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Advances in Brief

Does Oral Contraceptive Use Increase the Risk of Breast Cancer in Women with *BRCA1/BRCA2* Mutations More Than in Other Women?[1]

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Abstract

We conducted a study to determine whether the risk of breast cancer associated with oral contraceptive (OC) use is higher in women with *BRCA1/BRCA2* mutations than in other women by examining whether breast cancer patients with these mutations were more likely than breast cancer patients without mutations in *BRCA1/BRCA2* to have used OCs. We tested for *BRCA1* 185delAG and 5382insC and *BRCA2* 6174delT mutations in a population-based sample of 50 young Ashkenazi Jewish breast cancer patients. Nine patients (18%) had a *BRCA1* mutation, and five patients (10%) had a *BRCA2* mutation. Long-term OC use (>48 months) before a first full-term pregnancy was associated with an elevated risk of being classified as a mutBRCA carrier (odds ratio, 7.8; trend, $P = 0.004$). The results suggest that OC use may increase the risk of breast cancer more in mutBRCA carriers than in noncarriers; however, they must be interpreted with caution given the small sample size.

Introduction

Two studies have examined the prevalence of *BRCA1/BRCA2* mutations in young Jewish breast cancer cases not selected for family history. Eight of 39 Jewish breast cancer patients (21%) ages 40 years or younger had the 185delAG mutation in one report (1), as did 16 of 80 Jewish patients (20%) under the age of 42 in a second report (2). In the latter study, the *BRCA2* 6174delT mutation was detected in 6 women (8%; Ref. 3), whereas in the first study, only 1 of 39 Jewish women had this mutation (4). Combined, these two studies suggest that 24–28% of young Jewish breast cancer patients may have a *BRCA1* or *BRCA2* mutation. However, both studies used patients attending specific clinics or referral centers; this prevalence estimate has not been confirmed in a population-based study.

Based on published data to date, lifetime penetrance of *BRCA1* seems to be greater than that of *BRCA2*, although a recent study suggests that it may only be slightly above 50% (5). This suggests that other genes, other endogenous factors, or environmental risk factors (6) may be important for whether or when cancer develops in BRCA mutation carriers. *BRCA1* seems to be an important factor in cell growth, and experimental evidence suggests that *BRCA1* expression is under the control of steroid hormones (7). In *BRCA1* haplotype analyses, Narod *et al.* (6) reported an increased risk of breast cancer associated with low parity and with recent birth cohort in *BRCA1* carriers; however, no data on OC[3] use were presented. To our knowledge, this is the first report on a possible interaction between breast cancer susceptibility genes and environmental factors based on actual *BRCA1* and *BRCA2* mutations.

The current study was conducted to determine the frequency of the three most common *BRCA1/BRCA2* mutations in a population-based sample of Jewish women diagnosed with breast cancer at an early age and to provide pilot data as to whether breast cancer development in mutBRCA carriers could be associated with environmental risk factors. We chose to concentrate on hormonal risk factors known or suspected to be associated with breast cancer occurrence: OC use, age at first birth, parity, abortion, and physical exercise.

Materials and Methods

Study Participants. The cases in this study had participated in a previous study at our institution (8). Briefly, the participants were white female residents of Los Angeles County, ages 40 years or younger, diagnosed with *in situ* or invasive breast cancer between July 1, 1983 and January 1, 1989. The Los Angeles County Cancer Surveillance Program, the population-based cancer registry for the county, identified 969 eligible breast cancer patients, and interviews were completed with 744 (76.8%). Eligibility was restricted to women born in the United States, Canada, or Europe.

In-person interviews were conducted with all subjects by the same female nurse-interviewer from 1984–1989. We obtained complete reproductive, contraceptive, and physical exercise histories on all subjects up to the date of the case patient's diagnosis; however, only exposures occurring 12 or more months before the date of her diagnosis were considered in the analyses.

Ninety-two of 744 cases gave their religion as Jewish in the interview. In the current study, we recontacted the 81 cases known to be alive at last contact. The women were asked whether they would be willing to participate in an extension of the original study; an anonymous genetic study. Each subject provided a signed informed consent, and study procedures were approved by the University of Southern California Research Committee, in accord with assurances approved by the United States Department of Health and Human Services. Five women refused, 6 were deceased, 18 did not respond, and 52 (64.2%) agreed to have their blood drawn. At the current time, no blood has yet been obtained from 2 of these individuals; thus, we have blood samples on 50 women (61.7%). All participants were at least 50% Ashkenazi Jewish descent.

