Reproductive risk factors and oestrogen/progesterone receptor-negative breast cancer in the Breast Cancer Family Registry

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Background: Oestrogen receptor (ER)- and progesterone receptor (PR)-negative (ER − PR −) breast cancer is associated with poorer prognosis compared with other breast cancer subtypes. High parity has been associated with an increased risk of ER − PR − cancer, but emerging evidence suggests that breastfeeding may reduce this risk. Whether this potential breastfeeding benefit extends to women at high risk of breast cancer remains critical to understand for prevention.

Methods: Using population-based ascertained cases (n = 4011) and controls (2997) from the Breast Cancer Family Registry, we examined reproductive risk factors in relation to ER and PR status.

Results: High parity (⩾3 live births) without breastfeeding was positively associated only with ER − PR − tumours (odds ratio (OR) = 1.57, 95% confidence interval (CI), 1.10–2.24); there was no association with parity in women who breastfed (OR = 0.93, 95% CI 0.71–1.22). Across all race/ethnicities, associations for ER − PR − cancer were higher among women who did not breastfeed than among women who did. Oral contraceptive (OC) use before 1975 was associated with an increased risk of ER − PR − cancer only (OR = 1.32, 95% CI 1.04–1.67). For women who began OC use in 1975 or later there was no increased risk.

Conclusions: Our findings support that there are modifiable factors for ER − PR − breast cancer and that breastfeeding in particular may mitigate the increased risk of ER − PR − cancers seen from multiparity.

The extensive epidemiologic literature supports that risk factors vary by subtypes of breast cancer defined by oestrogen receptor (ER) and progesterone receptor (PR) expression (Mctiernan et al, 1986; Stanford et al, 1987; Potter et al, 1995; Yoo et al, 1997; Britton et al, 2002; Mccredie et al, 2003; Althuis et al, 2004; Colditz et al, 2004; Largent et al, 2005; Rusiecki et al, 2005;

Ursin et al, 2005; Ma et al, 2006a; Rosenberg et al, 2006; Lord et al, 2008; Kwan et al, 2009; Setiawan et al, 2009; Yang et al, 2011) and that many established breast cancer risk factors are more strongly associated with hormone receptor-positive (ER+ and/or PR+) cancers; for example, high parity, earlier age at first birth, and later age at menarche have been associated with reduced risk of ER+ and/or PR+ cancers (Althuis et al, 2004; Nichols et al, 2005; Ursin et al, 2005; Ma et al, 2006a, b, 2010a; Lord et al, 2008; Setiawan et al, 2009; Bao et al, 2011; Palmer et al, 2011; Yang et al, 2011), and postmenopausal hormone therapy use has been associated with an increased risk of ER+ and/or PR+ cancer (Althuis et al, 2004; Rosenberg et al, 2008; Setiawan et al, 2009; Slanger et al, 2009; Bao et al, 2011). In contrast, ER- and PR-negative breast cancer (ER−PR−), which is associated with a higher tumour grade and poorer prognosis, and is more prevalent in women of African-American race, and in younger age groups (Britton et al, 2002; Carey et al, 2006; Bauer et al, 2007; Brinton et al, 2008; Stead et al, 2009; Clarke et al, 2012), is not associated with reproductive and hormonal risk factors in the same way as hormone receptor-positive cancers. For example, age at first birth appears to be unrelated to ER−PR− cancer, and high parity has been associated with increased, rather than decreased risk (Rusiecki et al, 2005; Ma et al, 2006a, b; Rosenberg et al, 2006; Millikan et al, 2007; Kwan et al, 2009; Setiawan et al, 2009; Bao et al, 2011; Palmer et al, 2011; Yang et al, 2011).

Breastfeeding is one of the few factors found by a majority of studies to be consistently associated with a reduction in both hormone receptor-positive and -negative breast cancer (Althuis et al, 2004; Ma et al, 2006a, b, 2010a; Lord et al, 2008; Bao et al, 2011). For ER−PR− or triple-negative (ER−PR− human epidermal growth factor receptor 2 (HER2−)) cancer, in particular, breastfeeding may mitigate the increased risk of ER−PR− cancer associated with multiparity (Millikan et al, 2007; Kwan et al, 2009; Palmer et al, 2011; Redondo et al, 2012). Whether this risk reduction in ER−PR− cancer extends to women at high risk of breast cancer remains critical for prevention, as there are few prevention options available to these women apart from risk-reducing surgeries and chemoprevention; options that are particularly difficult to implement during childbearing age.

Given the consistent protective association between breastfeeding and ER−PR− and triple-negative cancers in populations unselected for family history of breast cancer, we evaluated associations between reproductive and hormonal risk factors and risk of breast cancer categorised by joint ER/PR status, using population-based data from the Breast Cancer Family Registry (BCFR). In particular, we focused on the associations with parity and breastfeeding and, more importantly, evaluated whether the reduction in risk from breastfeeding in the presence of multiparity extended to higher risk women. We also focused on evaluating oral contraceptive (OC) use, which has previously been associated with an increased risk of ER−PR− cancer (Althuis et al, 2004; Rosenberg et al, 2010).

MATERIALS AND METHODS

Study sample. We included population-based ascertained breast cancer cases and controls from three sites of the BCFR: Northern California, USA; Ontario, Canada; and Melbourne and Sydney, Australia. The details of the BCFR have been published elsewhere (John et al, 2004; Knight et al, 2006; Milne et al, 2011; Work et al, 2012). Briefly, cases included women aged 18–69 years diagnosed with a first primary invasive breast cancer from 1995 to 2004, with the sample enriched for women at increased genetic and/or familial risk of breast cancer, based on age at breast cancer diagnosis and family history of breast and other cancers (John et al, 2004).

