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Reproductive risk factor associations with lobular and ductal carcinoma in the Carolina Breast Cancer Study

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Abstract

Background—Invasive lobular breast tumors display unique reproductive risk factor profiles. Lobular tumors are predominantly Luminal A subtype and it is unclear whether reported risk factor associations are independent of molecular subtype.

Methods—Polytomous logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the associations between risk factors and histologic subtype [ductal (n=2,856), lobular (n=326), and mixed ductal-lobular (n=473)] in the Carolina Breast Cancer Study (1993–2013). Three-marker immunohistochemical clinical subtypes were defined as Luminal A (ER+ or PR+/HER2−), Luminal B (ER+ or PR+/HER2+), Triple Negative (ER−/PR−/HER2−), and HER2+ (ER−/PR−/HER2+).

Results—In case-case analyses compared to ductal, lobular tumors were significantly associated with lactation duration >12 months [OR 1.86, 95% CI (1.33–2.60)], age at first birth ≥26 years [OR: 1.35, 95% CI: (1.03–1.78)], and current oral contraceptive use [OR: 1.86, 95% CI: (1.08–3.20)]. Differences in risk factor associations between ductal and lobular tumors persisted after restricting to Luminal A subtype.

Conclusions—Lobular tumors were associated with older age at first birth, increased lactation duration, and current oral contraceptive use. Etiologic heterogeneity by histology persisted after restricting to Luminal A subtype, suggesting both tumor histology and intrinsic subtype play integral parts in breast cancer risk.

INTRODUCTION

The intrinsic breast cancer subtypes, including Luminal A, Luminal B, HER2-enriched, and Basal-like cancers, show distinct risk factor profiles and are hypothesized to be independent diseases within the breast [1, 2]. Ductal histologic subtype, diagnosed in up to 80% of invasive breast tumors [3–5], are approximately 50% Luminal A intrinsic subtype. While Basal-like and HER2-enriched intrinsic subtype tumors represent a minority of breast tumors, up to 20% and 10% of tumors, respectively [6, 7], the vast majority of Basal-like and HER2-enriched tumors are ductal histologic subtype and are rarely lobular or mixed ductal/lobular histologic subtypes [7–17]. Lobular and mixed ductal-lobular breast cancers, diagnosed in up to 15% of cases each [3–5], tend to be 80–90% Luminal A intrinsic subtype [3–5, 7–17]. Thus, there are strong associations between histologic and intrinsic subtype.

Previous studies of etiologic heterogeneity according to histology have suggested that lobular disease is more strongly associated with a number of reproductive risk factors and hormone-modulating exposures including younger age at menarche [18–22], older age at menopause [19, 22, 23], premenopausal status [23–25], combined estrogen and progesterone (E+P) hormone therapy (HT) use [26–29], and later age at first birth [18–22, 26, 28, 30]. The strongest differences in association for reproductive risk factors and lobular disease have been observed for combined hormone therapy use (odds ratios for current E+P HT use vs never range from 2.1–2.3 for lobular and 1.1–1.8 for ductal [27, 29]) and older age at first birth (case-control odds ratios for >30 vs ≤19 years of age range from 1.8–2.4 for lobular disease and 1.1–1.6 for ductal disease) [18–22, 26, 28, 30]. However, it is unclear if the observed associations depend on intrinsic breast cancer subtypes, which also have unique reproductive risk factor profiles [6, 7]. We sought to disentangle the associations between reproductive breast cancer risk factors and breast cancer subtype, considering both histology and Luminal A subtype in the Carolina Breast Cancer Study Phases 1–3 (1993–2013).

METHODS

Study population

The present analysis includes 3,655 cases of invasive breast cancer from the Carolina Breast Cancer Study (CBCS) Phases 1–3 (1993–2013). The CBCS is a population-based study among black and non-black women, initiated in 1993, that recruited participants from 24 (CBCS 1–2) to 44 (CBCS 3) of the 100 North Carolina counties [31]. CBCS oversampled women less than 50 years of age and black women [9, 32].

