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Oral Contraceptives and Post-menopausal Hormones and Risk of Contralateral Breast Cancer among *BRCA1* and *BRCA2* mutation carriers and non-carriers: The WECARE Study

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Competing Interests:

The authors declare that they have no competing interests.

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Abstract

The potential effects of oral contraceptive (OC) and post-menopausal hormone (PMH) use are not well understood among *BRCA1* or *BRCA2* deleterious mutation carriers with a history of breast cancer. In this study, we investigated the association between OC and PMH use and risk of contralateral breast cancer (CBC) in the WECARE (Women's Environment, Cancer and Radiation Epidemiology) Study. The WECARE Study is a population-based case-control study of 705 women with asynchronous CBC and 1,398 women with unilateral breast cancer, including 181 *BRCA1/2* mutation carriers. Risk factor information was assessed by telephone interview. Mutation status was measured using denaturing high-performance liquid chromatography followed by direct sequencing in all participants. Outcomes, treatment and tumor characteristics were abstracted from medical records. Ever use of OCs was not associated with risk among non-carriers (RR=0.87; 95% CI=0.66–1.15) or *BRCA2* carriers (RR=0.82; 95% CI=0.21–3.13). *BRCA1* carriers who used OCs had a non-significant greater risk than non-users (RR=2.38; 95% CI=0.72–7.83). Total duration of OC use and at least five years of use before age 30 were associated with a non-significant increased risk among mutation carriers, but not among non-carriers. Few women had ever used PMH and we found no significant associations between lifetime use and CBC risk among carriers and non-carriers. In conclusion, the association between OC/PMH use and risk of CBC does not differ significantly between carriers and non-carriers; however, because carriers have a higher baseline risk of second primaries even a potential small increase in risk as a result of OC use may be clinically relevant.

Keywords

breast cancer; asynchronous bilateral; contralateral; oral contraceptives; postmenopausal hormones; *BRCA1*; *BRCA2*

Introduction

Women with a past history of breast cancer who carry mutations in the *BRCA1* or *BRCA2* genes are at increased risk of asynchronous contralateral breast cancer (CBC) [1,2]. Studies suggest that long duration of exposure to oral contraceptives (OC) may increase risk of first primary breast cancer in healthy women who carry deleterious mutations in *BRCA1* [3,4] and *BRCA2* [4,5]. However, *BRCA1* and *BRCA2* mutation carriers also have an increased risk of ovarian cancer and OC use has been suggested as a means to lower risk [6]. The only evidence regarding the impact of PMH use on risk of second primary breast cancer in *BRCA1* or *BRCA2* carriers is from a case-control study of oophorectomized women; in these women PMH use was not associated with risk [7].

We previously reported that neither OC use nor PMH use were significantly associated with risk of CBC in the WECARE (Women's Environment, Cancer and Radiation Epidemiology) Study, a population-based, multi-center case-control study of 708 women with CBC and 1,399 women with unilateral breast cancer [8]. To date, no study has reported whether *BRCA1* or

BRCA2 carrier status modifies the association between OC and PMH use and the risk of second primaries, and, secondly, whether these hormonal exposures are associated with a substantial increased risk among carriers as suggested by studies of first primary breast cancer. In this study, we investigate these associations between OC and PMH use and risk of CBC among confirmed carriers of *BRCA1* and *BRCA2* deleterious mutations and non-carriers in the WECARE Study.

