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Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations

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Women with mutations of the genes BRCA1 or BRCA2 are at increased risk of ovarian cancer. Oral contraceptives protect against ovarian cancer in general, but it is not known whether they protect against the disease in carriers of these mutations. We obtained self-reported lifetime histories of oral contraceptive use from 451 women who carried mutations of BRCA1 or BRCA2. We used conditional logistic regression to estimate the odds ratios associated with oral contraceptive use, comparing the histories of 147 women with ovarian cancer (cases) to those of 304 women without ovarian cancer (controls) who were matched to cases on year of birth, country of residence and gene (BRCA1 *vs* BRCA2). Reference ages for controls had to exceed the ages at diagnosis of their matched cases. After adjusting for parity, the odds-ratio for ovarian cancer associated with use of oral contraceptives for at least 1 year was 0.85 (95 percent confidence interval, 0.53–1.36). The risk decreased by 5% (1–9%) with each year of use (*P* for trend = 0.01). Use for 6 or more years was associated with an odds-ratio of 0.62 (0.35–1.09). These data support the hypothesis that long-term oral contraceptive use reduces the risk of ovarian cancer among women who carry mutations of BRCA1 or BRCA2.
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Epidemiology

Women who carry deleterious mutations of the genes BRCA1 or BRCA2 are at increased risk of developing ovarian cancer (Struewing *et al*, 1997; Ford *et al*, 1998, Antoniou *et al*, 2003). Oral contraceptive use is associated with reduced ovarian cancer risk in the general population (Whittemore *et al*, 1992; La Vecchia and Franceschi, 1999). It is important to know if a similar association holds for mutation carriers. Previous investigations have addressed this question with conflicting results (Narod *et al*, 1998, 2001a; Modan *et al*, 2001; McGuire *et al*, 2004). Resolution of this issue is important because oral contraceptive use at early ages may increase the risk of breast cancer in mutation carriers (Ursin *et al*, 1997; Narod *et al*, 2002).

We report the results of an analysis of ovarian cancer risk in relation to oral contraceptive use among 451 carriers of BRCA1 or BRCA2 mutations, comprising 147 women with ovarian cancer (cases) and 304 women without ovarian cancer (controls) who were identified in one of five family registries in the US, Canada, England and Australia.

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METHODS

Subjects

We used five registry sources to ascertain female carriers with germline mutations of BRCA1 or BRCA2, and classified them as cases (those diagnosed with primary invasive cancer of the ovarian epithelium, confirmed by pathology report or death certificate) or controls. The first source (eight cases and 12 controls) was families enrolled with the United Kingdom Consortium for Clinical Cancer Research (UKCCCR) Ovarian Cancer Register. Eligible families were those containing at least two first- or second-degree relatives confirmed with invasive epithelial ovarian cancer. The second source (27 cases and 51 controls) was Australian families registered with the Kathleen Cuningham Foundation Consortium

for Research into Familial Breast Cancer (kConFab) (Osborne *et al*, 2000; http://www.kconfab.org). Eligible families contained two living women with breast or ovarian cancer, or one living affected plus one female carrier. The third source (54 cases and 24 controls) was families enrolled in the Gilda Radner Familial Ovarian Cancer Registry at the Roswell Park Cancer Institute in Buffalo, NY, USA. Eligible families contained two or more relatives with a confirmed diagnosis of cancer of the ovary, peritoneum or fallopian tubes. The fourth source (nine cases and 24 controls) was families identified by the Risk Assessment Program at the Fox Chase Cancer Center in Philadelphia, PA, USA. The fifth source (49 cases and 193 controls) was families from the US, Canada and Australia enrolled in the Breast Cancer Family Registry (Breast CFR) (John *et al*, 2004).

We included in the analysis women who were found by genetic testing to carry a germline mutation in BRCA1 or BRCA2 that was predicted to adversely affect protein function (National Human Genome Research Project, 2002) who provided information concerning their reproductive characteristics and oral contraceptive use in a structured questionnaire, and who had not participated as a study subject in any other study of oral contraceptive use and ovarian cancer risk.

