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EPIDEMIOLOGY

Timing of oral contraceptive use and the risk of breast cancer in *BRCA1* mutation carriers

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Abstract It is not clear if early oral contraceptive use increases the risk of breast cancer among young women with a breast cancer susceptibility gene 1 (*BRCA1*) mutation. Given the benefit of oral contraceptives for the prevention of ovarian cancer, estimating age-specific risk ratios for oral contraceptive use and breast cancer is important. We conducted a case–control study of 2,492 matched pairs of women with a deleterious *BRCA1* mutation. Breast cancer cases and unaffected controls were matched on year of birth and country of residence. Detailed information about oral contraceptive use was collected from a routinely administered questionnaire. Conditional logistic regression was used to estimate the odds ratios (OR) and 95 % confidence intervals (CI) for the association between oral contraceptive and breast cancer, by age at first use and by age at diagnosis. Among *BRCA1* mutation carriers, oral contraceptive use was significantly associated with an increased risk of breast cancer for women who started the pill prior to age 20 (OR 1.45; 95 % CI 1.20–1.75; $P = 0.0001$) and possibly between ages 20 and 25 as well (OR 1.19; 95 % CI 0.99–1.42; $P = 0.06$). The effect was limited to breast cancers diagnosed before age 40 (OR 1.40; 95 % CI 1.14–1.70; $P = 0.001$); the risk of early-onset breast cancer increased by 11 % with each additional year of pill use when initiated prior to age 20 (OR 1.11; 95 % CI 1.03–1.20; $P = 0.008$). There was no

Please refer the Appendix section for the other members of the Hereditary Breast Cancer Clinical Study Group.

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observed increase for women diagnosed at or after the age of 40 (OR 0.97; 95 % CI 0.79–1.20; $P = 0.81$). Oral contraceptive use before age 25 increases the risk of early-onset breast cancer among women with a *BRCA1* mutation and the risk increases with duration of use. Caution should be taken when advising women with a *BRCA1* mutation to take an oral contraceptive prior to age 25.

Keywords *BRCA1* · Oral contraceptives · Breast cancer

Abbreviations

BRCA1	Breast cancer susceptibility gene 1
OR	Odds ratios
CI	Confidence interval
RR	Relative risk

Introduction

The lifetime risk of developing breast cancer in a woman with an inherited breast cancer susceptibility gene 1 (*BRCA1*) mutation is approximately 70 % [1]. Women with *BRCA1* mutations are often diagnosed with breast cancer at a young age; approximately 50 % of breast cancers occur before age 40 [2]. Late age at menarche [3–5], breastfeeding [6] and bilateral oophorectomy [7] have all been reported to decrease the risk of breast cancer among women with a *BRCA1* mutation. Age at first birth does not appear to influence risk [8], and the impact of parity remains unclear [7, 9, 10]. Two observational studies of hormone replacement therapy following prophylactic oophorectomy reported no increase in breast cancer risk [11, 12]. Collectively, these data suggest important roles for hormonal exposures, particularly during the premenopausal years. In particular, adolescence represents a time period of rapid cellular proliferation when the breast is susceptible to carcinogenic insults [13].

Women with a *BRCA1* mutation face a lifetime risk of developing ovarian cancer estimated to be 40 % [1]. Given that oral contraceptives confer a significant protective effect against ovarian cancer development [7], women are often advised to consider using an oral contraceptive as a protective measure. In 2002, we reported a modestly increased risk of *BRCA1*-associated breast cancer with oral contraceptive use [14]. In this earlier smaller study of 981 matched pairs, we reported that ever use of an oral contraceptive was associated with an increased risk of breast cancer (odds ratio [OR] 1.20; 95 % CI 1.02–1.04). No effect was seen among *BRCA2* mutation carriers ($n = 330$ matched pairs) (OR 0.94; 95 % CI 0.72–1.24) [14]. The dual effects of oral contraceptive use in this context (i.e., the potential to increase breast cancer risk but protect against ovarian cancer) must be considered when counseling these women. Here we update the analysis of oral contraceptive use and risk of breast cancer in 2,492 matched pairs of *BRCA1* mutation carriers with the intent of clarifying the timing and duration of oral contraceptive use on breast cancer risk.