Materials and Methods

Study Population

The WECARE (Women's Environmental Cancer and Radiation Epidemiology) Study has been previously described [9]. In brief, the WECARE Study is a multi-center, population-based case-control study of women with CBC (cases) and women with unilateral breast cancer (controls). All participants were identified from five population-based tumor registries in the United States (SEER registries: Seattle, Iowa, Orange County/San Diego and Los Angeles County) and Denmark (Danish Cancer Registry). Cases were women with CBC who (1) were diagnosed between 01/01/1985 and 12/31/2000 with a first primary invasive breast cancer that did not spread beyond the regional lymph nodes at diagnosis and a second primary *in situ* or invasive breast cancer diagnosed in the contralateral breast at least 1 year after the first breast cancer diagnosis (reference date); (2) resided in the same study reporting area for both diagnoses; (3) had no previous or intervening cancer diagnosis except squamous cell or basal cell skin cancer or cervical carcinoma *in situ*; (4) were alive at the time of contact, and able to provide informed consent to complete the interview and provide a blood sample; and (5) were under age 55 years at the time of diagnosis of the first breast cancer. Two control subjects were individually matched to each case on year of birth, year of diagnosis, registry region, and race, and were 1:2 counter-matched on registry-reported radiation exposure (for treatment of first primary breast cancer) so that each triplet consisted of one radiation untreated and two radiation treated subjects. The sampling is accounted for in the analysis by the inclusion of "sampling weights."

Controls were women who (1) were diagnosed between 01/01/1985 and 12/31/1999 with a first primary invasive breast cancer that did not spread beyond the regional lymph nodes at diagnosis, (2) resided in the same study reporting area as the case to which they were matched at diagnosis and at a reference date equal to the date of diagnosis plus the number of days between the matched case's first and second diagnoses; (3) had no diagnosis of any other cancer (other than squamous or basal cell skin carcinoma or *in situ* cervical cancer) prior to their breast cancer diagnosis or during the at risk period between diagnosis and reference date; (4) were alive at time of contact and able to provide informed consent to complete the interview and provide a blood sample; and (5) had not had a prophylactic mastectomy of the contralateral breast prior to or within the at-risk interval. Among 998 eligible women with CBC, 708 participated in the study as cases; 1,399 of 2,112 eligible women with unilateral breast cancer (controls) participated. Reasons for non-participation included: physician refusal, subject interview refusal, and subject blood draw refusal.

Data Collection

All participants were interviewed by telephone using a structured questionnaire. Questions focused on events occurring prior to and following diagnosis. Data were collected on: personal demographics, medical history, family history, reproductive history, body size, smoking, alcohol intake, oral contraceptive use and post-menopausal hormone use. For all participants, medical records, pathology reports, and hospital charts, in addition to self-reported data, were used to collect detailed treatment information. Information on tumor characteristics was collected from medical records or cancer registry records.

The study protocol was approved by the Institutional Review Boards at each study site and by the ethical committee system in Denmark.

***BRCA1* and *BRCA2* Mutation Screening**

Screening for mutations in *BRCA1* and *BRCA2* [10] was performed in all cases and controls. In brief, coding and flanking intronic regions were screened for mutations or polymorphic variants by denaturing high-performance liquid chromatography (DHPLC). *BRCA1* was covered by 30 PCR amplicons, while 41 amplicons were used for *BRCA2*. A few fragments were screened by direct sequencing because they were unsuitable for or difficult to interpret with DHPLC. Nearly all variant DHPLC results were followed up by direct sequencing. Three laboratories performed the screening using fixed sets of primers and DHPLC protocols. Consistency in screening between and within laboratories was assured via a laboratory quality control plan previously described [11].

We classified mutations as deleterious according to the guidelines provided by the Breast Cancer Information Core (<http://research.nhgri.nih.gov/projects/bic/>). The following sequence variant categories were classified as deleterious (i) changes known or predicted to truncate protein production including all frameshift and nonsense variants with the exception of *BRCA2* K3326X and other variants located 3' thereof, (ii) splice site mutations occurring within 2 base-pairs of an intron/exon boundary or shown to result in aberrant splicing, and (iii) missense changes that have been demonstrated to have a deleterious effect on, for example, the function of the *BRCA1* RING finger and BRCT domains.