Mutation analysis

In the UKCCCR Ovarian Cancer Register and the GRFOCR Registry, one affected member from each family (hereafter called the index case) was tested for germline mutations in BRCA1 and BRCA2 by a combination of the protein truncation test (PTT) and single-strand conformation analysis/heteroduplex analysis (SSCP/HA), as described previously (Gayther *et al*, 1999). Direct sequence analysis was used to characterise the nucleotide alteration associated with PTT or SSCP/HA variants. When a mutation was identified in an index case, other family members were tested for that mutation by direct sequencing. Women registered with the Fox Chase Cancer Center were tested for mutations using the enzymatic mutation detection assay (Del Tito *et al*, 1998). Mutation testing for members of families enrolled in kConFab (Scott *et al*, 2003) and the Breast CFR (John *et al*, 2004) was undertaken in several different diagnostic laboratories using different strategies including HA, PTT, chemical cleavage of mismatch, allele-specific oligonucleotide hybridisation and direct sequencing.

Study protocol

Participants provided data on their histories of childbearing, oophorectomy and use of oral contraceptives. The women reported the ages when they started and stopped taking oral contraceptives and their total durations of use. No information from surrogate interviews was included in the analysis.

Statistical analysis

To each carrier we assigned a reference age, defined as her age at diagnosis if she was a case, or as her age at the earlier of oophorectomy or interview if she was a control. We matched each case to one or more controls. Controls were matched to the case on year of birth (within 3 years), country of residence (Australia, Canada, UK, US) and gene (BRCA1, BRCA2). In addition, the reference ages of controls must have exceeded those of their matched case. Within each matched set, we considered childbirth and oral contraceptive use only prior to the case's reference age. We performed a matched case–control analysis using conditional logistic regression (Breslow and Day, 1980), with parity (0, 1 or 2, 3+ live births) included in the regression models. Since we are testing the null hypothesis of no association between ovarian cancer risk and oral contraceptive use against the alternative hypothesis of reduced risk associated with oral contraceptive use, we report one-tailed *P*-values.

RESULTS

We were able to find at least one matched control for 114 cases with BRCA1 mutations (the mean number of controls per case was 2.0, with range 1–3) and for 33 cases with BRCA2 mutations (mean number of controls per case was 2.4, with range 1–3). Table 1 shows the distributions of matched case–control sets according to age at diagnosis, year of birth and country of residence of the cases, by gene. Most cases were diagnosed between the ages of 40 and 60 years, and most were born after 1930. Cases (and therefore controls) were more likely to carry mutations of BRCA1 than BRCA2 by a factor of more than three.

Table 2 shows the distributions of participants according to reproductive characteristics and oral contraceptive use, by gene and case–control status. Compared to controls, cases were less likely to use oral contraceptives and had used them for fewer years. Overall, 31% of ovarian cancer patients and 36% of control women carried one of the two common founder mutations of BRCA1 (185 del AG or 5382 ins C) or the single common founder mutation of BRCA2 (6174 del T).

Table 3 shows ovarian cancer odds-ratios in relation to oral contraceptive use. The odds-ratio associated with use for at least 1 year, compared to use for less than 1 year or nonuse, was 0.85 (95% confidence interval 0.53–1.4). Also shown are odds-ratios in relation to duration of oral contraceptive use. The odds-ratio among carriers who had used oral contraceptives for 6 or more years compared to those who had used them for less than 1 year was 0.62 (95% confidence interval 0.35–1.1). The data show a trend of decreasing risk with increasing duration of use, with an overall 5% (95% confidence interval 1–9%) reduction in risk per year of use (one-tailed $P = 0.01$).

When restricted to BRCA1 mutation carriers, estimates of associations with oral contraceptives use were similar to those shown in Table 3. Estimates based on BRCA2 mutation carriers alone were imprecise, and were not statistically different from those for BRCA1 mutation carriers.