Methods

Study population

Eligible study subjects were identified at one of 72 participating centers in 13 countries. These women were participants in ongoing research protocols at the host institutions. These women sought testing for *BRCA1* and *BRCA2* mutations because of a personal and/or family history of breast and/or ovarian cancer. All study subjects (with the exception of some participants from the research study of SLN) received genetic counseling. The institutional review boards of the host institutions approved the study. All subjects provided written informed consent. In most cases, testing was initially offered to women who had

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been previously diagnosed with breast or ovarian cancer. When a *BRCA1* or *BRCA2* mutation was identified in a proband or her relative, genetic testing was offered to other at-risk individuals in the family. Mutation detection was performed using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. A woman was eligible for the current study when the molecular analysis established that she was a carrier of a deleterious mutation in the *BRCA1* or *BRCA2* gene.

Data collection

All study subjects completed a baseline questionnaire at the individual center at the time of a clinic appointment or at their home at a later date. The questionnaire requested information on family and personal history of cancer, reproductive and medical histories, including preventive oophorectomy and mastectomy. Detailed information regarding oral contraceptive use was also collected. Women were asked if they ever used birth control pills to prevent pregnancy or for any other reason. If they answered 'yes,' they were also asked to the start and end date (year) and duration of use (in months and years). Information on current use was also queried. We limited this analysis to use of birth control pills.

Case and control subjects

Information on cancer status was available for 10,445 women who carried a *BRCA1* mutation. We previously reported no relationship between oral contraceptive use and breast cancer risk among women with a *BRCA2* mutation; thus, we limited this analysis to women with a *BRCA1* mutation. Case subjects were women with a diagnosis of invasive breast cancer and who carried a *BRCA1* mutation. Control subjects were women who never had breast cancer and who were carriers of a *BRCA1* mutation. Potential subjects were excluded if they were born prior to 1925 ($n = 123$), if information on oral contraceptive use (including start year) was missing ($n = 432$), if they had been diagnosed with ovarian cancer ($n = 1{,}511$), if they had a bilateral oophorectomy prior to the breast cancer diagnosis ($n = 264$), or if other pertinent information was missing ($n = 31$). After exclusions, there was a total of 8,084 eligible women, including 3,276 women with breast cancer (potential case subjects) and 4,808 women without breast cancer (potential control subjects).

A single control subject was selected for each case subject, matched according to year of birth (within 1 year) and country of residence. A control was eligible to be matched to a given case if the date of interview, date of prophylactic mastectomy or date of oophorectomy in the matched control occurred at or after the year of breast cancer diagnosis of the case. In total, 2,492 matched sets were identified.

Statistical analysis

A matched case–control analysis was performed to evaluate the association between oral contraceptive use and the risk of breast cancer. We censored oral contraceptive use for cases and controls in the year prior to the year of diagnosis of the matched case. The distributions of continuous and categorical variables between cases and controls were compared using the Student's t test and chi-square test, respectively. Conditional logistic regression was used to estimate the univariate odds ratios (OR) and 95 % confidence intervals (CI) for breast cancer associated with oral contraceptive use (ever/never) and duration of oral contraceptive use (years). A multivariate analysis was carried out to control for potential confounders. All analyses were performed using the SAS statistical package, version 9.1.3 (SAS Institute, Cary, NC, USA). All P values were based on two-sided tests and were considered statistically significant if $P \leq 0.05$.

Results

Case and control subjects were similar with respect to year of birth, age at first birth, age at last birth and smoking history (Table 1). Cases with a *BRCA1* mutation had an earlier age at menarche than controls (13.0 vs. 13.2 years; $P = 0.0008$) and a lower mean parity (1.78 vs. 1.84; $P = 0.08$), but the absolute differences were small. Ever use of oral contraceptives was similar between the cases and controls (59 vs. 57 %; $P = 0.06$); however, age at first use was slightly earlier for the cases than for the controls (21.6 vs. 22.1 years; $P = 0.01$). Among those who ever used an oral contraceptive, duration of use was 3.8 years for the cases and 3.5 years for the controls ($P = 0.05$).

Among all subjects, ever oral contraceptive use was associated with a significant 18 % increase in the risk of breast cancer compared with women who never used an oral contraceptive (OR 1.18; 95 % CI 1.03–1.36; $P = 0.02$) (Table 2). The adjusted OR for breast cancer among *BRCA1* mutation carriers who used oral contraceptives for <5 years was 1.14 (95 % CI 0.97–1.35; $P = 0.11$) and for those who used oral contraceptives for more than 5 years was 1.22 (95 % CI 1.04–1.49; $P = 0.02$).