Statistical Analysis

To investigate the association between OC use and PMH use and the risk of CBC by *BRCA1/2* mutation carrier status, we used conditional logistic regression analysis with the inclusion of a log weight 'covariate' in the model where the coefficient of this log weight is fixed at one (i.e., an "offset" in the model). The weights use the numbers of registry-reported radiation treated and untreated women in the risk set to account for the counter-matched sampling design [9,12]. The inclusion of interaction terms between the main exposures and *BRCA1/2* indicator variables permits investigation of potential effect modification by *BRCA1* and *BRCA2* mutation carrier status. Heterogeneity in risk estimates of the main exposures across carriers and non-carriers was evaluated using a likelihood ratio test comparing the carrier status specific model to a model including only the main effect for the exposure of interest.

In the current study, OC- and PMH-related variables were defined as previously reported [8]. In the multivariable analyses, we tested the following variables as potential confounders: age at diagnosis of the first primary breast cancer (continuous), age at menarche (<13, 13+ years), number of full-term pregnancies (0, 1, 2, 3, 4+), first degree family history of breast cancer (no parent, sibling or child with a diagnosis of breast cancer, at least one first degree relative with a diagnosis of breast cancer, adopted or unknown family history), histology (lobular, medullary, ductal or other) stage of the first primary (localized, regional), treated with chemotherapy (yes, no), treated with hormone therapy (yes, no), and menopausal status (pre-menopausal, post-menopausal with menopause before age 45 years, post-menopausal with menopause at age 45 years or older). These variables did not significantly change the estimates of risk and we present the more parsimonious models adjusted for subject age at first diagnosis and the sampling strategy. For ever use of OC and ever use of PMH, analyses were also stratified on time since first breast cancer diagnosis (<5, 5+ years) and age at first breast cancer diagnosis (<45, 45+ years) by inclusion of product terms in the conditional logistic models. We observed no significant dependence on latency and age at onset (data not shown).

When necessary, to account for missing information within a counter-matched set, a missing indicator variable was included in the conditional logistic regression models [13]. All statistical tests are two-sided. SAS release 9.1 (SAS Institute, Cary, NC) was used for the analyses.

Results

A total of 181 women carried a *BRCA1* (n=109) or *BRCA2* (n=72) mutation (Table 1). No individual had more than one deleterious mutation. *BRCA1* and *BRCA2* mutation carriers were more likely to be younger at first breast cancer diagnosis than non-carriers, but did not differ by year of diagnosis, study center, or race.

Lifetime ever use of OC was not associated with risk of CBC cancer among non-carriers (RR=0.87; 95% CI=0.66–1.15) or *BRCA2* mutation carriers (RR=0.82; 95% CI=0.21–3.13, Table 2). However, for *BRCA2* mutation carriers, total duration of OC use and at least 5 years of OC use before age 30 were associated with a non-significant increased risk of CBC. In addition, having used OCs more than 5 years before the woman's first full-term pregnancy was associated with a statistically non-significant 1.7-fold increased risk of CBC among *BRCA2* mutation carriers (95% CI=0.48–6.04). Among *BRCA1* mutation carriers, the risk of CBC associated with OC use was elevated, although the confidence interval was wide and included 1.0 (RR=2.38; 95% CI=0.72–7.83, p-heterogeneity=0.27). Longer duration of use did not appear to further increase risk (RR=2.07, 95% CI=0.60–7.11 comparing individuals with 5+ years of use to no use). Among non-carriers, there was no indication that age at first and last use (data not shown), total duration, years of use prior to age 30 and full-term pregnancy were associated with risk.

Lifetime ever use of PMH was not associated with risk of CBC among non-carriers (RR=1.09; 95% CI=0.84–1.42). Use among *BRCA1*- and *BRCA2*-mutation carriers showed a non-significant inverse association with CBC risk (RR=0.87; 95% CI=0.22–3.54 and RR=0.58; 95% CI=0.15–2.25, respectively). Among non-carriers, we observed no association with age at first or last use, duration of use, type of PMH, or recency of use (data not shown). We were not able to evaluate the association between duration and type of PMH among carriers due to small numbers.