One vacutainer (10 cc) of venous blood was drawn from each participant. The blood samples (and the corresponding questionnaire data) were marked with new seven-digit IDs, and the code linking the old IDs with the new IDs was destroyed. Questionnaire data were categorized to avoid the possibility that certain combinations of individual data would identify any one individual.

Laboratory Methods. Human genomic DNA samples were extracted and purified from fresh whole blood. Allele-specific oligonucleotide probes of three known mutations were used to screen these samples: two *BRCA1* mutations, namely 185delAG (exon 2) and 5382insC (exon 20; Ref. 9), and the 6174delT mutation (exon 11) in *BRCA2* (3). Exons 2 and 20 of the *BRCA1* gene and exon 11 of *BRCA2*, which contain the known mutations, were amplified using the following primers: *BRCA1* exon 2, (sense) 5′-gAAgTTgTCATTTTATAAACCTTT-3′ and (antisense) 5′-TgTCTTTTCTTCCCTAg-

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[3] The abbreviations used are: OC, oral contraceptive; OR, odds ratio; CI, confidence interval; ID, identification number.

TATgT-3'; *BRCA1* exon 20, (sense) 5'-ATATgACgTgTCTgCTCCAC-3' and (antisense) 5'-gggAATCCAAATTACACAgC-3'; and *BRCA2* exon 11, (sense) 5'-gggAAgCTTCATAAgTCAgTC-3' and (antisense) 5'-TTTgTAATgAAgCATCTgATACC-3'.

PCR reactions were performed as standard protocol, except that the $MgCl_2$ concentrations and annealing temperatures were: 1.5 mM, 55°C (*BRCA1* exon 2); 2.5 mM, 50°C (*BRCA1* exon 20); and 1.0 mM, touchdown (*BRCA2* exon 11). PCR products were denatured and dotted onto wet Hybond N+ nylon membranes using a BioRad Bio-dot apparatus.

Membranes were UV cross-linked at 312 nm and hybridized with end-labeled oligonucleotide probes at 45°C. Duplicate blots were prepared; one was probed for the wild-type allele, and one was probed for the mutant allele. Membranes were washed in 2× SSC at just below the melting temperature of the probe. Probe sequences and washing temperatures were: *BRCA1* exon 2-185delAG (AAAATCTTAgTgTCCCAT) and *BRCA1* exon 2 wild type (AAAATCTTAgAgTgTCCC) washed at 50°C; *BRCA1* exon 20-5382insC (gAgAATCCCCAggACA) and *BRCA1* exon 20 wild type (gAgAATCCCAggACAgA) washed at 52°C; and *BRCA2* exon 11-6174delT (CACAgCAAgggAAAATCT) and *BRCA2* exon 11 wild type (CACAgCAAgTggAAAATC) washed at 58°C.

Membranes were wrapped in plastic wrap and exposed to X-ray film for 1 h. Samples having dots of approximately equal intensity for the wild-type and mutant probes were called heterozygous for the mutation. Samples having distinctly positive dots for the wild-type and no dots for the mutant probe were called homozygous for the normal allele. Known positive and negative controls were included on each blot. All mutants were repeated to confirm the calling.

Statistical Methods. We used a case-only approach (also known as case-case comparison) to study whether OC use and reproductive factors interacted with *BRCA* mutation (mutBRCA) status with respect to risk of breast cancer (10, 11). In this method, only cases are included, and a relative risk (OR) is calculated of being a mutBRCA carrier associated with each of the exposures. Under the assumption that there is independence between genotype and exposure, this is equivalent to estimating the relative risk of breast cancer associated with an exposure in mutBRCA carriers compared to the relative risk of breast cancer associated with the exposure in noncarriers. If there is an interaction (on a multiplicative scale) between the exposure and mutBRCA status with respect to breast cancer, for instance, if a certain exposure is more strongly associated with breast cancer in mutBRCA carriers than in noncarriers, then the relative risk would be greater than 1.

The method assumes independence between genotype and exposure, *i.e.*, that women in the source population who are mutBRCA carriers will not be more or less likely to have any of these exposures than women who are noncarriers. This seems to be a reasonable assumption for most exposures considered in this study among Ahskenazi Jewish women in which we adjust for family history (first-degree or first- and second-degree relative *versus* none), although we consider an alternative explanation in the discussion regarding OC use.

In the analyses, the mutBRCA carriers were considered as the cases, and the noncarrier women were considered as controls, and the results were analyzed using standard multivariate methods, estimating the ORs of being a mutBRCA carrier associated with the various exposures. Ninety-five percent CIs were estimated by standard methods. To test for dose-response effects across categories of exposure, we estimated a slope coefficient fit to the midpoint of each exposure category or for nonquantitative variables to ordinal values 0, 1, 2, and so forth. The reported *P* values for these tests for trend are two-sided.