We then considered the risk of breast cancer associated with age at first use (Fig. 1, Table 2). *BRCA1* mutation carriers who started using oral contraceptives before age 20 had a significant 45 % increased risk of breast cancer compared to never users (OR 1.45; 95 % CI 1.20–1.75;

Table 1 Characteristics of breast cancer cases and controls with a *BRCA1* mutation

Characteristic	Controls (n = 2,492)	Cases (n = 2,492)	P[a]
Date of birth, mean (SD)	1,958.1 (9.9)	1,958.0 (10.4)	0.71
Age, mean (SD)	46.6 (9.4)	46.3 (9.5)	0.26
Year of diagnosis, mean (SD)	n/a	1,997.2 (8.7)	
Age at diagnosis, mean (SD)	n/a	39.7 (7.9)	
Age at menarche, mean (SD)	13.2 (1.6)	13.0 (1.6)	0.0008
Missing, *n* (%)	193 (7)	232 (9)	
Parity, *n* (%)			
0	481 (19.4)	469 (19.0)	
1	425 (16.8)	470 (19.1)	
2	921 (37.2)	941 (38.2)	
≥3	658 (26.6)	586 (23.8)	0.05
Missing	17	26	
Parity, mean (SD)	1.84 (1.3)	1.78 (1.3)	0.08
Age at first birth, mean (SD)	24.8 (4.7)	24.8 (4.6)	0.61
Age at last birth, mean (SD)	29.2 (5.0)	29.0 (5.0)	0.30
Oral contraceptive use, *n* (%)			
Never	1,084 (43.5)	1,018 (40.9)	
Ever	1,408 (56.5)	1,474 (59.2)	0.06
Age at first use, mean (range)	22.1(8–48)	21.6 (8–46)	0.01
Duration of use, mean years (SD)			
Among ever users	3.6 (5.0)	3.8 (5.1)	0.05
Among current users	6.3 (5.2)	6.5 (5.2)	0.33
Smoking history, *n* (%)			
Never	1,374 (57.0)	1,356 (55.6)	
Ever	1,037 (43.0)	1,084 (44.4)	0.32
Missing	81	52	
Country of residence, *n* (%)			
USA	793 (31.8)	Matched	
Canada	500 (20.1)		
Poland	859 (34.5)		
Israel	78 (3.1)		
Netherlands	75 (3.0)		
Norway	86 (3.5)		
Italy	28 (1.1)		
France	4 (0.2)		
Austria	49 (2.0)		
Sweden	9 (0.4)		
United Kingdom	8 (0.3)		
China	1(0.04)		
Bahamas	2 (0.1)		
Ethnicity, *n* (%)			
French Canadian	86 (3.5)	97 (3.9)	
Jewish	419 (16.8)	372 (14.9)	
Other white	44 (1.8)	87 (3.5)	
Other[b]	1,943 (78.0)	1,936 (77.7)	0.28

SD standard deviation, *n/a* not applicable

[a] All P values are univariate and derived using the Student's t test for continuous variables and the chi-square test for categorical variables

[b] Due to small numbers, participants included in the 'Other' category were not included in the calculation

$P = 0.0001$). In this subgroup, there was a significant increased risk with any duration of oral contraceptive use (P trend = 0.0003; Table 3). The risk of breast cancer in this group of women increased by 10 % for each additional year of oral contraceptive use (OR 1.10; 95 % CI 1.03–1.17; $P = 0.005$) (Table 2). There was a small but nonsignificant increased risk among women who starting using oral contraceptives between ages 20–25 compared to never users (OR 1.19; 95 % CI 0.99–1.42; $P = 0.06$) (Table 2).

We next asked whether the relationship between oral contraceptive use and breast cancer risk differed by age at diagnosis (Table 2). Oral contraceptive use increased the risk of breast cancer diagnosed before the age of 40 (OR 1.40; 95 % CI 1.14–1.70; $P = 0.001$). In this subgroup, the risk of breast cancer increased by 3 % for each additional year of oral contraceptive use (OR 1.03; 95 % CI 1.01–1.05; P trend = 0.004) (Table 4). Among women diagnosed before age 40, the effect of oral contraceptive use was strongest for those women who first used an oral contraceptive at or before the age of 20 (OR 1.74; 95 % CI 1.36–2.22; $P = 0.00001$). In this group, for each additional year of oral contraceptive use before age 20, the OR for breast cancer increased by 11 % (OR 1.11; 95 % CI 1.03–1.20; $P = 0.008$) (Table 4) (Fig. 1). Use between the ages of 20–25 also significantly increased the risk of breast cancer before age 40 (OR 1.36; 95 % CI 1.07–1.73; $P = 0.02$) with a 7 % increase in risk per year of oral contraceptive use ($P = 0.03$). There was no significant relationship between oral contraceptive use and risk for women with a diagnosis of breast cancer between the ages of 40 and 50 (OR 0.95; 95 % CI 0.76–1.20) or after the age of 50 (OR 1.08; 95 % CI 0.66–1.77).