Discussion

In this large, population-based, case-control study, we found no evidence that *BRCA1* or *BRCA2* carrier status modifies the associations between OC or PMH use and risk of CBC. The increased CBC risk associated with OC use among *BRCA1* carriers is potentially important, but was not statistically significant. Total duration of OC use and at least five years of OC use before age 30 also were associated with statistically non-significant increased risks among *BRCA1* carriers and *BRCA2* mutation carriers. In addition, for *BRCA2* mutation carriers, OC use more than 5 years before first full-term pregnancy was associated with a statistically non-significant increased CBC risk. In line with previous studies among women untested for *BRCA1* and *BRCA2* mutations, we observed little indication that OC use increased risk of second primaries among non-carriers [8,14–17]. No association between age at use, duration, recency or type of PMH was observed among non-carriers, as suggested by other reports [8, 14,16]. Our sample size was more limited for our evaluation of PMH use in *BRCA1* and *BRCA2* carriers, and our results showed no significant evidence that the risk associated with PMH use differed among carriers and non-carriers. These results merit further investigation in larger studies of *BRCA1/2*-carriers with breast cancer.

Previous studies of first primary breast cancer have also observed an increased risk associated with OC use in carriers [3–5,18], although results among these studies differed. Narod (2002)

observed that among *BRCA1* mutation carriers, women who first used OCs before 1975, who used them before age 30, or who used them for 5 or more years had an increased risk of early-onset breast cancer [3]. OC use was not associated with risk of breast cancer in *BRCA2* mutation carriers, but data for *BRCA2* carrier status were limited. A larger population-based study, found no evidence that overall use of OC for at least one year was associated with breast cancer risk among either *BRCA1* or *BRCA2* mutation carriers [5]. However, OC use for longer than 5 years, use for at least 4 years before first full-term pregnancy, and use before age 30 were associated with a significant increased risk among *BRCA2*, but not *BRCA1* mutation carriers [5]. Recently, the International *BRCA1/2* Carrier Cohort Study (IBCCS) of 1,593 carriers found an increased risk for both *BRCA1* and *BRCA2* mutation carriers who ever used OC as well as a longer duration of use, especially before full-term pregnancy [4].

Additionally, a few studies investigating OC use and breast cancer risk comparing affected carriers to unaffected non-carriers have been reported. Milne (2005) found that OC use for at least one year was associated with a decreased risk among *BRCA1* mutation carriers, but not *BRCA2* mutation carriers and a group of untested women unlikely to carry mutations [19]. However, a recent case-control study in Los Angeles County found no association between OC use (overall and low-dose) and risk of breast cancer regardless of *BRCA1/2* status [20]. In a small case-case analysis of 50 Ashkenazi Jewish breast cancer patients tested for founder mutations in *BRCA1* (185delAG and 5382insC) and *BRCA2* (6174delT), long-term use of oral contraceptives before first full-term pregnancy (OR=7.8; 95% CI=1.1–55.0) was associated with a significantly increased risk of *BRCA1/2*-associated breast cancer compared to non-*BRCA1/2* breast cancer [18].

Considerably less is known about the relationship between PMH use and breast cancer risk among carriers and non-carriers. In a prospective cohort study of healthy women with confirmed *BRCA1* or *BRCA2* deleterious mutations, PMH use was not associated with an increased risk of breast cancer [7]. In addition, Armstrong (2004) using a Markov decision analysis, observed that for mutation carriers who had been oophorectomized and selected against prophylactic mastectomy, the use of PMH appeared to have minimal effect on life expectancy [21]. Furthermore, a meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer in which *BRCA1* and *BRCA2* status was undetermined, showed that PMH does not increase the risk of breast carcinoma in familial high-risk women [22].

