, one explanation may be that we did not differentiate between estrogen-only and estrogen-plus-progestin regimens. Two studies which did examine HRT (estrogen and progesterone) and ERT (estrogen only) separately found HRT associated with DCIS (OR=1.75, 95% CI 1.10-2.80 for Longnecker et al, OR=2.3, 95% CI 1.3-3.9 for Schairer et al) but not with IBC (OR=1.14, 95% CI 0.91-1.43 and OR=1.1, 95% CI 0.9-1.4, respectively), while ERT was not associated with either outcome (33, 45). A third study found ERT associated with IBC (OR=2.22, 1.18-4.17) but not with DCIS and no association between HRT and either outcome (44). Another reason for the difference between our results and those of other studies for HRT could be that a higher percentage of our controls reported ever using HRT (50.3% for invasive, 63.9% for DCIS) than the rate of HRT use in the general population (44%) (46).

A strength of the CBCS is that the population base in North Carolina includes African Americans, who have been under-represented in previous epidemiologic studies of DCIS. Differences between our results and other studies could reflect the underlying study populations. For example, in our study population, African-American participants were statistically significantly less likely to use postmenopausal hormone replacement therapy

than Caucasians (47). Unlike the invasive portion of the CBCS where African Americans were over-sampled, all cases of DCIS were eligible the *in-situ* portion of the study. The number of minority participants with DCIS was not sufficient to conduct separate analyses by race, so it is difficult to draw specific conclusions about risk factors for DCIS among African Americans. In addition, overall response rates in our study were lowest for African-American controls, suggesting that future studies should focus recruitment efforts on increasing participation among minorities and controls in particular.

Selection bias was a potential issue for this study, since case participants could have had better and more frequent access to healthcare and therefore mammography screening. However, the data was analyzed stratified on frequency of doctor's visits and having had a mammogram in the two years previous to participation in the study, and neither affected the odds ratios (data not shown). Finally, because there is no universal classification system for DCIS pathology, comedo and non-comedo cases could have been misclassified. Unpublished data by the authors of the current study on DCIS subtype classification errors indicate that pathologist errors are predominantly in favor of the more severe (comedo) category. Therefore, a sensitivity analysis was conducted by increasing the number of comedo cases using the methods described by Rothman and Greenland (48), which determined that over one-third would have to be incorrectly classified to have had any impact on the results.

It has already been established that women with non-comedo type DCIS should be evaluated and treated using criteria different from those of the more aggressive types of DCIS. Our results support this conclusion, suggesting that comedo type DCIS may be more similar to invasive breast cancer with regard to underlying etiology. However, future studies will need to include larger numbers of both DCIS subtypes in order to clarify associations between each subtype and potential risk factors. With more women being diagnosed at earlier stages of breast cancer, large epidemiologic studies of DCIS with sufficient power to stratify on comedo versus non-comedo histology are feasible and likely to be highly informative.

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Table 1

Characteristics of ductal carcinoma *in situ* (DCIS)* and invasive cases and controls

	Comedo DCIS N=163		Non-comedo DCIS N=230		DCIS Controls N=458		Phase I Invasive Cases N=861		Phase II Invasive Cases N=947		Invasive Controls N=1564	
Covariate	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Age at selection/diagnosis												
Mean (SD)	54.8 (10.8)		55.2 (10.7)		54.5 (10.3)		51.0 (11.8)		51.9 (11.3)		52.0 (11.5)	
Median	55		55		53		48		50		49	
Range	27-74		28-74		27-74		21-74		24-74		21-74	
Race												
Non African-American	128	78.5	179	77.8	388	84.7	526	61.1	494	52.2	846	54.1
African-American	35	21.5	51	22.2	70	15.3	335	38.9	453	47.8	718	45.9
First degree family history of breast cancer												
Yes	36	22.8	44	19.8	58	12.9	126	15.1	166	18.1	183	12.1
No	122	77.2	178	80.2	392	87.1	711	84.9	752	81.9	1331	87.9
Missing	5		8		8		24		29		50	
Highest education level												
<High school (HS)	16	9.8	26	11.4	63	13.8	158	18.4	172	18.2	295	18.9
High school/post-HS	98	60.1	140	61.1	256	55.9	460	53.4	510	53.8	863	55.2
College+	49	30.1	63	27.5	139	30.4	243	28.2	265	28.0	405	25.9
Missing			1								1	
Income												
<$15,000/yr	23	15.3	43	20.1	46	11.0	202	25.2	202	23.0	321	22.4
$15K - <$30K/yr	32	21.3	42	19.6	114	27.1	176	22.0	216	24.6	322	22.5
$30K - <$50K/yr	32	21.3	56	26.2	101	24.0	192	24.0	207	23.6	350	24.4
$50,000/yr+	63	42.0	73	34.1	159	37.9	231	28.8	253	28.8	439	30.7
Missing	13		16		38		60		69		132	

*Excluding 56 DCIS cases not classified into subtype by the study pathologist.