Results

Among the 50 Ashkenazi Jewish patients participating in the study, 5 patients had the 185delAG mutation, and 4 women had the 5382insC mutation in *BRCA1*, whereas 5 women had the 6174delT mutation in *BRCA2*. The ORs of being classified as a mutBRCA carrier (having one of these three mutations) are displayed for selected characteristics in Table 1. Compared to women with no family history, women who reported a history of breast or ovarian cancer in a first- or second-degree relative were not at an increased risk of being classified as a mutBRCA carrier. In fact, nine mutBRCA-carrying patients had no known family history. Age was not associated with risk, but the study was limited to women diagnosed by age 40. Women with more advanced disease at diagnosis were more likely to be classified as mutBRCA carriers than women with less advanced disease.

Cases who had used OCs for a long time period were at increased risk of being classified as mutBRCA carriers (mutBRCA+) after adjusting for age, first-degree family history, and education (Table 2). Essentially all OC use occurred before a first full-term pregnancy. The risk was unchanged when adjusted for parity (ever/never; data not shown). Cases who had used OCs recently were also at an increased risk of being classified as mutBRCA, although this trend did not reach statistical significance (data not shown).

When mutBRCA2 carriers were excluded, the OR associated with OC use became stronger, but the CIs were very wide. Long-term OC use (>48 months) was associated with an OR of being mutBRCA1 of 10.3 (95% CI, 0.7–144.6; trend, $P = 0.05$), whereas long-term OC use (>48 months) before a first full-term pregnancy was associated with an OR of 36.7 (95% CI, 1.1–1203; trend, $P = 0.003$).

Neither average hours of physical exercise during reproductive years nor any of the reproductive variables displayed any remarkable association with mutBRCA. However, compared to nulliparous women, being parous was associated with a 30% decreased risk of being mutBRCA, but this was not statistically significant. Further-

Table 1 *ORs of being a mutBRCA-carrying case (see text) associated with selected characteristics among Ashkenazi Jewish breast cancer patients ages 40 years or younger at time of diagnosis*

Exposure	mutBRCA+ cases	mutBRCA− cases	Unadjusted OR	Adjusted OR[a]	Adjusted 95% CI	Trend *P*
Age at diagnosis (yrs)						
<36	6	13	1.0	1.0		
37–38	3	12	0.5	0.6	0.1–2.9	
39–40	5	11	1.0	1.0	0.2–4.5	0.91
First-degree family history of breast cancer						
None known	11	30	1.0	1.0		
Yes	3	6	1.4	1.3	0.2–6.5	0.79
First- or second-degree family history of breast or ovarian cancer[b]						
None known	9	24	1.0	1.0		
Yes	5	12	1.1	0.8	0.1–4.9	0.77
Education						
Graduate/professional training	2	12	1.0	1.00		
College graduate	3	9	2.0	1.9	0.3–13.9	
High school/some college	9	15	3.6	3.5	0.6–19.7	0.11
Stage at diagnosis						
In situ	1	9	1.0	1.0		
Localized	5	21	2.1	2.1	0.2–24.3	
Direct extension/node involvement	8	6	12.0	41.7	2.2–787.0	0.0008

[a] Mutually adjusted for other variables in this table.
[b] History of breast or ovarian cancer in mother, sister, or grandmother or history of breast cancer in aunt.

Table 2 *ORs of being a mutBRCA-carrying case (see text) associated with OC use among Ashkenazi Jewish breast cancer patients ages 40 years or younger at time of diagnosis*

Exposure	mutBRCA+ cases	mutBRCA− cases	Unadjusted OR	Adjusted OR[a]	Adjusted 95% CI	Trend *P*
OC use (months)						
0–11	3	15	1.0	1.0		
12–48	4	11	1.8	1.6	0.2–10.9	
49+	7	10	3.5	4.3	0.5–24.6	0.09
OC use before first full-term pregnancy (months)[b]						
0–11	3	15	1.0	1.0		
12–48	4	11	1.8	1.9	0.3–13.2	
49+	7	7	5.0	7.8	1.1–55.0	0.004

[a] Adjusted for age (tertiles), first-degree family history of breast cancer, and education (high school or some college, college graduate, and graduate/professional training).
[b] Excluding three noncarrier women who used OCs only after a first full-term pregnancy.

more, there was a suggestion of an increased risk of being mutBRCA with late age (>25 years) at first birth, but this was also not statistically significant (data not shown).