For CBCS1–3, case eligibility criteria included: women with a first diagnosis of breast cancer [invasive or *in situ* (CBCS2 only)], aged 20–74 years at diagnosis, and residence in specified counties. Cases were enrolled following rapid case ascertainment from the NC Central Cancer Registry and controls (CBCS1–2) were identified using DMV and Medicare lists. Controls were frequency matched to cases by race and five-year age-group. All participants provided informed consent for study enrollment and cases granted access to tumor tissue blocks/slides and medical records from treatment centers. Self-report, risk factor data was collected during in-person interviews by a trained study nurse. Cases eligible for this analysis had invasive tumor tissue available for centralized pathology review and

were classified as ductal (n=2,856), lobular (n=326), or mixed ductal/lobular (n=473) (henceforth referred to as mixed) breast cancer. The study maintains Institutional Review Board approval at the University of North Carolina.

Histologic subtype

Histologic subtype for CBCS1–3 was determined via centralized pathologist review. Tumors classified as ductal, lobular, and mixed ductal-lobular comprise 84% of all CBCS1–3 cases with histologic subtype available. Ductal or lobular histologic subtypes tumors were defined as at least 80% representative of that histology. Mixed tumors contained ≥20% of one histologic subtype and <80% of the second histologic subtype. The following histologic subtypes were excluded: mixed ductal/non-lobular (n=285), mucinous (n=89), mixed ductal/metaplastic (n=63), metaplastic (n=44), DCIS w/focal invasion (n=44), undifferentiated high grade (n=29), tubular (n=23), micropapillary (n=21), papillary (n=19), medullary (n=18), pleomorphic lobular (n=17), anaplastic (n=14), apocrine (n=11), cribriform (n=9), neuroendocrine (n=3), and others (n=15). Cases with unknown (n=99) or missing (n=376) were also excluded.

Immunohistochemistry (IHC)-based clinical breast cancer subtypes

For CBCS1–2, estrogen receptor (ER) and progesterone receptor (PR) status was abstracted from medical records for 80% of cases. The remaining 20% of cases with tumor tissue available had ER and PR status determined using IHC, which was performed at UNC. For tissue that was stained at UNC, a study pathologist determined ER and PR positivity using contemporaneous clinical cut points [9]. HER2 staining was performed at UNC for all CBCS1–2 cases with available tissue as described previously. HER2 positivity was defined as in ≥10% of tumor cells displaying weak or greater intensity of membrane/membrane plus cytoplasmic staining [9].

In CBCS3, 98% of cases had ER, PR, and HER2 information in their medical records. For the remaining 2% of cases without medical record ER, PR, and HER2 data, IHC data was used. IHC staining was performed at UNC with positivity cut points of ≥10% for ER and PR status. HER2 positivity was defined as 3+ staining intensity [negativity was defined as 0/1+ (equivocal cases with 2+ staining were excluded)], as described in Allott *et al.* (2016) [33].

For CBCS1–3, 3-marker clinical subtypes were defined as follows: Luminal A (ER+ or PR+ and HER2−), Luminal B (ER+ or PR+ and HER2+), Triple Negative (TN) (ER− and PR− and HER2−), and HER2+ (ER− and PR− and HER2+).

Statistical analyses

Patient characteristics—The associations between histologic subtype and race, age, menopausal status, and clinical subtype were estimated using generalized linear models that were adjusted for age, race, and study phase (1, 2, 3) [34]. Relative frequency differences (RFDs), interpretable as the percentage difference between index and referent groups, and 95% confidence intervals (95% CIs) were estimated as the measure of association [34]. To account for the CBCS sampling design, weighted percentages are presented alongside unweighted sample size counts. Patient characteristics were defined as: race [self-report:

black, non-black (>98% white, henceforth referred to as white)], age (years) (<40, 40–49, 50–59, ≥60), menopausal status (pre-, post-), and clinical subtype as defined above.