Table 1 Distribution of matched ovarian cancer case–control sets[a], according to case's age at diagnosis, year of birth and country of residence, by gene

	BRCA1 *N* (%)	BRCA2 *N* (%)	Total *N* (%)
Case's age at dx (%)			
<40	18 (16)	3 (9)	21 (14)
40–49	55 (48)	12 (36)	67 (46)
50–59	29 (25)	10 (31)	39 (27)
60+	12 (11)	8 (24)	20 (13)
Case's year of birth (%)			
<1930	12 (11)	6 (18)	18 (12)
1930–1944	44 (39)	15 (46)	59 (40)
1945+	58 (50)	12 (36)	70 (48)
Case's country of residence			
Australia	29 (25)	4 (12)	33 (23)
Canada	2 (2)	1 (3)	3 (2)
UK	8 (7)	0 (0)	8 (5)
US	75 (66)	28 (85)	103 (70)
Total no. of matched sets	114	33	147

[a]Controls had intact ovaries at the age when the case was diagnosed, and were matched to cases on gene (BRCA1 or BRCA2), year of birth (±3 years) and country of residence (Australia, Canada, UK, USA).

Table 2 Characteristics of ovarian cancer cases and control women, by gene

	BRCA1		BRCA2		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
No.	114	225	33	79	147	304
Mean no. live births	2.5	2.5	2.6	2.5	2.5	2.5
Mean age of (years) first birth among parous	23.5	24.6	24	24.5	23.6	24.6
Ever used oral contraceptives (%)	53	63	54	58	53	62
Mean years of oral contraceptive use among users	3.0	4.7	3.1	4.3	3.0	4.6
Prophylactic bilateral oophorectomy (%)	—	15	—	6	—	12
Carrier of Ashkenazi founder mutation[a] (%)	32	39	27	29	31	36

[a]Mutations 185 del AG, 5382 ins C or 6174 del T.

Table 3 Ovarian cancer risk according to oral contraceptive use among carriers of BRCA1 or BRCA2 mutations

	Cases (*N* = 147) No. (%)	Controls (*N* = 304) No. (%)	OR[a]	CI[b]
Any use[c]				
No	69 (46.9)	116 (38.2)	1.0	—
Yes	78 (53.1)	188 (61.8)	0.85	0.53–1.4
Years of use				
<1	69 (46.9)	116 (38.2)	1.0	—
1–2	31 (21.1)	40 (13.2)	1.5	0.82–2.9
3–5	14 (9.5)	44 (14.4)	0.69	0.33–1.4
6+	33 (22.5)	104 (34.2)	0.62	0.35–1.1
Trend per year of use among users			0.95	0.91–0.99

[a]OR = odds ratio, adjusted for study centre, parity and age. [b]CI = 95% confidence interval. [c]For at least 1 year.

DISCUSSION

Among women who carry mutations of BRCA1 or BRCA2, we found reduced risk associated with use of oral contraceptives and evidence for increasing risk reduction with increasing duration of use. The reduction in risk of 14% among ever users and 38% among long-term users are consistent with, but somewhat weaker than, reductions observed in the general population. In a pooled analysis of six population-based case–control studies of oral contraceptives and the risk of ovarian cancer in the US, the risk reduction associated with ever use was 34%, and that associated with 6 or more years of use was 70% (Whittemore *et al*, 1992).

Other studies have produced conflicting results on the relationship between ovarian cancer risk and oral contraceptive use among carriers of BRCA1 or BRCA2 mutations. Narod *et al* (1998, 2001a) found risk reductions of magnitude similar to those seen here. The risk reductions did not vary when the authors separated carriers by type of mutation (BRCA1 *vs* BRCA2). In a population-based case–control study of ovarian cancer among women in Northern California, McGuire *et al* (2004) also found an inverse relationship between oral contraceptive use and ovarian cancer risk when comparing patients carrying a BRCA1 mutation with control women from the general population. In contrast, in a similar population-based case–control study of ovarian cancer among women in Israel, Modan *et al* (2001) found no differences in oral contraceptive use when comparing patients carrying one of the three common BRCA1 or BRCA2 founder mutations with control women from the general Israeli population. The discrepancies between these results, if not due to chance or bias, could reflect differences in the populations at risk, the specific types of mutations studied, or study design (Modan and Wacholder, 2001; Narod *et al*, 2001b).