Growing evidence suggests that breast cancer is a heterogeneous disease with *BRCA1*- and *BRCA2*-associated tumors exhibiting a distinct morphologic and molecular signature. *BRCA2* tumors are more likely to exhibit the luminal phenotype with estrogen receptor (ER) positive receptors [23], while *BRCA1* tumors exhibit a basal-phenotype and have ER negative receptors [24]. Paradoxically, estrogen suppression by oophorectomy in pre-menopausal women has been shown not only to substantially reduce risk of subsequent breast and ovarian cancer in *BRCA2* mutation carriers, but also *BRCA1* mutation carriers [25,26]. The use of tamoxifen has also been shown to reduce risk of contralateral breast cancer in both *BRCA1* and *BRCA2* carriers [27]. Functional studies show that *BRCA1* expression is responsive to estrogen levels and represses estrogen-dependent and estrogen-independent transactivational activity of estrogen receptor (ER)-alpha [28,29]. Mutations in *BRCA1* may remove this inhibitory effect, thereby increasing epithelial proliferation in the breast. Estrogen also activates *BRCA2* function to increase DNA repair responses in ER-positive breast cancer cells [30]. In addition, *BRCA1* regulates progesterone receptor signaling [31] and a progesterone antagonist has been shown to prevent *BRCA1*-mediated tumorigenesis in mouse models [31]. These findings support the potential increased risk associated with estrogen exposure in both *BRCA1* and *BRCA2* mutation carriers.

This study has several limitations. We did not screen for larger genomic deletions or duplications in *BRCA1* or *BRCA2* that may occur in up to 12% of women with strong family histories and who test negative for deleterious mutations [32]. There may be additional misclassification due to limited information on function of variants in *BRCA1* and *BRCA2* not included as deleterious. Lastly, we are limited by the number of *BRCA1* and *BRCA2* carriers, which precluded us from investigating associations in more detail with respect to age at first and last use, duration of use, and use before and after a diagnosis of breast cancer especially for PMH. Investigation into the inter-relationships between ER/PR status or molecular profiles, OC and PMH use and risk among *BRCA1* and *BRCA2* mutation carriers was also prohibited by our sample size, but merits attention in future studies.

This is the first study to investigate the role of OC and PMH use in the development of contralateral breast cancer in *BRCA1/2* mutation carriers. Additional strengths of this study include: systematic collection of data, careful matching of cases to controls, the abstraction of medical records to confirm cancer-free interval for controls and treatment history for both cases and controls. In addition, by limiting initial breast cancer diagnoses to localized and regional disease and specifying a minimum interval of one year between first and second diagnosis of the case subjects, we limited the potential for misclassification of metastases as second primary cancers. This study has avoided biases associated with use of high-risk or selected populations by ascertaining cases and controls via multiple population-based cancer registries, which leads to greater generalizability of the findings. We have also implemented strong quality control procedures to ensure accurate genotyping of mutations in *BRCA1* and *BRCA2*.

In this study, we observed no significant evidence that the effects of OC/PMH use on risk of contralateral breast cancer differs between non-carriers and *BRCA1* and *BRCA2* mutation carriers. However, because *BRCA1* and *BRCA2* mutation carriers have a higher baseline risk of second breast primaries compared to non-carriers [1,2], the potential increased risks associated with OC use may be clinically relevant. These results merit further confirmation in larger studies of *BRCA1/2*-carriers with breast cancer.

