

ORAL CONTRACEPTIVES AND THE RISK OF HEREDITARY OVARIAN CANCER

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ABSTRACT

Background Women with mutations in either the *BRCA1* or the *BRCA2* gene have a high lifetime risk of ovarian cancer. Oral contraceptives protect against ovarian cancer in general, but it is not known whether they also protect against hereditary forms of ovarian cancer.

Methods We enrolled 207 women with hereditary ovarian cancer and 161 of their sisters as controls in a case-control study. All the patients carried a pathogenic mutation in either *BRCA1* (179 women) or *BRCA2* (28 women). The control women were enrolled regardless of whether or not they had either mutation. Lifetime histories of oral-contraceptive use were obtained by interview or by written questionnaire and were compared between patients and control women, after adjustment for year of birth and parity.

Results The adjusted odds ratio for ovarian cancer associated with any past use of oral contraceptives was 0.5 (95 percent confidence interval, 0.3 to 0.8). The risk decreased with increasing duration of use (P for trend, <0.001); use for six or more years was associated with a 60 percent reduction in risk. Oral-contraceptive use protected against ovarian cancer both for carriers of the *BRCA1* mutation (odds ratio, 0.5; 95 percent confidence interval, 0.3 to 0.9) and for carriers of the *BRCA2* mutation (odds ratio, 0.4; 95 percent confidence interval, 0.2 to 1.1).

Conclusions Oral-contraceptive use may reduce the risk of ovarian cancer in women with pathogenic mutations in the *BRCA1* or *BRCA2* gene. (N Engl J Med 1998;339:424-8.)

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APPROXIMATELY 10 percent of cases of invasive epithelial ovarian cancer are hereditary, occurring predominantly in women with germ-line mutations in the *BRCA1* or the *BRCA2* gene (unpublished data). The lifetime risk of ovarian cancer is approximately 45 percent among women with *BRCA1* mutations and 25 percent among those with *BRCA2* mutations.¹⁻³

Current strategies for reducing the risk of ovarian cancer in women carrying *BRCA1* or *BRCA2* mutations include prophylactic oophorectomy and ultrasound screening, but the extent of risk reduction associated with either of these procedures is not known.⁴ A third potential strategy is chemoprevention. The risk of ovarian cancer is reduced by 50

percent or more in unselected women with long-term use of oral contraceptives.^{5,6} An oral contraceptive agent is appealing as a possible preventive treatment, because these agents are well tolerated and their side effects are known. To evaluate the potential benefit of oral-contraceptive use in women at high risk for ovarian cancer, we studied 207 patients with *BRCA1* or *BRCA2* mutations and ovarian cancer and 161 of their sisters, who served as controls.

METHODS

Subjects

The patients were 207 women born between 1925 and 1960 in whom invasive epithelial ovarian cancer had been diagnosed and who were found by molecular testing to carry a germ-line mutation in either the *BRCA1* or the *BRCA2* gene (Table 1). They were identified in three ways. Sixteen were women in whom ovarian cancer had been diagnosed in Ontario, Canada, after January 1, 1995. Twenty-six were Ashkenazi Jewish women with a history of ovarian cancer who were identified from the gynecology-oncology records of 11 hospitals in North America. One hundred sixty-five were women identified by members of the Breast Cancer Linkage Consortium: 37 from the United Kingdom, 39 from other European countries, 67 from the United States, and 22 from Canada. The women's average ages at the time of diagnosis in the three groups were 49, 52, and 49 years, respectively.