Questionnaire data were obtained for 76%, 72%, and 75% of eligible cases from Northern California, Ontario, and Australia, respectively. Controls were randomly sampled from the population living in the same catchment area as the cases and frequency matched according to 5-year age groupings. Of the eligible controls, 67%, 64%, and 74% participated from Northern California, Ontario, and Australia, respectively, for a total of 5107 cases and 2997 unrelated controls. The ER/PR information was available for 4011 (79%) cases, including 1994 from Northern California, 1088 from Ontario, and 929 from Australia. We also had data available on HER2 status for a subgroup of these women from Northern California and Ontario ($N = 792$).

Risk factor data collection. We collected epidemiologic data through structured questionnaire interviews (conducted either in-person or by telephone) assessing breast cancer risk factors before diagnosis, including OC use, menopausal hormone therapy use, age at menarche, parity, age at first childbirth, breastfeeding history, smoking history, alcohol use, education, body mass index (BMI), and menopausal status.

Tumour marker data collection. For 2351 cases, BCFR study pathologists ascertained ER and PR status from patient tumour tissue using immunohistochemistry (IHC) and/or pathology reports using a standardised protocol and pathology reporting forms. For the remaining cases ($N = 1660$), ER and PR status was provided by the relevant Cancer Registry for that population, or through patient medical records. For all cases with HER2 status available ($N = 792$), the information on HER2 status was provided by the California Cancer Registry ($N = 639$), or patient medical records ($N = 153$). The distribution of risk factors did not differ between cases that did or did not have ER/PR data available for review (data not shown).

Where tumour tissue was available, BCFR study pathologists used IHC testing for ER and PR, and categorised tumours as ER or PR positive if ⩾10% of tumour cells stained positive. Where tissue samples were not obtained, pathologists reviewed pathology reports and recorded the ER and PR status listed on the report, or, if information existed on the percent of cells staining positive, employed the same requirements that ⩾10% of cells stained positive resulted in a definition of ER or PR positive.

Of the cases, 2486 were ER+PR+, 920 were ER−PR−, 397 were ER+PR−, and 208 were ER−PR+. Of the sub-population for whom HER2 data were available, 468 were classified as Luminal A (ER+ and/or PR+, HER2−), 118 as Luminal B (ER+ and/or PR+, HER2+), 67 as HER2+ (ER− and PR−, HER2+), and 139 as triple negative (ER−, PR−, and HER2−).

Statistical analysis. Using multivariable unordered polytomous regression, adjusted for age, race/ethnicity, and study site, we compared known or suspected breast cancer risk factors, including OC use (never, ⩽5 years, >5 years), starting date of OC use (never, any use before 1975, all use in 1975 or later; the year 1975 was chosen as a cutpoint because oestrogen and progesterone doses in OC brands had a marked change in formulation in 1975); time since last OC use (never, ⩽10 years, >10–⩽20 years, >20 years); age at menarche (⩽11, 12, ⩾13 years); parity (nulliparous, 1–2 live births, ⩾3 live births); age at first birth (continuous); lifetime breastfeeding duration (never, 0–<12 months, ⩾12 months); combined parity and breastfeeding (nulliparous, 1–2 children never breastfed, 1–2 children ever breastfed, ⩾3 children never breastfed, ⩾3 children ever breastfed); smoking history (never smoker, former smoker, current smoker), BMI (continuous), education (< high school, completed high school), alcohol consumption (<7 drinks per week, ⩾7 drinks per week, current non-drinker), history of ⩾1 first-degree relative with breast cancer (yes, no), and menopausal status (premenopausal or postmenopausal). Cutpoints for categorical variables were selected

based on meaningful cutpoints (e.g., education defined by high school graduation, as well as selected cutpoints used in the prior literature for replication purposes).

We compared each of the four subgroups defined by ER and PR status with the reference group of controls, for the total population as well as by site (Northern California, Ontario, Australia). Findings did not differ by site (results not shown). We also examined associations separately for premenopausal and post-menopausal women. Because some associations with ER − PR − cancer differed from associations with ER + PR + cancer when using controls as the referent group, we also conducted a case-only analysis directly comparing ER − PR − cases with ER + PR + cases. For the molecular subtypes, we conducted a case-only analysis comparing Luminal B, HER2 +, and triple-negative cases with Luminal A cases.

Because we examined multiple risk factors, we focused on patterns in risk factor associations as well as formal tests for trends. We did not formally adjust for multiple comparisons by altering the significance level but regarded associations that did not follow patterns (by increasing levels of the covariate) as more likely to be spurious.

We analysed the level of missingness for each of the variables used in the multivariable regression. Rates of missingness were very low, < 2% of the sample, for most variables modelled: there was 0% missingness for parity, 1.7% missingness for OC use, and 0.7% missingness for breastfeeding. Menopausal status was missing for 12% of the participants, however, when we considered the ages and/or surgical history (i.e., bi-lateral oophorectomy) of the participants, we were able to classify menopausal status for 61% of the women missing data by assigning postmenopausal status to women over the age of 50 or those who had undergone surgical menopause, and included them in the analysis as postmenopausal. Findings did not differ when these women were excluded from the analysis (results not shown).

We considered results statistically significant if the 95% confidence interval (CI) did not include the value of '1'. All statistical analyses used SAS Version 9.2 Software (SAS Institute, Cary, NC, USA).

RESULTS

Table 1 summarises frequencies of demographic characteristics, risk factors, and tumour characteristics for breast cancer cases categorised by joint ER/PR status. The ER − cases were more likely to be younger and premenopausal compared with ER + cases, and were more likely than ER + cases to have grade 3 cancer. ER and PR status was very similar across sites (ER + PR +: 64%, 60%, and 61%, ER + PR −: 9%, 10%, and 11%; ER − PR +: 5%, 8%, and 4%; and ER − PR − 22%, 21%, and 24% for Ontario, Australia, and California, respectively). Compared with controls, cases were more likely to be non-white and to have a family history of breast cancer, partly reflecting enrollment criteria for cases that favoured racial minorities and those with family history. Cases regardless of hormone status had a higher rate of nulliparity and were less likely to breastfeed than controls, reflecting differences in known breast cancer risk factors.