Table 2

Multivariate-adjusted * Odds Ratios of Reproductive Risk Factors for Ductal Carcinoma *in situ* (DCIS) and Invasive Breast Cancer (IBC)

	DCIS			IBC		
Variable	**Cases N=446**	**Controls N=458**	**OR (95% CI)**	**Cases N=1808**	**Controls N=1564**	**OR (95% CI)**
Parity (No. of full-term pregnancies						
None	69	56	1.00	275	174	1.00
One	74	62	0.98 (0.60, 1.61)	316	279	0.76 (0.59, 0.98)
Two	159	175	0.73 (0.48, 1.12)	557	496	0.78 (0.62, 0.98)
Three or more	144	165	0.62 (0.40, 0.97)	660	615	0.79 (0.63, 0.99)
P for trend			0.02			0.14
Age at First Full-Term Pregnancy						
Nulliparous	69	56	1.00	275	174	1.00
<26 years	250	297	0.63 (0.42, 0.95)	1124	1057	0.77 (0.62, 0.95)
26+ years	127	105	0.99 (0.64, 1.55)	403	330	0.80 (0.63, 1.03)
Missing	0	0		7	3	
Lactation						
Never	261	273	1.00	1174	950	1.00
Ever	185	185	1.02 (0.78, 1.34)	634	614	0.77 (0.67, 0.89)
Oral Contraceptive (OC) Use						
Never	161	156	1.00	625	572	1.00
Ever	282	300	1.11 (0.80, 1.53)	1177	981	1.11 (0.94, 1.32)
Missing	3	2		6	11	
Age at first OC use						
Never	161	156	1.00	625	572	1.00
<20	78	101	0.74 (0.46, 1.18)	444	347	1.04 (0.83, 1.31)
20+	202	198	1.18 (0.85, 1.63)	730	632	1.13 (0.95, 1.34)
Missing	5	3		9	13	
Duration of OC Use						
Never	161	156	1.00	625	572	1.00
<5 years	140	136	1.21 (0.85, 1.74)	538	489	1.06 (0.88, 1.28)
5 to 10 years	94	107	1.03 (0.69, 1.53)	411	323	1.15 (0.93, 1.42)

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	DCIS			IBC		
Variable	**Cases N=446**	**Controls N=458**	**OR (95% CI)**	**Cases N=1808**	**Controls N=1564**	**OR (95% CI)**
>10 years	48	57	0.95 (0.59, 1.55)	228	169	1.21 (0.94, 1.56)
Missing	3	2		6	11	
Age at menarche						
≤11	98	87	1.00	405	306	1.00
12	131	136	0.85 (0.58, 1.25)	516	413	0.95 (0.78, 1.16)
13	105	140	0.66 (0.45, 0.98)	484	422	0.86 (0.70, 1.05)
14+	111	95	0.98 (0.65, 1.47)	401	415	0.72 (0.59, 0.89)
Missing	1	0		2	8	
P for trend			0.13			0.001
Age at menopause †						
<40	47	67	0.61 (0.39, 0.95)	185	213	0.68 (0.54, 0.87)
40-49	138	123	1.00	440	388	1.00
≥50	111	105	0.89 (0.61, 1.28)	290	212	1.25 (1.00, 1.57)
Missing	8	10				
Postmenopausal HRT use †						
Never	122	110	1.00	518	420	1.00
Ever	182	195	0.94 (0.66, 1.32)	417	426	0.81 (0.66, 0.99)
Duration of HRT use †						
Never	122	110	1.00	518	420	1.00
<5 years	64	88	0.75 (0.49, 1.15)	202	204	0.80 (0.63, 1.02)
5-10 years	60	50	1.27 (0.79, 2.04)	115	98	0.99 (0.73, 1.35)
>10 years	55	55	0.94 (0.59, 1.49)	94	121	0.67 (0.49, 0.91)
Missing	3	2				

*All odds ratios adjusted for age, race, and frequency-matching offset terms.

†Among postmenopausal women only.