Reproductive risk factor analyses—The association between each reproductive breast cancer risk factor and histologic subtype was estimated in case-control (CBCS1–2) and case-case (CBCS1–3) analyses. Polytomous logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (95% CIs) as the measure of association. The following risk factors were studied in association with histologic breast cancer subtype: parity (nulliparous, 1, 2, ≥3), years since last birth (defined as: age at diagnosis/enrollment minus age at last birth; among parous women only) (0–≤10, 10–≤20, >20), age at first live birth (years) (parous women only) (<26, ≥26), lifetime lactation duration (months) (parous women only) (never, 0–≤12, >12), oral contraceptive use (never, former, current), and hormone therapy (HT) use [never, estrogen alone, combined estrogen + progesterone (E+P)]. Additional variables used in case-control analyses included: study phase (1, 2, 3), age continuous (20–74), family history of breast cancer (yes, no), alcohol intake (ever, never), smoking duration (years) (never, <10, 11–19, ≥20), oral contraceptive use (ever, never), breastfeeding (ever, never) and age at menarche (years) (<13, ≥13), and the offset term to account for the sampling design of CBCS. Case-case analyses are presented for CBCS1–3 to assess etiologic heterogeneity by histologic subtype [6, 35]. In case-case analyses, ductal served as the referent group compared to lobular and mixed. Case-case models are adjusted for age, race, and study phase.

We tested the null hypothesis that the slope of the line equals zero for age at diagnosis, parity, and lactation duration, each modeled as continuous variables. We conducted a race-stratified sensitivity analysis of the risk factor-histologic subtype associations, but we were unable to assess racial differences in oral contraceptive and HT use due to low sample size among black women for current OC use and combined E+P use. All analyses were done in SAS version 9.4 (SAS Institute, Cary, NC). P-values were produced for a two-sided test with an alpha of 0.05 for statistical significance.

RESULTS

Women from the Carolina Breast Cancer Study Phases 1–3, displayed patterns consistent with established histological associations by age, race, menopausal status, and clinical subtype (Table 1). Relative to ductal histologic subtype, lobular, and mixed tumors (Supplemental Table 1) were less frequent among young women and black women, and in age-, race-, and study phase-adjusted analysis, lobular and mixed tumors were more frequent among premenopausal women. As other studies have shown, lobular and mixed tumors were predominantly Luminal A clinical subtype (ER+ or PR+/HER2−) (lobular 88.8%, mixed 83.1%); whereas ductal tumors are less frequently Luminal A (57.9%) subtype. After adjusting for age, race, and study phase, associations with molecular subtype were statistically significant, with lobular tumors significantly more likely to be Luminal A clinical subtype [Relative Frequency Difference (RFD), or percent difference, compared to ductal: 26.3%, 95% CI (24.0, 28.5)].

We observed unique risk factor patterns for lobular tumors relative to ductal tumors (Table 2). Ductal tumors were inversely associated with parity, increasing lactation duration, and estrogen-only hormone therapy (HT) use. Among lobular tumors, parity was inversely associated with having 1 child versus being nulliparous, but the association was attenuated as parity increased. We observed a positive association between age ≥26 years at first birth and lobular disease [Lobular OR: 1.32; 95% CI (0.86–2.03)] and a null effect for ductal tumors [Ductal OR: 0.94; 95% CI (0.77–1.16)]. Lifetime lactation duration >12 months was positively associated with lobular disease [Lobular OR: 1.62; 95% CI (0.99–2.67)] and reduced for ductal disease [Ductal OR: 0.78, 95% CI (0.60–1.02)]. Former oral contraceptive (OC) use was associated with lobular disease [Lobular OR: 1.43, 95% CI (0.92–2.22)] but not ductal disease [Ductal OR: 0.96, 95% CI (0.79–1.71)]. Associations with hormone therapy use were stronger for lobular disease than ductal disease, with both estrogen alone and having a larger inverse association with lobular disease [OR: 0.59, 95% CI (0.33–1.06)] and combined estrogen plus progesterone (E+P) hormone therapy (HT) use having a larger positive association with lobular disease [OR: 1.74, 95% CI (0.99–3.06)].

To assess whether these risk factor patterns were indicative of significant etiologic differences between ductal (referent) and lobular disease, we conducted case-case analyses. Case-case analyses showed a statistically significant difference in the associations between lobular and ductal disease for age ≥26 years at first birth [OR: 1.35, 95% CI (1.03–1.78)], lifetime lactation duration >12 months [OR: 1.86, 95% CI (1.33–2.60)], and current OC use [OR: 1.86, 95% CI (1.08–3.20)]. These associations did not appear to differ by race (all p-values for heterogeneity >0.50) (Supplemental Table 2). We also observed that associations for mixed tumors were typically intermediate in magnitude, between the estimates for lobular and ductal disease (Supplemental Table 3).