Table 2 presents the multivariate-adjusted ORs for each breast cancer subtype, categorised as ER + PR +, ER + PR −, ER − PR +, or ER − PR −, compared with the control group, and also includes the findings for parity and breastfeeding from case-only analyses comparing ER − PR − cases with ER + PR + cases.

High parity (⩾ 3 live births) was associated with an increased risk of ER − PR − cancer (odds ratio (OR) = 1.59, 95% CI 1.15–2.18, vs nulliparity). When stratified by menopausal status, high parity was associated with an increased risk in premenopausal

women only (OR = 1.68, 95% CI 1.10–2.56, ⩾ 3 live births, vs nulliparity). Breastfeeding was associated with a reduced risk of all breast cancer subtypes, but most strongly with ER − PR − cancer (OR = 0.52, 95% CI 0.40–0.68, ⩾ 12 months of breastfeeding vs never), with even greater risk reduction found in postmenopausal women (OR = 0.34, 95% CI 0.21–0.54, ⩾ 12 months of breast-feeding vs never). When combined with breastfeeding behaviour, the increased risk of ER − PR − breast cancer associated with high parity was only found in women who had children but did not breastfeed (OR = 1.57, 95% CI 1.10–2.24, ⩾ 3 live births, no breastfeeding, vs nulliparity). Case-only comparisons (with ER + PR + tumours as the referent) showed an increased risk of ER − PR − tumours for parity combined with a lack of breastfeeding (OR = 1.59, 95% CI 1.19–2.13, 1 − 2 live births, no breastfeeding and OR = 1.69, 95% CI 1.20–2.38, ⩾ 3 live births, no breastfeeding, vs nulliparity). These associations were not materially different by study site and the tests for statistical interaction by site were not significant (data not shown).

Table 3 presents the multivariate-adjusted ORs for each breast cancer subtype, compared with the control group, for OC use and OC start date, and also includes the findings on OC use for the case-only comparisons comparing ER − PR − cases with ER + PR + cases.

Oral contraceptive use was not associated with ER − PR − breast cancer (OR = 1.13, 95% CI 0.89–1.44 for use > 5 years vs never). However, first OC use before 1975 compared with never use was positively associated with ER − PR − breast cancer (OR = 1.32, 95% CI 1.04–1.67), but not with hormone receptor-positive cancers. Use in 1975 or later was not associated with ER − PR − cancer.

Oral contraceptive use was inversely associated with ER + PR +, ER + PR −, and ER − PR + breast cancer, with OR estimates statistically significant for ER + PR + cancer (OC use > 5 years vs none: OR = 0.83, 95% CI = 0.69–0.98). Inverse associations with hormone receptor-positive subtypes were stronger when OC use began in 1975 or later (OR = 0.59, 95% CI 0.48–0.73, ER + PR +; OR = 0.52, 95% CI, 0.36–0.76, ER + PR −, OR = 0.34, 95% CI, 0.21–0.56, ER − PR +). Findings did not differ for cancer diagnosed premenopausally or post-menopausally. There was a stronger association between OC use and ER − PR − cancer compared with ER + PR + cancer (OR = 1.35, 95% CI = 1.07–1.70, OC use > 5 years vs none). Case–case differences also existed for OC use pre- or post-1975, with statistically significant associations for ER − PR − cancer compared with ER + PR + cancer.

Differences by race/ethnicity. African-American women (OR = 1.71, 95% CI 1.22–2.40) and Hispanic women (OR = 1.43, 95% CI 1.02–2.00) were more likely to be ER − PR − than ER + PR +, compared with non-Hispanic White women. We found that the trend for the combined parity–breastfeeding measure held across race/ethnicities, with our findings supporting higher associations for ER − PR − cancer among women who did not breastfeed than among women who did, for all races/ethnicities examined (non-Hispanic Whites, African Americans, Hispanics, and Asians) (Figure 1).

Differences by molecular subtype. Table 4 presents findings by molecular subtype. Three or more live births were associated with an increased risk of HER2 + and triple-negative breast cancer (OR = 2.88, 95% CI 0.98–8.51, for HER2 vs Luminal A cancer; OR = 2.82, 95% CI 1.37–5.83, for triple-negative vs Luminal A cancer), whereas breastfeeding was inversely associated with triple-negative cancer (OR = 0.49, 95% CI 0.29–0.82, < 12 months of breastfeeding vs none; OR = 0.57, 95% CI 0.31–1.04, ⩾ 12 months of breastfeeding vs none). Parous women who did not breastfeed were more likely to have HER2 + (OR = 3.32, 95% CI 1.26–8.73, HER2 + vs Luminal A, for parous, no breastfeeding) or