Discussion

The prevalence of the *BRCA1* and *BRCA2* mutations observed in this study is consistent with findings from non-population-based studies that the prevalence of *BRCA1/BRCA2* mutations in young Jewish breast cancer patients is 24–28% (1–4). In our study, the majority of women with a mutation did not have a known family history of breast cancer. This was not an unexpected finding, given the young age of the cases. Although we did not obtain an extensive family history, the patients were asked if there was a history of breast or ovarian cancer in their sisters, mothers, or grandmothers and whether there was a history of breast cancer in their father's or mother's sisters. We did not collect information on family size.

We found no strong associations with reproductive variables, although risks of being mutBRCA associated with being parous and of having an early birth were somewhat reduced. In a retrospective cohort study of 333 women who were found by haplotype analysis to carry *BRCA1* mutations, low parity was associated with increased risk of breast cancer, whereas early age at first birth did not offer any protection (6). No risk estimate comparing nulliparity to parity was provided. This analysis requires the same assumption as in our study, *i.e.*, independence between genotype and exposure.

Of potential clinical significance, breast cancer cases with a *BRCA1/BRCA2* mutation were more likely than other breast cancer cases to have used OCs. The finding was particularly strong for OC use before a first pregnancy. This could suggest a crucial role of first full-term pregnancy in limiting risk in women with such germ-line mutations who use OCs. The trend in risk with increasing duration of use was highly significant and was extremely unlikely to be due to chance. The estimate of risk had wide CIs because of the small sample size, and our results are compatible both with a barely elevated risk and an enormously elevated risk.

Even if larger studies confirm a more substantial elevated risk associated with long-term OC use, there are at least two explanations for this finding: (*a*) all mutBRCA carriers are more likely than noncarriers to use OCs, but the relative risk of breast cancer associated with OC use is not higher for mutBRCA carriers than for noncarriers; and (*b*) OC use increases the relative risk of breast cancer substantially more in mutBRCA carriers than in noncarriers.

The first explanation would imply that the major assumption underlying the case-case analysis was violated. We have no data to support or refute this hypothesis, and we are not aware of any data on OC use in nonaffected mutBRCA carriers. However, because we controlled for race and ethnicity by restriction (only white Jewish cases were included) and for family history (by adjustment), and because we believe that there is independence between genotype and exposure within these strata, we find it unlikely that the assumption was violated.

The second explanation would imply that OC use increases breast cancer risk substantially more in mutBRCA carriers than in noncarriers. Although we cannot distinguish between these two competing explanations, the second explanation is to some extent supported by other evidence. Six population-based case-control studies of OC use and breast cancer risk in young women (<45 years) have looked at the interaction between OC use and family history (12–17). All of these studies reported an excess risk of breast cancer associated with OC use in young women with a family history, although the interactions in most studies were borderline or were not statistically significant (13–16), or the significance level was not specified (17).

A recent study suggests that cell proliferation is particularly strong in OC users with a family history of breast cancer (18). Thus, if the second explanation is true, OCs could exert their effect by causing a strong effect on breast cell proliferation in the mutBRCA carriers. Several experimental studies have suggested that *BRCA1* is important in regulating growth and differentiation in hormonally responsive epithelial cells. In mice mammary cells, Brca1 (the mouse homologue of BRCA1) mRNA is highest during puberty, pregnancy, and after stimulation with 17β-estradiol and progesterone (19–20). Estrogen treatment of estrogen-depleted MCF-7 and BT202 cells and progesterone treatment of progesterone depleted T-47D cells have been reported to result in an increase in BRCA1 mRNA and protein expression; this seems to be due to increased cell proliferation caused by these hormones (7).

The statistical power of our study to determine environmental-genetic interactions was low, with only 14 mutBRCA-carrying cases. However, as far as we are aware, this is the first population-based study that has attempted to determine whether there is an interaction between a BRCA mutation and an environmental exposure. Because we only tested for three mutations, there may be mutBRCA carriers misclassified as noncarriers. However, assuming that this BRCA misclassification is likely to be nondifferential with respect to OC use, this would only result in a bias toward the null value.

In conclusion, our results suggest that OC use may increase the risk of breast cancer more in mutBRCA carriers than in noncarriers, but given the small sample size of our study, our results should be interpreted cautiously. Our CIs are wide, and the clinical implications of our findings depend on the exact magnitude of this risk, which can only be determined by larger studies. Additional data on the effects of OCs and other hormonal risk factors in mutBRCA carriers are urgently needed.

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