To address our main research question of whether risk factor-histologic subtype associations were independent of molecular breast cancer subtype, which is not evenly distributed by histologic subtype, we tested whether etiologic associations for lobular disease persisted after restricting to Luminal A subtype. After restricting to Luminal A clinical subtype, associations for lobular disease relative to ductal were similar in direction and magnitude particularly for age at first birth ≥26 years [OR: 1.26, 95% CI: 0.82–1.93)], lactation duration >12 months [OR: 1.51, 95% CI (1.02–2.25)], and oral contraceptive use [current OR: 1.82, 95% CI (0.99–3.36); former OR: 1.48, 95% CI (1.06–2.06)].

DISCUSSION

In the Carolina Breast Cancer Study, we observed differences in reproductive risk factor profiles between ductal and lobular invasive breast cancers. Lobular disease was consistently, positively associated with more than 10 and up to 20 years since last birth, older age (≥26 years) at first birth, lactation duration greater than 12 months, oral contraceptive use, and combined estrogen plus progesterone (E+P) hormone therapy (HT) use. These associations did not vary by race and were not altered by restriction to Luminal A tumors only, suggesting that histology and molecular subtype contribute to observed risk factor associations for breast cancer.

In agreement with the previous literature, we found that relative to ductal cancers, lobular cancers were less frequent among black versus white women [36–39], less frequent among younger women [22, 36–38, 40–43], but more common among premenopausal women after controlling for age [23–25]. As has been shown previously, we observed that 88% of lobular tumors in our study were Luminal A subtype, which closely matches previous studies of lobular tumors (~80–90%, [7, 8, 11, 15, 17, 44, 45]), and is considerably higher than the overall prevalence of Luminal A subtype among invasive breast cancers (50%, [6, 7]). We also found that ductal tumors displayed diversity in clinical subtype and contained a majority of the TN and HER2+ tumor types, as others have reported [7–17].

Associations between histology and a number of reproductive risk factors among women from the CBCS were similar to associations reported elsewhere. We and others have shown lobular tumors are more strongly associated with older age at first birth with ORs ranging from 1.8–2.4 for lobular disease and 1.1–1.6 for ductal disease in other studies [18, 19, 21, 22, 26, 28, 30]. We also observed an increased risk of lobular disease for women who reported using oral contraceptives. These findings are similar to a larger study by Newcomer *et al.* (2003) who included nearly 500 cases of lobular disease, and observed that for former versus never OC use, only lobular histology showed a positive association with OC use [21, 46, 47]. Additionally, we observed an increased risk of lobular disease among current users of combined E+P HT compared to ductal disease, with similar magnitude and direction to previous reports [26–29].

In case-case analyses, lobular tumors were significantly associated with older age at first birth, lactation duration greater than 12 months, and current OC use suggesting that these risk factors may contribute to etiologic differences between ductal and lobular tumors. Even after restricting to the predominant lobular clinical subtype, Luminal A, the aforementioned risk factor associations persisted, which mirrors work by Kotsopoulos *et al.* (2010) who reported risk factor associations among lobular tumors persisted after restricting to ER+ and PR+ tumors [28]. Concerning lactation duration and risk of lobular disease, our findings differed from those reported previously in case-control studies where slightly inverse (OR=0.9) or null associations for lactation duration and lobular disease have been reported [18, 19, 47, 48]. We found that among parous women only, lactation duration greater than 12 months was significantly associated with lobular disease relative to ductal, even after restricting to Luminal A subtype in our case-case analyses. Previous studies have included more women over the age of 50 and had lower proportions of women who reported never breastfeeding (30–40%) than was observed in our study (50%) [18, 19, 47, 48]. Generational differences in breastfeeding practices and geographic variation of breastfeeding initiation[49] may contribute to the observed differences in the literature for lactation duration and lobular carcinoma. Overall, our study supports different risk factor profiles between ductal and lobular tumors, particularly for risk factors that are thought to impact hormone levels.