Table 1. Demographic and tumour characteristics by ER/PR status, Breast Cancer Family Registry					
	Controls N = 2997 N (%)	ER + PR + N = 2486 N (%)	ER + PR − N = 397 N (%)	ER − PR + N = 208 N (%)	ER − PR − N = 920 N (%)
Age					
Age (mean ± s.d.)	47.6 ± 10.3	47.1 ± 9.3	48.6 ± 9.8	43.8 ± 8.0	44.5 ± 9.8
Race/Ethnicity					
Non-Hispanic White	2487 (86)	1542 (62)	222 (56)	158 (76)	506 (55)
African American	96 (3)	221 (9)	45 (11)	16 (8)	131 (14)
Hispanic	72 (2)	229 (9)	46 (11)	7 (3)	113 (12)
Asian	165 (6)	445 (18)	79 (20)	23 (11)	149 (16)
Other	82 (3)	35 (1)	5 (1)	4 (2)	14 (2)
First-degree family history of breast cancer					
No	2732 (91)	1761 (71)	291 (73)	161 (78)	673 (73)
Yes	263 (9)	714 (29)	106 (27)	45 (22)	244 (27)
Menopausal status					
Premenopausal	1566 (55)	1431 (60)	172 (46)	149 (76)	574 (65)
Postmenopausal	1262 (45)	951 (40)	205 (54)	47 (24)	310 (35)
Education					
< High school	908 (30)	710 (29)	114 (29)	56 (27)	289 (32)
High school or more	2082 (70)	1740 (71)	275 (71)	150 (73)	602 (68)
Oral contraceptive (OC) use					
Never	646 (22)	648 (27)	124 (32)	49 (24)	198 (23)
≤ 5 years	1117 (37)	948 (39)	129 (34)	71 (34)	328 (37)
> 5 years	1216 (41)	847 (35)	131 (34)	86 (42)	353 (40)
Year of first OC use					
Never	646 (22)	648 (27)	124 (32)	49 (24)	198 (23)
Before 1975	1435 (48)	1165 (48)	167 (43)	97 (47)	370 (42)
1975 or later	898 (30)	630 (26)	93 (24)	60 (29)	310 (35)
Time of last OC use					
Never user	646 (24)	648 (30)	124 (36)	49 (27)	198 (26)
≥ 10 years ago	489 (18)	340 (15)	42 (12)	42 (23)	152 (20)
> 10, ≤ 20 years ago	704 (26)	613 (28)	80 (23)	52 (29)	199 (27)
> 20 years ago	913 (33)	604 (27)	98 (28)	39 (21)	202 (27)
Menopausal hormone therapy use					
Never	2081 (70)	1756 (74)	264 (70)	175 (88)	699 (80)
Former	246 (8)	199 (8)	37 (10)	9 (5)	59 (7)
Current	663 (22)	424 (18)	74 (20)	16 (8)	111 (13)
Age at menarche (years)					
≤ 11	598 (20)	528 (22)	64 (16)	43 (20)	183 (21)
12	711 (24)	590 (24)	100 (26)	44 (21)	215 (24)
≥ 13	1670 (56)	1317 (54)	225 (58)	125 (59)	482 (55)
Parity (number of live births)					
Nulliparous	531 (18)	565 (23)	95 (24)	51 (25)	191 (21)
1–2	1334 (45)	1015 (41)	166 (42)	71 (34)	391 (42)
≥ 3	1132 (38)	906 (36)	136 (34)	86 (41)	338 (37)
Mean age at first birth					
Mean age at first birth	24.8 ± 5.1	25.1 ± 5.3	25.0 ± 5.3	24.7 ± 5.0	24.6 ± 5.5
Breastfeeding duration (months)					
Never	1203 (40)	1105 (45)	194 (49)	95 (46)	448 (50)
< 12	991 (33)	764 (31)	113 (29)	51 (25)	267 (30)
≥ 12	803 (27)	595 (24)	86 (22)	60 (29)	187 (21)

Table 1. (Continued)					
	Controls N = 2997 N (%)	ER + PR + N = 2486 N (%)	ER + PR − N = 397 N (%)	ER − PR + N = 208 N (%)	ER − PR − N = 920 N (%)
Parity and breastfeeding (BF)					
Nulliparous	531 (15)	565 (23)	95 (24)	51 (25)	191 (21)
1–2 live births, never BF	448 (15)	340 (14)	61 (16)	31 (15)	157 (17)
≥3 live births, never BF	224 (7)	200 (8)	38 (10)	13 (6)	100 (11)
1–2 live births, ever BF	886 (30)	663 (27)	103 (26)	39 (19)	201 (25)
≥3 live births, ever BF	908 (30)	696 (28)	96 (24)	72 (35)	221 (25)
Mean BMI (kg m^{-2})					
Mean BMI (kg m^{-2})	25.9 ± 5.5	26.0 ± 5.5	26.0 ± 5.5	24.7 ± 5.1	26.6 ± 5.7
Tumour grade					
1, 2	NA	1546 (74)	220 (67)	60 (39)	154 (20)
3	NA	554 (26)	109 (33)	93 (61)	628 (80)
Abbreviations: BMI = body mass index; ER = oestrogen receptor; NA = Not Applicable; PR = progesterone receptor.					