The present results, based on data that have not been reported in any previous studies of oral contraceptive use and ovarian cancer, support previous findings of Narod *et al* (1998, 2001a). Our study and those of Narod *et al* share some limitations. First, they included data only from living affected carriers because of the difficulty of obtaining accurate histories from relatives of deceased patients. These living patients were prevalent cases who reported their prediagnostic oral contraceptive histories some time after their cancer diagnoses. If oral contraceptive use is associated with an altered mortality in women with ovarian cancer, then this selection strategy may result in a biased odds-ratio estimate. Second, most study subjects were members of families with multiple cases of breast and ovarian cancer, and therefore the mutations in the women we have studied may have been those that cause a higher risk of these cancers. Odds-ratios for oral contraceptive uses in these carriers may not pertain to the general population of carriers. Third, some of the unaffected carriers were relatives of ovarian cancer patients. While this design limits potential confounding by ethnicity, a disadvantage is that correlation among sisters in oral contraceptive use could distort both the magnitude of the association and the lengths of confidence intervals. Yet we found only modest correlation between sisters in duration of oral contraceptive use. In addition, our inclusion of control carriers who had undergone prophylactic oophorectomy could overestimate the protection afforded by oral contraceptive use, if these carriers were more likely to use oral contraceptives than other carriers. However, we found no difference in the prevalence of oral contraceptive use between carriers with and without prophylactic oophorectomy.

The studies by Modan *et al* (2001) and McGuire *et al* (2004) avoided these limitations by including only incident cases of ovarian cancer in mutation carriers and unrelated controls. Prevalence of oral contraceptive use among carrier cases was compared to that in control women from the general population. Inferences based on such a comparison are valid only if oral contraceptive use is similar among carriers and noncarriers in the general population. The null findings of Modan *et al* (2001) may have occurred because the oral contraceptive use of carrier cases was compared to that of controls who were older than they were. This difference occurred because controls were age-matched to all cases, whereas the carrier cases were younger than the noncarrier cases, and the analytic comparisons were stratified only in broad 10-year age categories. Thus, the comparison controls were born earlier than the carrier cases, and had less opportunity for long-term exposure to oral contraceptives, which did not become widespread until after 1960. This problem was mitigated in the report of McGuire *et al* (2004) by the more recent birth years of all subjects, and by finer age stratification in the analysis.

In conclusion, we found reduced ovarian cancer risk associated with long-term oral contraceptive use among carriers of BRCA1 or BRCA2 mutations. Both the reduced incidence among ever-users and the trend of decreasing risk with increasing duration of use are consistent with a protective effect for oral contraceptives in these women. If such protection exists, the benefits of oral contraceptive use must be weighed against its possible adverse effects on breast cancer risk. Although there are data to suggest that oral contraceptive use is associated with a small increased breast cancer risk in carriers of BRCA1 (but not BRCA2) mutations (Narod *et al* 2002), this effect was being driven by use prior to the mid 1970s. A more recent population-based study has found no evidence for an increased risk in mutation carriers associated with use of current formulations of oral contraceptives, and evidence that current formulations may even be protective for BRCA1 mutation carriers (Milne *et al*, 2004). Therefore, oral contraceptive use in women with BRCA1 mutations should be considered in light of any planned prophylactic surgery. The current data suggest that women with intact ovaries who undergo prophylactic mastectomy would be good candidates for oral contraceptives. Further data are needed to advise those who undergo prophylactic oophorectomy but not mastectomy.

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