The findings for invasive lobular carcinoma displaying consistent associations with a host of hormone-modulating, reproductive risk factors and independent of Luminal A subtype beg the question: is histologic subtype etiologic in origin or is it a result of selective pressures in the breast that encourage a tumor to develop into one histologic subtype over another?

Intrinsic breast cancer subtypes are hypothesized to be etiologic in nature with Luminal A and B arising from the luminal epithelial cells of the mammary gland and Basal-like and HER2-enriched arising from the basal cells of the mammary gland [2]. Conversely, histologic subtype is subjective in nature and determined by a pathologist from the visual appearance of the epithelial cells where ductal histology is characterized by tubules and solid nests of epithelial cells and lobular carcinoma is characterized by a non-cohesive phenotype with single-file strands of epithelial cells scattered throughout the stroma [5, 42]. Lobular carcinomas are characterized by down regulation of E-cadherin in >90% of cases; however, this can also be observed in a smaller percentage of ductal carcinomas [40]. Therefore, it is not clear that histologic subtype is truly etiologic in nature or if histology is a result of exposure to phenotype-modulating selective pressures present in breast tissue over the life course.

Our study should be interpreted in light of some limitations. We were unable to include rare histologic subtypes (e.g. medullary, papillary, metaplastic, etc.) in our analyses due to limited sample sizes. Because lobular tumors are predominantly Luminal A subtype, we were unable to study differences in risk factor profiles between lobular tumors that were of Triple Negative or HER2+ subtype. We, like other studies of histology, acknowledge some uncertainty around histologic classification. Interobserver reliability for histologic subtype is reported to be around 80% [50], possibly leading to some instability in associations across studies. We sought to eliminate this problem by using centralized pathology review to classify CBCS invasive breast tumors into histologic subtypes, by focusing on tumors that had a dominant ductal or lobular phenotype (at least 80% ductal or lobular), and by considering mixed ductal-lobular tumors separately. This may have impacted our power, though, and TCGA found that molecularly, mixed tumors were not a distinct disease and displayed genomic features that would classify them as ductal- or lobular-like [8]. Therefore, applying these molecular classifications to mixed ductal-lobular tumors in epidemiologic studies may be a step toward better characterizing risk factor profiles for mixed tumors.

To conclude, we observed differences in risk factor profiles between ductal and lobular tumors in the Carolina Breast Cancer Study that persisted after restricting to Luminal A subtype. Using both case-control and case-case analyses, we found that lobular tumors have unique risk factor profiles from ductal tumors when considering older age at first birth, increasing lactation duration, current oral contraceptive use, and combined E+P HT use. When we restricted to Luminal A subtype, we found that the observed reproductive risk factor-histologic subtype associations were not altered. Overall, our findings suggest potential etiologic or phenotype-modulating differences between ductal and lobular disease that are not driven by intrinsic subtype alone. Our findings strengthen the evidence that lobular tumors are sensitive to hormone-modulating exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Relative Frequency Differences (RFD) and 95% Confidence Intervals (95% CI) for the association between race, age at diagnosis, menopausal status, and clinical subtype comparing lobular to ductal histologic subtype breast tumors (CBCS 1–3)

	Ductal	Lobular		
Risk factor	**N (%*)**	**N (%*)**	**RFD (95% CI)**	**p-value**
Age at diagnosis[a]				
≥60	697 (37.4)	109 (46.1)	Ref	
50–59	591 (28.1)	65 (27.6)	**−2.5 (−4.3, −0.7)**	<0.01
40–49	1,105 (24.7)	131 (23.0)	**−2.9 (−4.7, −0.2)**	<0.01
<40	463 (9.8)	21 (3.3)	**−8.8 (−10.8, −6.8)**	<0.01
Race[b]				
White	1,463 (76.7)	200 (83.9)	Ref	
Black	1,393 (23.3)	126 (16.1)	**−3.5 (−5.0, −2.0)**	<0.01
Menopausal Status[c]				
Pre	1,400 (33.2)	141 (26.9)	2.0 (0.0, 4.0)	0.05
Post	1,456 (66.8)	185 (73.1)	Ref	
Clinical Subtype[c,d]				
Luminal A	1382 (57.9)	270 (88.8)	**26.3 (24.0, 28.5)**	<0.01
Non-Luminal A	1302 (41.3)	36 (11.2)	Ref.	
Luminal B	282 (10.3)	16 (6.3)		
HER2+	193 (6.3)	4 (0.7)		
Triple Negative	827 (25.5)	16 (4.2)		
Missing	172	20		

*Percentages weighted for sampling fractions.