We also evaluated the risk of breast cancer associated with oral contraceptive use, stratified by time since last use (Table 2). Compared with women who never used an oral contraceptive, current use was not associated with an increased risk of breast cancer. In fact, compared to never users, current use was associated with a significant 20 %

Table 2 Relationship between oral contraceptive use and breast cancer risk among *BRCA1* mutation carriers

Variable	Controls (*n*)	Cases (*n*)	OR (95 % CI)[a]	*P*
Oral contraceptive use				
Never	1,084	1,048	1.00	
Ever	1,408	1,474	1.18 (1.03–1.36)	0.02
Trend per year			1.01 (1.00–1.03)	0.05
Duration of use (years)				
Never	1,084	1,018	1.00	
0–<5	629	630	1.14 (0.97–1.35)	0.11
5–<10	431	455	1.19 (0.99–1.43)	0.07
10–<15	225	258	1.27 (1.02–1.60)	0.04
15–<30	123	131	1.23 (0.92–1.65)	0.16
Trend[b]				0.02
Age at first use (years)				
Never	1,084	1,018	1.00	
<20	526	619	1.45 (1.20–1.75)	0.0001
20–<25	235	534	1.19 (0.99–1.42)	0.06
25–<30	205	191	1.06 (0.84–1.33)	0.62
30–<60	142	130	0.98 (0.76–1.27)	0.88
Trend[b]				0.0003
Annual risk by age at first use				
Never	n/a	n/a	1.00	
Risk per year ≤20			1.10 (1.03–1.17)	0.005
Risk per year >20–≤25			1.02 (0.98–1.07)	0.36
Risk per year >25–≤30			1.04 (0.99–1.09)	0.11
Risk per year >30			0.97 (0.94–0.99)	0.02
Age of diagnosis, ever/never use				
<40 years	1,302	1,302	1.40 (1.14–1.70)	0.001
40–50 years	980	980	0.95 (0.76–1.20)	0.68
>50 years	210	210	1.08 (0.66–1.77)	0.75
Time since last use				
Never	1,084	1,018	1.00	
Current use	184	80	0.80 (0.66–0.97)	0.03
Stopped >10 years	174	160	1.27 (1.06–1.53)	0.01
Stopped within 5–10 years	230	278	1.55 (1.25–1.77)	<0.0001
Stopped within 5 years	820	955	1.42 (1.13–1.77)	0.002
Trend[b]				0.38

n/a not applicable

[a] All ORs and 95 % CIs were calculated using a multivariate conditional logistic regression model, adjusting for ethnicity and parity

[b] *P* value for trend across categories

reduction in breast cancer risk (OR 0.80; 95 % CI 0.66–0.97), whereas women who stopped taking oral contraceptives five or more years ago had a statistically significant 38 % increased risk of breast cancer (OR 1.38; 95 % CI 1.18–1.61).

Discussion

We evaluated the relationship between oral contraceptive use and breast cancer risk in a large sample of women with an inherited *BRCA1* mutation. We observed that in the overall study group, ever use of an oral contraceptive was associated with a significantly increased risk of early-onset breast cancer (OR 1.40; 95 % CI 1.14–1.70; $P = 0.001$). The association was strong for women who started using oral contraceptives before the age of 20 (OR 1.74; 95 % CI 1.36–2.22) (Fig. 1). Furthermore, there was evidence for an increase in risk for use initiated between ages 20 and 25, but the increase in risk was smaller (OR 1.36; 95 % CI 1.07–1.74). Oral contraceptive use was not associated with breast cancer risk after age 40 (OR 0.97; 95 % CI 0.79–1.20).