Table 2. Association between parity and breastfeeding, and breast cancer classified by hormone receptor status and menopausal status, Breast Cancer Family Registry					
	ER + PR + [a] N = 2174 OR (95% CI)	ER + PR − [a] N = 341 OR (95% CI)	ER − PR + [a] N = 179 OR (95% CI)	ER − PR − [a] N = 791 OR (95% CI)	ER − PR − vs ER + PR + OR (95% CI)
Parity (number of live births)					
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–2	**0.80 (0.65–0.99)**	0.93 (0.64–1.35)	1.20 (0.71–2.02)	1.33 (1.00–1.76)	**1.62 (1.24–2.13)**
≥3	0.93 (0.73–1.17)	0.97 (0.64–1.49)	1.50 (0.85–2.65)	**1.59 (1.15–2.18)**	**1.66 (1.23–2.25)**
Breastfeeding duration (months)					
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
<12	1.04 (0.87–1.23)	0.84 (0.61–1.16)	0.66 (0.41–1.05)	**0.72 (0.57–0.91)**	**0.70 (0.56–0.88)**
≥12	**0.80 (0.66–0.98)**	**0.69 (0.48–0.99)**	**0.57 (0.35–0.94)**	**0.52 (0.40–0.68)**	**0.64 (0.50–0.84)**
Parity and breastfeeding (BF)					
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–2 live births, never BF	0.80 (0.63–1.00)	0.92 (0.62–1.38)	1.49 (0.86–2.60)	1.30 (0.96–1.75)	**1.59 (1.19–2.13)**
≥3 live births, never BF	0.90 (0.68–1.19)	0.95 (0.58–1.54)	1.01 (0.49–2.07)	**1.57 (1.10–2.24)**	**1.69 (1.20–2.38)**
1–2 live births, ever BF	**0.78 (0.64–0.93)**	0.73 (0.52–1.05)	0.63 (0.38–1.05)	0.88 (0.68–1.14)	1.12 (0.87–1.45)
≥3 live births, ever BF	**0.82 (0.67–0.99)**	0.72 (0.50–1.04)	1.00 (0.64–1.56)	0.93 (0.71–1.22)	1.09 (0.84–1.42)
Premenopausal women					
Parity (number of live births)					
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–2	0.86 (0.65–1.15)	1.14 (0.78–2.54)	1.27 (0.66–2.42)	**1.50 (1.04–2.17)**	**1.73 (1.21–2.48)**
≥3	0.96 (0.69–1.33)	1.12 (0.57–2.21)	1.62 (0.81–3.26)	**1.68 (1.10–2.56)**	**1.70 (1.14–2.55)**
Breastfeeding duration (months)					
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
<12	1.05 (0.81–1.35)	0.86 (0.51–1.46)	0.75 (0.42–1.35)	0.74 (0.54–1.02)	**0.70 (0.51–0.96)**
≥12	0.76 (0.58–1.01)	0.88 (0.50–1.54)	0.68 (0.36–1.19)	**0.61 (0.43–0.87)**	0.80 (0.56–1.13)
Parity and breastfeeding (BF)					
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–2 live births, never BF	0.80 (0.59–1.09)	1.43 (0.76–2.67)	1.62 (0.83–3.18)	**1.56 (1.06–2.32)**	**1.94 (1.32–2.85)**
≥3 live births, never BF	1.05 (0.70–1.58)	1.08 (0.45–2.62)	1.04 (0.41–2.62)	1.49 (0.87–2.55)	1.35 (0.89–2.29)
1–2 live births, ever BF	0.84 (0.67–1.06)	1.23 (0.75–2.01)	0.79 (0.44–1.41)	1.03 (0.75–1.40)	1.21 (0.89–1.64)
≥3 live births, ever BF	0.80 (0.63–1.01)	0.99 (0.58–1.68)	1.20 (0.72–2.00)	1.13 (0.81–1.56)	1.37 (0.99–1.89)

Table 2. (Continued)

	ER + PR + [a] N = 2174 OR (95% CI)	ER + PR − [a] N = 341 OR (95% CI)	ER − PR + [a] N = 179 OR (95% CI)	ER − PR − [a] N = 791 OR (95% CI)	ER − PR − vs ER + PR + OR (95% CI)
Postmenopausal women					
Parity (number of live births)					
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–2	**0.66 (0.47–0.93)**	**0.54 (0.33–0.91)**	0.62 (0.25–1.54)	0.84 (0.52–1.33)	1.26 (0.81–1.97)
⩾3	0.84 (0.58–1.21)	0.77 (0.44–1.34)	0.82 (0.30–2.28)	1.11 (0.68–1.85)	1.30 (0.80–2.11)
Breastfeeding duration (months)					
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
<12	1.08 (0.83–1.39)	0.83 (0.54–1.26)	0.56 (0.24–1.30)	0.75 (0.53–1.07)	**0.70 (0.49–0.99)**
⩾12	0.91 (0.67–1.27)	**0.49 (0.29–0.83)**	0.37 (0.13–1.03)	**0.34 (0.21–0.54)**	**0.37 (0.23–0.58)**
Parity and breastfeeding (BF)					
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–2 live births, never BF	0.70 (0.48–1.00)	**0.58 (0.34–0.98)**	0.73 (0.29–1.85)	0.80 (0.39–1.30)	1.13 (0.72–1.81)
⩾3 live births, never BF	0.75 (0.50–1.14)	0.70 (0.38–1.28)	0.61 (0.19–1.67)	1.12 (0.66–1.92)	1.46 (0.88–2.44)
1–2 live births, ever BF	**0.65 (0.46–0.91)**	**0.38 (0.22–0.65)**	**0.24 (0.08–0.72)**	**0.57 (0.35–0.93)**	0.88 (0.55–1.41)
⩾3 live births, ever BF	0.86 (0.62–1.20)	**0.51 (0.31–0.85)**	0.44 (0.17–1.10)	**0.54 (0.83–0.88)**	**0.60 (0.38–0.97)**

Abbreviations: BMI = body mass index; ER = oestrogen receptor; HT = hormone therapy; OC = oral contraceptive; PR = progesterone receptor. Odds ratios (ORs) and 95% confidence interval (CI), adjusted for age, race/ethnicity, study site, OC use, HT use, BMI, menopausal status, age at menarche, age at first birth, and education. ORs in **bold** are statistically significant.
[a]Compared with population-based controls (N = 2683).

Table 3. Association between oral contraceptive use and breast cancer classified by hormone receptor status and menopausal status, Breast Cancer Family Registry

	ER + PR + [a] N = 2174 OR (95% CI)	ER + PR − [a] N = 341 OR (95% CI)	ER − PR + [a] N = 179 OR (95% CI)	ER − PR − [a] N = 791 OR (95% CI)	ER − PR − vs ER + PR + OR (95% CI)
OC use					
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
⩽5 years	0.97 (0.82–1.15)	**0.73 (0.54–0.99)**	0.67 (0.44–1.04)	1.16 (0.92–1.47)	1.18 (0.94–1.49)
>5 years	**0.83 (0.69–0.98)**	0.74 (0.55–1.01)	0.79 (0.52–1.20)	1.13 (0.89–1.44)	**1.35 (1.07–1.70)**
Year of first OC use					
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Before 1975	1.06 (0.91–1.25)	0.80 (0.59–1.07)	1.12 (0.73–1.73)	**1.32 (1.04–1.67)**	**1.28 (1.03–1.60)**
1975 or later	**0.59 (0.48–0.73)**	**0.52 (0.36–0.76)**	**0.34 (0.21–0.56)**	0.82 (0.63–1.08)	**1.36 (1.06–1.75)**
OC use (premenopausal)					
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
⩽5 years	0.97 (0.76–1.22)	0.65 (0.41–1.05)	0.62 (0.37–1.04)	1.00 (0.73–1.38)	1.05 (0.78–1.41)
>5 years	**0.75 (0.59–0.94)**	0.83 (0.52–1.31)	0.67 (0.41–1.11)	0.98 (0.72–1.33)	1.31 (0.97–1.77)
OC use (postmenopausal)					
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
⩽5 years	0.89 (0.69–1.14)	0.77 (0.51–1.15)	0.58 (0.25–1.32)	1.38 (0.95–1.99)	**1.50 (1.05–2.15)**
>5 years	0.89 (0.68–1.16)	**0.63 (0.41–0.98)**	0.76 (0.35–1.67)	1.23 (0.83–1.81)	1.36 (0.96–1.98)