All living sisters of the patients who were born between 1925 and 1960 were eligible to be control subjects. The use of these women as controls ensured that the geographic and ethnic characteristics of the patients and the control women would be similar. Furthermore, the sisters had the same a priori familial risk of ovarian cancer as the patients; that is, before the diagnosis of breast or ovarian cancer in the latter, both a patient and her sister would have had the same risk of ovarian cancer on the basis of family history alone. Fifty-one of the patients had no sisters, and no information on family history was available for another 12 pa-

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*Other members of the study group are listed in the Appendix.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH OVARIAN CANCER AND CONTROL WOMEN.*

CHARACTERISTIC	PATIENTS WITH OVARIAN CANCER (N=207)	CONTROL WOMEN (N=161)
Age (yr)	54±8	52±8
Residence (%)		
United States	44	38
Canada	19	29
Europe	37	33
Race or ethnic group (%)		
Ashkenazi Jewish	26	10
Other white	68	88
Black	2	2
Unknown	3	1
Parity (%)		
0	14	15
1	9	13
≥2	77	72
Mean age at first childbirth (yr)	24	24
Mean age at last childbirth (yr)	29	29
Any use of oral contraceptives (%)	50	70†
Duration of oral-contraceptive use (yr)	4±5	6±5‡
Age at beginning of oral-contraceptive use (yr)	24±5	22±5

*Plus-minus values are means ±SD. Because of rounding, percentages do not always total 100.

†P<0.001 for the comparison with the women with ovarian cancer.

‡P=0.01 for the comparison with the women with ovarian cancer.

tients. The remaining 144 patients had a total of 328 sisters. Of these, 167 sisters were not studied because they had died, had ovarian cancer (these women were invited to be study patients), were born before 1925 or after 1960, were too ill to respond, or were unwilling to be questioned. Thus, there were 161 control women, or 0.8 per patient (range, 0 to 7).

Data on mutations were available for 95 of the 161 control women. According to molecular testing, 53 were carriers of the same *BRCA1* or *BRCA2* mutations as their sisters, and 42 were not carriers. Ideally, the group of control women would have been restricted to mutation-positive women who did not have ovarian cancer and had not undergone oophorectomy at the age at which ovarian cancer was diagnosed in their sisters. However, this approach was impractical, because there were only 42 unaffected mutation-positive sisters who had both ovaries at the time of the diagnosis of ovarian cancer in their sisters. Women with a history of breast cancer were not excluded from the study; 63 of the patients (30 percent) and 29 of the control women (18 percent) had a previous diagnosis of breast cancer.

Analysis of Mutations

Mutation analysis was performed by several established detection techniques, and all mutations were confirmed by direct sequencing of DNA samples. For the women in Ontario, DNA samples were screened by the protein-truncation test for mutations in exons 10 and 11 of *BRCA1* and exon 11 of *BRCA2*.⁷ The Ashkenazi Jewish women were screened for three founder mutations, two in *BRCA1* (185delAG and 5382insC) and one in *BRCA2* (6174delT).⁸ The women in the group identified by the Breast Cancer Linkage Consortium were screened for mutations by techniques routinely used in the participating laboratories. These techniques included direct sequencing of DNA, heteroduplex analysis, single-strand conformation analysis, and allele-specific oligonucleotide hybrid-

ization. In every woman, the actual sequence variant in *BRCA1* or *BRCA2* was established by direct sequencing of DNA.

Study Protocol

The patients and control women were asked about their reproductive histories, methods of contraception (including use of oral contraceptive agents and tubal ligation), and history with respect to oophorectomy. The women were asked at what age they first took an oral contraceptive, at what age they stopped, and the total duration of oral-contraceptive use. No information was requested about the specific oral contraceptive agent taken. Two patients had undergone unilateral oophorectomy for a benign condition before the diagnosis of ovarian cancer. Among the control women, 72 had undergone oophorectomy (5 unilateral and 67 bilateral). The average age at the time of bilateral oophorectomy was 45 years.

Statistical Analysis

The mean duration of oral-contraceptive use in the patients and control women was compared by the nonparametric Wilcoxon two-sample test. Odds ratios were estimated by unconditional logistic-regression analysis with control for other covariates, including geographic area of residence (United States, Canada, United Kingdom, or elsewhere in Europe), year of birth, parity, and age at delivery of a first child. The last three variables were included as continuous terms.