These findings are in agreement with our earlier publication, which was based on a subset of these women [14]. We reported that oral contraceptive use increased the risk

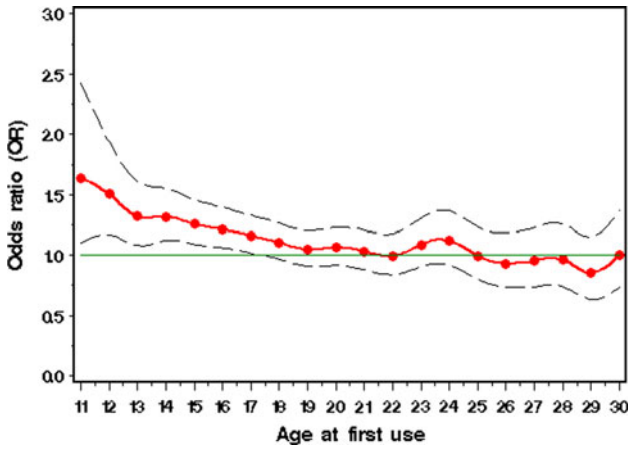

Fig. 1 Odds ratio associated with ever oral contraceptive use, by age at first use. Each point on the graph represents the mean of a five-year moving average

Table 3 Relationship between duration of oral contraceptive use prior to age 20 and breast cancer risk among *BRCA1* mutation carriers

Variable	Controls (*n*)	Cases (*n*)	OR (95 % CI)[a]	*P*
Duration of use <20 years old				
Never	1,084	1,018	1.00	
<5 years	154	164	1.39 (1.06–1.83)	0.02
5–<10 years	180	208	1.39 (1.07–1.80)	0.01
10–<15 years	118	152	1.49 (1.12–1.99)	0.007
≥15 years	74	95	1.63 (1.14–2.35)	0.007
Trend[b]				0.0003

[a] All ORs and 95 % CIs were calculated using a multivariate conditional logistic regression model, adjusting for ethnicity and parity

[b] *P* value for trend across categories

Table 4 Relationship between oral contraceptive use and breast cancer risk among *BRCA1* mutation carriers diagnosed prior to age 40

Variable	Controls (*n*)	Cases (*n*)	OR (95 % CI)[a]	*P*
Oral contraceptive use				
Never	487	417	1.00	
Ever	815	885	1.40 (1.14–1.70)	0.001
Trend per year			1.03 (1.01–1.05)	0.004
Age at first use (years)				
Never	487	417	1.00	
<20	355	443	1.74 (1.36–2.22)	0.00001
20–<25	307	307	1.36 (1.07–1.73)	0.02
25–<30	111	99	1.12 (0.82–1.53)	0.48
30–<60	42	36	1.05 (0.65–1.69)	0.84
Trend[b]				
Annual risk by age at first use				
Never	n/a	n/a	1.00	
Risk per year ≤20			1.11 (1.03–1.20)	0.008
Risk per year >20–≤25			1.07 (0.99–1.13)	0.03
Risk per year >25–≤30			1.00 (0.94–1.07)	0.97
Risk per year >30			0.96 (0.91–1.02)	0.19
Duration of use (years)				
Never	487	417	1.00	
0–<5	360	365	1.31 (1.05–1.65)	0.02
5–<10	267	288	1.40 (1.09–1.81)	0.008
10–<15	139	167	1.51 (1.12–2.03)	0.007
15–<30	49	65	1.75 (1.12–2.75)	0.01
Trend[b]				0.0009

n/a not applicable

[a] All ORs and 95 % CIs were calculated using a multivariate conditional logistic regression model, adjusting for ethnicity and parity

[b] *P* value for trend across categories

of breast cancer among *BRCA1* mutation carriers who first used oral contraceptives before age 30, who used them for 5 or more years and for those who were diagnosed before age 40. In a meta-analysis of the literature (5 studies), Iodice et al. [15] reported no overall relationship between oral contraceptive use and breast cancer risk in *BRCA* mutation carriers (summary relative risk [SRR] for *BRCA1* and *BRCA2* combined = 1.13; 95 % CI 0.88–1.45 and SRR for *BRCA1* only = 1.09; 95 % CI 0.77–1.54); however, oral contraceptives used prior to 1975 were associated with a significantly increased risk (SRR = 1.47; 95 % CI 1.06–2.04). The association was not significant for more recent formulations (SRR = 1.17; 95 % CI 0.74–1.86). A more recent meta-analysis (5 studies; 4 of which were in the aforementioned meta-analysis) found a nonsignificant increased risk of *BRCA1*-associated breast cancer (pooled OR 1.19; 95 % CI 0.92–1.55) [16]. The latter study did not evaluate time since last use. Cibula et al. [17] reported a significant increased risk of *BRCA1*-associated breast cancer with oral contraceptive use in a pooled meta-analysis of two cohort studies (pooled hazard ratio = 1.48; 95 % CI 1.14–1.92), but no association in the pooled analysis of three case–control studies (pooled OR 1.08; 95 % CI 0.94–1.25).