[a]Adjusted for race (white, black) and study phase (1, 2, 3).

[b]Adjusted for age (continuous) and study phase.

[c]Adjusted for age, race, and study

[d]Luminal A (ER+ or PR+/HER2−); Non-Luminal A [Luminal B (ER+ or PR+/HER2+), Triple Negative (ER−/PR−/HER2−), HER2+ (ER−/PR−/HER2+)]

Table 2

Case-Control and Case-Case Odds Ratios and 95% Confidence Intervals (95% CI) for the association between parity, years since last birth, lactation duration, oral contraceptive use, and hormone therapy use comparing lobular and ductal histologic subtype breast tumors to controls (CBCS1–2) and lobular to ductal histologic subtype breast tumors (CBCS1–3)

	Case-Control					Case-Case[f]			Luminal A: Case-Case[f]		
	Controls	Ductal		Lobular		Ductal	Lobular		Ductal	Lobular	
Risk factor	**N (%[*])**	**N (%[*])**	**OR (95% CI)**	**N (%[*])**	**OR (95% CI)**	**N (%[*])**	**N (%[*])**	**OR (95% CI)**	**N (%[*])**	**N (%[*])**	**OR (95% CI)**
Parity[a]											
Nulliparous	174 (22.6)	193 (15.0)	Ref	19 (10.9)	Ref	428 (14.4)	47 (12.6)	Ref	226 (15.3)	38 (12.7)	Ref
1	281 (16.8)	219 (16.9)	0.80 (0.60–1.06)	22 (12.0)	0.77 (0.39–1.52)	560 (19.8)	46 (11.7)	0.75 (0.49–1.15)	278 (20.1)	41 (12.9)	0.87 (0.54–1.40)
2	495 (32.8)	372 (32.3)	0.83 (0.63–1.08)	44 (32.3)	0.87 (0.47–1.60)	937 (34.7)	123 (43.4)	1.14 (0.80–1.63)	433 (33.5)	108 (46.1)	1.44 (0.96–2.16)
≥3	614 (27.8)	425 (35.8)	0.85 (0.65–1.12)	59 (44.8)	1.02 (0.55–1.88)	931 (31.1)	110 (32.4)	1.01 (0.70–1.46)	445 (31.0)	83 (28.4)	1.04 (0.68–1.59)
p-value			0.53		0.63			0.82			0.76
Years since last live birth (parous only)[b]											
0–≤10	194 (32.0)	182 (12.1)	0.77 (0.54–1.10)	12 (5.8)	0.79 (0.33–1.93)	480 (13.3)	34 (6.8)	1.16 (0.68–1.99)	204 (11.6)	26 (6.5)	0.73 (0.39–1.34)
>10–≤20	365 (24.9)	271 (19.5)	0.93 (0.72–1.22)	40 (25.3)	1.57 (0.86–2.86)	612 (18.2)	84 (22.6)	**1.80 (1.23–2.64)**	291 (17.2)	68 (20.8)	1.26 (0.82–1.93)
>20	829 (43.0)	562 (68.4)	Ref.	73 (68.8)	Ref	1330 (68.6)	161 (70.6)	Ref	657 (71.2)	138 (72.6)	Ref
Missing	2	1		0		6	0		4	0	
Age at first live birth (parous only; years)[b]											
<26	1050 (70.3)	760 (73.4)	Ref.	85 (71.0)	Ref	1710 (67.4)	180 (66.2)	Ref.	782 (65.3)	146 (64.6)	Ref
≥26	335 (29.7	247 (26.6)	0.94 (0.77–1.16)	39 (29.0)	1.32 (0.86–2.03)	702 (32.6)	98 (33.8)	**1.35 (1.03–1.78)**	364 (34.7)	85 (35.4)	1.31 (0.96–1.78)
Missing	5	9		1		16	1		10	1	
Lactation duration (parous only)[c]											
Never	794 (56.1)	622 (58.7)	Ref	67 (48.5)	Ref	1399 (55.1)	136 (43.6)	Ref	634 (54.8)	117 (45.2)	Ref
>0–≤12 months	408 (31.6)	272 (28.9)	**0.90 (0.66–0.98)**	30 (28.2)	0.69 (0.43–1.12)	714 (30.9)	84 (32.6)	1.19 (0.89–1.59)	371 (31.9)	73 (34.0)	1.08 (0.78–1.50)
>12	186 (12.2)	121 (12.4)	0.78 (0.60–1.02)	28 (23.3)	1.62 (0.99–2.67)	313 (14.1)	59 (23.8)	**1.86 (1.33–2.60)**	151 (13.2)	42 (20.8)	**1.51 (1.02–2.25)**
Missing	2	1		0		2	0		0	0	
p-value			0.02		0.24						0.15
Oral Contraceptive Use[d]											