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Abbreviations used

OC	Oral contraceptives
PMH	post-menopausal hormones
ER	estrogen receptor
DHPLC	high-performance liquid chromatography

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Table 1
Selected characteristics of the *BRCA1* and *BRCA2* carriers and non-carriers in the WECARE Study*

		Non carriers [†]		<i>BRCA1</i> mutation carrier		<i>BRCA2</i> mutation carrier	
		Bilateral n (%)	Unilateral n (%)	Bilateral n (%)	Unilateral n (%)	Bilateral n (%)	Unilateral n (%)
Total		597	1325	67	42	41	31
Age at first breast cancer	20–34	22 (3.7)	76 (5.7)	22 (32.8)	9 (21.4)	4 (9.8)	5 (16.1)
	35–44	204 (34.2)	484 (36.5)	35 (52.2)	23 (54.8)	22 (53.7)	10 (32.3)
	45–55	371 (62.1)	765 (57.7)	10 (14.9)	10 (23.8)	15 (36.6)	16 (51.6)
Age at reference date[§]	Mean Age	46.5 (5.8)	45.7 (6.1)	38.3 (6.0)	40.1 (6.8)	42.8 (6.3)	43.8 (7.2)
	22–34	8 (1.4)	27 (2.1)	7 (10.4)	7 (16.7)	1 (2.4)	2 (6.5)
	35–44	73 (12.2)	217 (16.3)	35 (52.2)	17 (40.5)	12 (29.3)	7 (22.6)
At risk period (years)[¥]	≥ 45	516 (86.5)	1081 (81.7)	25 (37.3)	18 (42.9)	28 (68.3)	22 (71.0)
	Mean Age	51.6 (6.6)	50.8 (6.8)	42.8 (7.1)	43.8 (7.7)	47.3 (6.9)	47.7 (8.0)
	Mean time interval	5.1 (3.2)	5.1 (3.1)	4.9 (2.8)	4.2 (2.7)	5.0 (3.0)	4.5 (2.5)
Geographic Location	Denmark	151 (25.2)	339 (25.5)	13 (19.4)	8 (19.0)	12 (29.3)	10 (32.3)
	USA	446 (74.8)	986 (74.5)	54 (80.6)	34 (81.0)	29 (70.7)	21 (67.7)
	White	552 (92.5)	1223 (92.3)	59 (88.1)	38 (90.5)	35 (85.4)	26 (83.9)
Race	Hispanic White	17 (2.8)	44 (3.3)	4 (6.0)	2 (4.8)	3 (7.3)	2 (6.5)
	Black	18 (3.0)	35 (2.6)	2 (3.0)	1 (2.4)	1 (2.4)	3 (9.7)
	Asian or other	10 (1.7)	23 (1.7)	2 (3.0)	1 (2.4)	2 (4.9)	0 (0.0)

[†] Includes individuals with unclassified *BRCA1* and *BRCA2* variants

* Frequency counts do not necessarily sum to the total number of individuals due to missing data

[§] Reference date = date at 2nd breast cancer for cases (bilateral breast cancer) and equivalent date for controls (unilateral breast cancer)

[¥] Time interval between 1st and 2nd diagnoses for cases and 1st diagnosis and equivalent date for controls

Table 2

Association of OC and PMH use on risk of asynchronous bilateral breast cancer among *BRCA1* and *BRCA2* carriers and non-carriers