The literature surrounding oral contraceptive use in the etiology of breast cancer in the general population has evolved in recent years. Early studies suggest an increased risk of breast cancer with current oral contraceptive use [18], whereas more recent studies suggest a slight increase or no increased risk [19–21] (reviewed in [22]). Data from the Collaborative Group on Hormonal Breast Factors in Breast Cancer, a re-analysis of data from 54 epidemiological studies, reported that current users were at an increased risk of breast cancer, but the risk diminished after stopping pill use, with no excess risk remaining 10 years after last use (relative risk [RR] for current users = 1.24; 95 % CI 1.15–1.33). The authors also reported that the strongest effect was seen among women who started using

the pill prior to age 20 (RR = 1.22), whereas women who first started using oral contraceptives after age 20 had combined RRs between 1.04 and 1.11. A recent meta-analysis of 13 prospective cohort studies reported a non-significant increased risk of breast cancer with ever use (combined RR = 1.08; 95 % CI 0.99–1.17) [20]. Similarly, a different meta-analysis of 44 epidemiologic studies reported an 8 % increase in risk with ever use (pooled OR 1.08; 95 % CI 1.00–1.17) [19]. The discordance in the findings from earlier versus later pooled analyses is likely due to changing formulations (i.e., lower doses of estrogens and progestins in the latest generation of oral contraceptive pills) and that the majority of the studies were case–control studies and prone to selection and recall bias. In summary, the overall findings are suggestive of a positive association between oral contraceptive use and breast cancer risk, yet the point estimates are close to unity.

Given that the mean age of breast cancer diagnosis in our population of *BRCA1* mutation carriers was 39.7 years, studies conducted among premenopausal women may be the most relevant here. In a meta-analysis of studies evaluating risk factors for breast cancer in women at general population risk between the ages of 40 and 49 years, Nelson et al. [21] found no significant relationship between oral contraceptive use and the risk of premenopausal breast cancer. The pooled estimate for ever use of an oral contraceptive from 12 studies was 1.08 (95 % CI 0.96–1.23). Among women with a family history of breast cancer, Gaffield et al. [23] reported no relationship between oral contraceptive use and risk. Two studies have reported a positive association, and one study reported no association between oral contraceptive use and the risk of developing triple-negative breast cancer (women with a *BRCA1* mutation are also more likely to develop a triple-negative breast cancer) [2, 24–26].

Oral contraceptives prevent ovulation by inhibiting pituitary gonadotropin secretion [27]. In addition, oral contraceptive use has been associated with lower circulating levels of estrogen and progesterone [28]. Fortner et al. [29] recently reported that oral contraceptive use was not associated with levels of individual urinary estrogen metabolite levels or estrogen metabolism pathways in 603 premenopausal women aged 33–51 who were participants in the Nurses Health Study II. Despite this, higher levels of breast cell proliferation have been reported among oral contraceptive users versus nonusers [30, 31].

Here we confirm a potentially harmful effect of oral contraceptives for *BRCA1* mutation carriers when initiated early in life (i.e., prior to age 25) and for any duration of use. This increase in risk was attenuated for use after age 30. We did not observe a harmful effect of current use (OR 0.80; 95 % CI 0.66–0.97) or for breast cancer diagnosed after age 40. This finding differs from what has been reported in studies conducted among women in the general population where current or more recent use has been associated with an increased risk [18, 19]. These opposing results can likely be accounted for by the fact that the mean age at diagnosis was 39.7 years, while the mean age at interview was 46.3 years.

Although recall bias represents a potential limitation with self-administered questionnaires, this was unlikely in our study population as there was no significant difference in the proportion of cases and controls that reported ever using an oral contraceptive. In addition, Hunter et al. [32] have previously reported acceptable validity for self-reported oral contraceptive use history in the Nurses' Health Study. We have collected extensive information on potential confounders and performed a matched analysis to adjust for differences between the cases and controls. This represents the largest analysis to date of the relationship between oral contraceptive use and breast cancer among women with a *BRCA1* mutation.

Our findings suggest a potentially harmful effect of oral contraceptive use for early-onset *BRCA1*-associated breast cancers if use is initiated prior to age 25. Based on this data, women with a *BRCA1* mutation should be advised to avoid any oral contraceptive use for the purpose of preventing ovarian cancer before the age of 25.

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Conflict of interest The authors declare that they have no conflict of interest.

Appendix: Other Members of the Hereditary Breast Cancer Clinical Study Group

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