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Table 3

Multivariate-adjusted * Odds Ratios for DCIS Reproductive Risk Factors, Stratified by Histology

Variable	Comedo DCIS N	Comedo vs. Controls OR (95% CI)	Non-comedo DCIS N	Non-comedo vs. Controls OR (95% CI)	Comedo vs. Non-comedo OR (95% CI)
Parity (# of full-term pregnancies)					
None (nulliparous)	29	1.00	31	1.00	1.00
One	27	0.81 (0.42, 1.55)	43	1.36 (0.74,2.47)	0.67 (0.33, 1.35)
Two	53	0.57 (0.33, 1.00)	84	0.91 (0.54, 1.54)	0.68 (0.37, 1.25)
Three or more	54	0.53 (0.30, 0.95)	72	0.73 (0.42, 1.27)	0.82 (0.43, 1.54)
P for trend		0.02		0.06	0.52
Age at first full-term pregnancy					
Nulliparous	29	1.00	31	1.00	1.00
<26 years	94	0.55 (0.33, 0.94)	129	0.77 (0.47, 1.29)	0.79 (0.44, 1.42)
26+ years	40	0.71 (0.39, 1.28)	70	1.29 (0.74, 2.23)	0.61 (0.32, 1.16)
Lactation					
Never	102	1.00	135	1.00	1.00
Ever	61	0.82 (0.57, 1.20)	95	1.02 (0.72,1.42)	0.85 (0.56, 1.29)
Oral Contraceptive (OC) Use					
Never					
Ever	61	1.00	86	1.00	1.00
Missing	101	1.08 (0.69, 1.69)	142	1.10 (0.75, 1.64)	1.00 (0.62, 1.59)
	1		2		
Age at first OC use					
Never	61	1.00	86	1.00	1.00
<20	27	0.67 (0.34, 1.32)	40	0.78 (0.44, 1.40)	0.93 (0.45, 1.92)
20+	73	1.14 (0.78, 1.79)	101	1.16 (0.78, 1.73)	1.00 (0.62, 1.62)
Missing	2		3		
Duration of OC use					
Never	61	1.00	86	1.00	1.00
<5 years	52	1.21 (0.74, 1.98)	76	1.31 (0.85, 2.03)	0.96 (0.57, 1.62)
5 to 10 years	26	0.78 (0.43, 1.39)	52	1.09 (0.67, 1.76)	0.70 (0.38, 1.31)
>10 years	23	1.31 (0.70, 2.47)	14	0.51 (0.25, 1.04)	2.33 (1.06, 5.09)

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Variable	Comedo DCIS N	Comedo vs. Controls OR (95% CI)	Non-comedo DCIS N	Non-comedo vs. Controls OR (95% CI)	Comedo vs. Non-comedo OR (95% CI)
Missing	1		2		
Age at menarche					
<11	37	1.00	49	1.00	1.00
12	46	0.76 (0.45, 1.28)	67	0.88 (0.56, 1.40)	0.91 (0.51, 1.60)
13	37	0.61 (0.36, 1.04)	54	0.66 (0.41,1.06)	0.91 (0.50, 1.65)
14+	43	1.00 (0.58, 1.71)	59	1.01 (0.62, 1.65)	0.97 (0.54, 1.73)
Missing	0		1		
Age at menopause†					
<40	21	0.83 (0.46, 1.52)	21	0.48 (0.27, 0,84)	1.67 (0.83, 3.40)
40 to 49	48	1.00	79	1.00	1.00
50+	42	0.97 (0.59, 1.59)	54	0.75 (0.48, 1.17)	1.27 (0.27, 2.22)
Missing	1		5		
Postmenopausal hormone replacement therapy (HRT) use†					
Never	50	1.00	62	1.00	1.00
Ever	62	0.78 (0.49, 1.23)	97	1.00 (0.66, 1.52)	0.77 (0.46, 1.30)
Duration of postmenopausal HRT use†					
Never	50	1.00	62	1.00	1.00
<5 years	23	0.66 (0.37, 1.18)	35	0.82 (0.49, 1.38)	0.81 (0.41, 1.58)
5 to 10 years	20	1.03 (0.54, 1.95)	34	1.48 (0.84, 2.61)	0.71 (0.35, 1.43)
>10 years	19	0.78 (0.42, 1.47)	25	0.86 (0.48, 1.54)	0.90 (0.44, 1.87)
Missing	0		3		

*All odds ratios adjusted for age, race, and frequency-matching offset terms.

†Among postmenopausal women only

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