	Case-Control					Case-Case[f]			Luminal A: Case-Case[f]		
	Controls	Ductal		Lobular		Ductal	Lobular		Ductal	Lobular	
Risk factor	N (%*)	N (%*)	OR (95% CI)	N (%*)	OR (95% CI)	N (%*)	N (%*)	OR (95% CI)	N (%*)	N (%*)	OR (95% CI)
Never	572 (23.5)	412 (39.4)	Ref	48 (28.5)	Ref	756 (27.5)	82 (23.4)	Ref	402 (29.8)	65 (24.7)	Ref
Current	76 (4.9)	77 (6.4)	1.01 (0.68–1.50)	4 (2.8)	0.86 (0.28–2.71)	193 (5.3)	24 (5.0)	**1.86 (1.08–3.20)**	96 (5.3)	20 (4.6)	1.82 (0.99–3.36)
Former	905 (58.3)	716 (59.4)	0.96 (0.79–1.17)	91 (63.6)	1.43 (0.92–2.22)	1889 (67.2)	217 (69.6)	1.33 (0.99–1.78)	880 (65.0)	182 (70.7)	**1.48 (1.06–2.06)**
Missing	11	4		1		18	3		4	3	
Hormone Therapy Use[e]											
Never	1080 (77.9)	893 (64.6)	Ref	98 (53.1)	Ref	2196 (68.0)	229 (60.3)	Ref	1031 (64.8)	188 (60.8)	Ref
Estrogen alone	307 (13.8)	164 (16.8)	**0.68 (0.54–0.86)**	18 (19.6)	0.59 (0.33–1.06)	377 (17.7)	49 (21.0)	0.97 (0.69–1.38)	186 (18.3)	41 (20.4)	1.07 (0.72–1.60)
Combined E+P	149 (8.2)	126 (18.6)	1.20 (0.89–1.60)	25 (27.3)	1.74 (0.99–3.06)	229 (14.3)	41 (18.7)	1.25 (0.85–1.83)	137 (16.9)	35 (18.8)	1.23 (0.80–1.90)
Missing	28	26		3		54	7		28	6	

*All percentages weighted for study sampling design.

[a]Adjusted for race (black, white), age (continuous), study phase (1,2, 3), family history (yes, no), alcohol intake (ever, never), smoking duration (never, <10 years, 11–19, ≥20), oral contraceptive use (ever, never) breastfeeding (ever, never), menopausal status (pre-, post-), age at menarche (<13,≥13), CBCS offset term.

[b]Among parous women only. Adjusted for race, age, study phase, menopausal status, family history, parity, alcohol intake, smoking duration, oral contraceptive use, age at menarche, CBCS offset term.

[c]Among parous women only. Adjusted for race, age, study phase, menopausal status, family history, alcohol intake, smoking duration, oral contraceptive use, age at menarche, CBCS offset term.

[d]Adjusted for race, age, study phase, family history, alcohol intake, smoking duration, oral contraceptive use, parity (nulliparous, 1–2, ≥3), breastfeeding, age at menarche, CBCS offset term.

[e]Adjusted for race, age, study phase, family history, alcohol intake, smoking duration, oral contraceptive use, parity, breastfeeding, menopausal status, age at menarche, CBCS offset term.

[f]Adjusted for race, age, study phase.