Abbreviations: BMI = body mass index; ER = oestrogen receptor; HT = hormone therapy; OC = oral contraceptive; PR = progesterone receptor. Odds ratios (ORs) and 95% confidence interval (CI) adjusted for age, race/ethnicity, study site, parity, breastfeeding, HT use, BMI, menopausal status, age at menarche, age at first birth, and education. ORs in **bold** are statistically significant.
[a]Compared with population-based controls (N = 2683); Premenopausal refers to cases diagnosed premenopausally, postmenopausal refers to cases diagnosed postmenopausally. All OC use occurred before menopause.

triple-negative cancer (OR = 2.33, 95% CI 1.22–4.45, triple negative vs Luminal A, for parous, no breastfeeding) compared with nulliparous women. Parous women who breastfed had no increased risk of triple-negative cancer (OR = 1.22, 95% CI 0.67–2.22, vs Luminal A). Oral contraceptive use of >5 years, compared with never use, was positively associated with triple-negative cancer (OR = 1.63, 95% CI 0.97–2.76), as was OC use that began in 1975 or later (OR = 2.02, 95% CI 1.11–3.68).
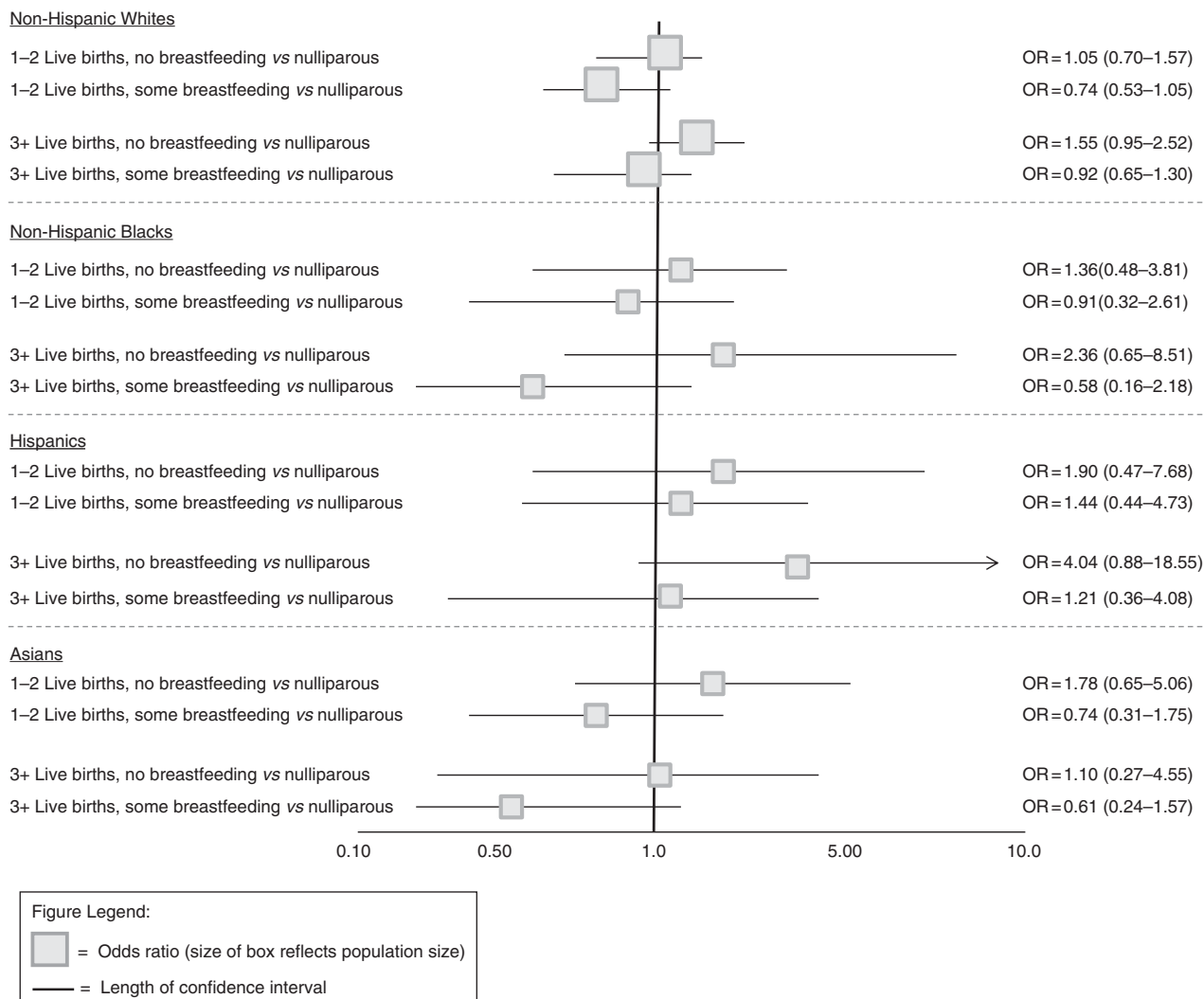
Non-Hispanic Whites