	Non carriers			<i>BRCA1</i> mutation carrier			<i>BRCA2</i> mutation carrier		
	Bilateral N (%) *	Unilateral N (%) *	Adjusted ^{***} RR (95% CI)	Bilateral N (%) *	Unilateral N (%) *	Adjusted ^{***} RR (95% CI)	Bilateral N (%) *	Unilateral N (%) *	Adjusted ^{***} RR (95% CI)
OC ever use									
No	154 (25.8)	281 (25.8)	1.00	8 (11.9)	9 (21.4)	1.00	9 (22.0)	6 (19.4)	1.00
Yes	443 (74.2)	1041 (78.7)	0.87 (0.66–1.15)	59 (88.1)	33 (78.6)	2.38 (0.72–7.83)	32 (78.1)	25 (80.7)	0.82 (0.21–3.13)
<i>p</i> -heterogeneity	0.27								
Age at first OC use[†]									
Never	154 (25.9)	281 (21.3)	1.00	8 (12.3)	9 (12.3)	1.00	9 (22.0)	6 (19.4)	1.00
<20 y	111 (18.7)	276 (20.9)	0.97 (0.67–1.41)	28 (43.1)	17 (40.5)	1.88 (0.57–6.38)	9 (22.0)	11 (35.5)	0.64 (0.14–3.00)
20+ y	330 (55.5)	761 (57.7)	0.86 (0.65–1.14)	29 (44.6)	16 (38.1)	1.52 (0.42–5.54)	23 (56.0)	14 (45.2)	0.97 (0.23–4.00)
p-trend	0.23								
p-heterogeneity	0.75								
Total duration of OC use									
Never	154 (26.0)	281 (21.4)	1.00	8 (11.9)	9 (21.4)	1.00	9 (22.0)	6 (20.7)	1.00
<5 y	218 (36.8)	467 (35.6)	0.92 (0.68–1.25)	25 (37.3)	11 (26.2)	2.91 (0.75–11.3)	14 (34.2)	12 (41.4)	0.86 (0.21–3.57)
5+ y	220 (37.2)	564 (43.0)	0.85 (0.63–1.15)	34 (50.8)	22 (52.4)	2.07 (0.60–7.11)	18 (43.9)	11 (37.9)	2.02 (0.52–7.81)
p-trend	0.20								
p-heterogeneity	0.25								
OC use before age 30									
Never	255 (42.9)	481 (36.6)	1.00	17 (26.6)	17 (40.5)	1.00	13 (31.7)	10 (32.3)	1.00
<5 y	141 (23.7)	321 (24.4)	0.85 (0.64–1.14)	8 (12.5)	7 (16.7)	0.76 (0.18–3.23)	8 (19.5)	9 (29.0)	0.53 (0.12–2.24)
5+ y	198 (33.3)	514 (39.1)	0.87 (0.66–1.14)	39 (60.9)	18 (42.9)	1.83 (0.67–4.88)	20 (48.8)	12 (38.7)	1.48 (0.43–5.16)
p-trend	0.35								
p-heterogeneity	0.33								
OC use before 1st pregnancy									
Never	286 (59.2)	627 (56.8)	1.00	20 (38.5)	15 (45.4)	1.00	17 (51.5)	15 (55.6)	1.00
<5 y	77 (15.9)	204 (18.5)	0.82 (0.59–1.14)	10 (19.2)	5 (15.2)	1.10 (0.29–4.17)	6 (18.2)	5 (18.5)	1.39 (0.32–5.99)
5+ y	120 (24.8)	273 (24.7)	1.11 (0.82–1.50)	22 (42.3)	13 (39.4)	0.95 (0.35–2.52)	10 (30.3)	7 (25.9)	1.70 (0.48–6.04)

	Non carriers			BRCA1 mutation carrier			BRCA2 mutation carrier		
	Bilateral N (%) *	Unilateral N (%) *	Adjusted ^{***} RR (95% CI)	Bilateral N (%) *	Unilateral N (%) *	Adjusted ^{***} RR (95% CI)	Bilateral N (%) *	Unilateral N (%) *	Adjusted ^{***} RR (95% CI)
p-trend			0.11			0.89			0.43
p-heterogeneity	0.90								
PMH ever use									
No	432 (72.6)	983 (74.2)	1.00	60 (89.6)	37 (88.1)	1.00	36 (87.8)	24 (77.4)	1.00
Yes	163 (27.4)	342 (25.8)	1.09 (0.84–1.42)	7 (10.5)	5 (11.9)	0.87 (0.22–3.54)	5 (12.2)	7 (22.6)	0.58 (0.15–2.25)
p-heterogeneity	0.13								

* Frequency counts do not necessarily sum to the total number of individuals due to missing data

** All models included the log counter-matching weights and were adjusted for exact age at first BC diagnosis.

[†] Restricted to individuals > 20 y