1–2 Live births, no breastfeeding *vs* nulliparous	OR = 1.05 (0.70–1.57)
1–2 Live births, some breastfeeding *vs* nulliparous	OR = 0.74 (0.53–1.05)
3+ Live births, no breastfeeding *vs* nulliparous	OR = 1.55 (0.95–2.52)
3+ Live births, some breastfeeding *vs* nulliparous	OR = 0.92 (0.65–1.30)

Non-Hispanic Blacks

1–2 Live births, no breastfeeding *vs* nulliparous	OR = 1.36(0.48–3.81)
1–2 Live births, some breastfeeding *vs* nulliparous	OR = 0.91(0.32–2.61)
3+ Live births, no breastfeeding *vs* nulliparous	OR = 2.36 (0.65–8.51)
3+ Live births, some breastfeeding *vs* nulliparous	OR = 0.58 (0.16–2.18)

Hispanics

1–2 Live births, no breastfeeding *vs* nulliparous	OR = 1.90 (0.47–7.68)
1–2 Live births, some breastfeeding *vs* nulliparous	OR = 1.44 (0.44–4.73)
3+ Live births, no breastfeeding *vs* nulliparous	OR = 4.04 (0.88–18.55)
3+ Live births, some breastfeeding *vs* nulliparous	OR = 1.21 (0.36–4.08)

Asians

1–2 Live births, no breastfeeding *vs* nulliparous	OR = 1.78 (0.65–5.06)
1–2 Live births, some breastfeeding *vs* nulliparous	OR = 0.74 (0.31–1.75)
3+ Live births, no breastfeeding *vs* nulliparous	OR = 1.10 (0.27–4.55)
3+ Live births, some breastfeeding *vs* nulliparous	OR = 0.61 (0.24–1.57)

0.10   0.50   1.0   5.00   10.0

Figure Legend:

☐ = Odds ratio (size of box reflects population size)

— = Length of confidence interval

Figure 1. Comparison of odds ratios by race/ethnicity for breastfeeding and parity, Breast Cancer Family Registry, ER − PR − cases *vs* controls.

DISCUSSION

Our study sample was enriched with women at higher than population risk for breast cancer (due to oversampling of cases with early-onset breast cancer and/or a family history of breast cancer). We found that high parity was associated with an increased risk of ER − PR − cancer, compared with controls, and that breastfeeding for a total duration of ⩾12 months reduced this risk. Previous studies have found that duration of breastfeeding, coupled with parity levels, is an important factor for risk of triple-negative (ER − PR − HER2 −) breast cancer (Bauer *et al*, 2007; Kwan *et al*, 2009; Redondo *et al*, 2012). When we examined this combined variable for ER − PR − cancer, we also observed that multiparity, combined with no breastfeeding, was associated with an increased risk of ER − PR − cancer, and triple-negative cancer, but not with hormone receptor-positive cancer. We found that the association for ER − PR − cancer was similar across race/ethnicity.

In other studies examining higher risk women, the inverse association with parity was also limited to ER + /PR + cancers (Nichols *et al*, 2005; Ma *et al*, 2006b). However, in a study of very young women, aged ⩽ 35 years, ER status was not associated with parity (Largent *et al*, 2005). While our analysis did not find an association between parity and reduced cancer risk for hormone receptor-positive breast cancer, we did find this to be true among postmenopausal women in our study for women with 1 − 2 births.

We also found a positive association between parity and ER − PR − cancer, similar to the findings of Yang *et al* (2011), in their case-only analysis, and reflecting similarities to findings among studies that examined triple-negative breast cancer (Millikan *et al*, 2007; Phipps *et al*, 2011).

Our study confirms earlier findings that breastfeeding decreases the risk of breast cancer, regardless of hormone receptor status. A recent review supported that ER or PR expression was not differentially associated with breastfeeding (Althuis *et al*, 2004), and most other studies have confirmed this finding for subtypes defined by ER/PR status (Ursin *et al*, 2005; Ma *et al*, 2006b, 2010a; Lord *et al*, 2008; Sweeney *et al*, 2008; Bao *et al*, 2011) and subtypes defined by ER/PR/HER2 status (Ma *et al*, 2010b; Xing *et al*, 2010; Gaudet *et al*, 2011). Some studies have shown, as ours did, that the inverse association with breastfeeding is stronger for ER − , ER − PR − , or triple-negative breast cancer (Largent *et al*, 2005; Millikan *et al*, 2007; Kwan *et al*, 2009; Gaudet *et al*, 2011). The Collaborative Group on Hormonal Risk Factors in Breast Cancer (2002) determined that breastfeeding is protective against breast cancer above and beyond the protection conferred by parity. Hypothesised potential protective mechanisms include the removal of oestrogens *via* breast fluid, excretion of carcinogenic agents through breast milk, delay in ovulation associated with breastfeeding, and induction of terminal differentiation of breast epithelial cells (Lipworth *et al*, 2000). It has been shown that *BRCA1* mutation carriers, who are typically diagnosed with ER − PR − cancer, were

Table 4. Association among oral contraceptive use, parity and breastfeeding and breast cancer classified by molecular status, Breast Cancer Family Registry (compared with Luminal A cases, N = 468)			
	Luminal B N = 118 OR (95% CI)	HER2 + N = 67 OR (95% CI)	Triple negative N = 139 OR (95% CI)
OC use			
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)
⩽ 5 years	0.82 (0.48–1.41)	1.30 (0.64–2.62)	1.19 (0.69–2.04)
> 5 years	0.83 (0.48–1.43)	1.32 (0.65–2.67)	1.63 (0.97–2.76)
Timing of first OC			
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)
Before 1975	0.94 (0.54–1.63)	1.10 (0.53–2.26)	1.11 (0.65–1.89)
1975 or later	0.73 (0.40–1.33)	1.65 (0.75–3.60)	**2.02 (1.11–3.68)**
Parity (number of live births)			
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)
1–2	1.43 (0.72–2.85)	**3.39 (1.31–9.31)**	**2.16 (1.10–4.21)**
⩾ 3	1.32 (0.61–2.88)	2.88 (0.98–8.51)	**2.82 (1.37–5.83)**
Breastfeeding duration (months)			
Never	1.0 (ref)	1.0 (ref)	1.0 (ref)
< 12	0.77 (0.43–1.39)	0.70 (0.36–1.39)	**0.49 (0.29–0.82)**
⩾ 12	1.10 (0.58–2.11)	0.77 (0.35–1.69)	0.57 (0.31–1.04)
Breastfeeding and parity			
Nulliparous	1.0 (ref)	1.0 (ref)	1.0 (ref)
Parous, never breastfed	1.38 (0.71–2.71)	**3.32 (1.26–8.73)**	**2.33 (1.22–4.45)**
Parous, ever breastfed	1.22 (0.69–2.18)	2.40 (0.98–5.86)	1.22 (0.67–2.22)

Abbreviation: OC = oral contraceptive. Luminal A is defined as ER and/or PR +, HER2 −; Luminal B is defined as ER and/or PR +, HER2 +; HER2 + is defined as ER −, PR −, HER2 +; Triple negative is defined as ER −, PR −, HER2 −. Odds ratios (OR) and 95% confidence interval (CI) adjusted for age, race, study site, and menopausal status. OC findings adjusted for breastfeeding and parity; parity findings adjusted for OC use and breastfeeding; breastfeeding findings adjusted for OC use and parity, combined parity–breastfeeding findings adjusted for OC use. **Bold** indicates $P < 0.05$.

less likely to develop breast cancer if they breastfed for at least 1 year, compared with *BRCA1* mutation carriers who did not breastfeed; there was no association with breastfeeding among *BRCA2* mutation carriers, who usually have ER + tumours (Jernstrom *et al*, 2004).

Overall, OC use greater than 5 years was associated with a reduced risk of hormone receptor-positive breast cancer, and was not associated with ER − PR − cancer. Earlier published studies reported positive associations between ER − PR − breast cancer and OC use (reviewed in Althuis *et al*, 2004), whereas most recent studies, including ours, have found no overall association between ER − PR − breast cancer and OC use (Ma *et al*, 2006b; Bao *et al*, 2011), although some studies have reached different conclusions (Rosenberg *et al*, 2010). We found that OC use in 1975 or later was inversely associated with ER + PR + breast cancer, and a positive association between OC use and ER − PR − breast cancer was limited to women who initiated the use before 1975. Year of initiation of OC has been used previously (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Grabrick *et al*, 2000; Kahlenborn *et al*, 2006), but has not generally been examined in previous research on OC use and breast cancer risk by hormone receptor status. Data on OC use and breast cancer risk in *BRCA1* mutation carriers, including some from our own study sample (Milne *et al*, 2005; Haile *et al*, 2006; Iodice *et al*, 2010), have demonstrated no increased risk with OC use initiated after 1974, and examination of OC use among women with a family history of breast cancer found an increased risk of breast cancer only among women who began OC use before 1975 (Grabrick *et al*, 2000). In our study, findings were similar for any hormone-positive

(ER + and/or PR +) subtype, and only different for the ER − PR − type, indicating that any aetiology related to OC use may be through both oestrogen and progesterone-related mechanisms. It is unclear why OCs used before 1975 would be more strongly associated with ER − PR − cancer. Studies of synthetic progestins used in OCs have generally found that the proliferative actions of progestins used in OCs are mediated through the ER (Jeng *et al*, 1992; Jordan, 1993), which does not explain why ER − breast cancer is more likely to be affected, unless the ER is effectively 'turned off' by such proliferation. Typical oestrogen doses used in the 1960s were more than double the doses used in the 1980s, and progestin doses were also higher and included different types of progestins than current OCs (Grabrick *et al*, 2000).

Methodologic considerations. Distributions of parity and other risk factors for our sample where tumour characteristics were available and the entire case sample was similar (data not shown). Breast Cancer Family Registry pathologists used common laboratory procedures and conducted a centralised pathology view to categorise the majority of cases. A recent study has demonstrated that cancer registry-provided data may undercount the rarer ER/PR combinations, such as ER − PR + and ER + PR − tumours, and that centralised pathology review should be considered as a gold standard when classifying tumours by hormone receptor status (Ma *et al*, 2009). For the analysis of molecular subtypes, the population differed from the overall study sample in that it comprised mostly racial/ethnic minority cases from Northern California and Ontario, as few non-Hispanic white families were enrolled in the BCFR after 2000 when HER2 data

became available in the cancer registries. Due to these limitations, we conducted a case-only analysis and acknowledge that our findings are preliminary, although they are in agreement with those of other studies. In the BCFR, differences have been observed between population controls and sister controls in some risk factors that are possibly associated with participation in research (Milne *et al*, 2011). Specifically, our population-based controls are more likely to have been highly educated, and have fewer births and higher average age at first birth, than those sister controls. The possibility of recall bias exists because we relied on participants' recalls of their exposures. However, the purpose of this analysis was to determine whether risk factor associations differed by subtype, using controls as a common comparison group. Because it is unlikely that cases report exposures differently based on their ER, PR, or HER2 status, it is unlikely that differences across tumour subtypes can be explained by recall bias.

Summary. Overall, we found that multiparity is associated with an increased risk of ER − PR − cancer, but this risk was reduced by breastfeeding, such that multiparous women with a history of breastfeeding were no longer at increased risk. In the United States, initiation of breastfeeding has increased steadily since the 1970s and the average duration of breastfeeding is also increasing (U.S. Department of Health and Human Services, 2011). Recent trends examining SEER incidence data suggest that rates of ER − PR − breast cancer are decreasing and will likely continue to decrease in the coming years (Anderson *et al*, 2011). Despite these trends, however, there remain large differences in both ER − PR − breast cancer incidence and breast feeding prevalences across racial and ethnic groups, suggesting that increasing breast feeding in all women is essential to breast cancer prevention.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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