To control for possible confounding effects of ethnic group, a separate matched analysis was performed. Patients were matched with their sisters, and conditional logistic regression for matched sets (with variable ratios of patients to controls) was performed. This analysis was based on 89 case-control pairs, because patients with no sisters were excluded. All statistical tests were two-sided.

RESULTS

The characteristics of the 207 patients with ovarian cancer and the 161 controls were similar (Table 1). Fifty percent of the patients and 70 percent of the control women reported a history of oral-contraceptive use (P<0.001). The average duration of oral-contraceptive use for the patients was four years, significantly less than the average duration for the control women (six years; P=0.01).

Among the 207 patients, 179 had *BRCA1* mutations and 28 had *BRCA2* mutations. Among the 161 control women, 53 were known to have mutations (50 had *BRCA1* mutations and 3 had *BRCA2* mutations) and 42 were known to be noncarriers; the remaining 66 were not tested. In these three subgroups of women, a history of oral-contraceptive use was reported by 77 percent, 64 percent, and 67 percent, respectively (as compared with 50 percent of the patients). The average duration of use was also greater for each of the three subgroups of control women (five, five, and seven years, respectively) than for the patients (four years). Because the duration of oral-contraceptive use was similar in the three subgroups of control women, and because of the small sizes of those subgroups, they were combined for most of the multivariate analyses. The pattern of oral-contraceptive use did not differ significantly between the control women who had undergone bilateral oophorectomy (69 percent; mean duration of use,

TABLE 2. ASSOCIATION BETWEEN ORAL-CONTRACEPTIVE USE AND RISK OF OVARIAN CANCER.*

VARIABLE	ALL CONTROL WOMEN		CONTROL WOMEN WITH <i>BRCA1</i> OR <i>BRCA2</i> ONLY†
	UNIVARIATE ANALYSIS	MULTIVARIATE ANALYSIS	MULTIVARIATE ANALYSIS
	odds ratio (95% CI)		
Any use vs. none	0.4 (0.3–0.7)	0.5 (0.3–0.8)	0.4 (0.2–0.7)
Duration of use (yr)			
0	1.0	1.0	1.0
<3	0.7 (0.4–1.2)	0.8 (0.4–1.4)	0.4 (0.3–0.9)
3 to <6	0.4 (0.2–0.7)	0.4 (0.2–0.9)	0.4 (0.1–1.0)
≥6	0.3 (0.2–0.6)	0.4 (0.2–0.7)	0.3 (0.1–0.7)
Trend per year of use	0.9 (0.9–1.0)	0.9 (0.9–1.0)	0.9 (0.9–1.0)

*CI denotes confidence interval. Multivariate odds ratios have been adjusted for year of birth, parity, age at the delivery of a first child, and geographic area of residence. Multivariate analyses of carriers of a *BRCA1* or *BRCA2* mutation have also been adjusted for the mutation type (*BRCA1* or *BRCA2*). Each oral-contraceptive variable was considered in a separate model.

†This analysis includes only the 53 control women who were confirmed carriers of mutations.

five years) and those with both ovaries (72 percent; mean duration of use, six years; $P=0.37$).

The odds ratios for ovarian cancer associated with oral-contraceptive use according to unconditional logistic-regression analysis are shown in Table 2. The risk of ovarian cancer decreased with the duration of use (multivariate P for trend, <0.001). Women who took an oral contraceptive agent for six or more years had a reduction in risk of 60 percent. The reduction in risk was similar for carriers of the *BRCA1* and *BRCA2* mutations. The odds ratio for carriers of the *BRCA1* mutation who had used oral contraceptives, as compared with those who had not, was 0.5 (95 percent confidence interval, 0.3 to 0.9), and that for carriers of the *BRCA2* mutation was 0.4 (95 percent confidence interval, 0.2 to 1.1). Adjustments for parity, age at the delivery of a first child, and age at the delivery of a last child did not significantly change the magnitude of the odds-ratio estimates associated with oral-contraceptive use.

The results of the matched analysis were very similar to those shown in Table 2. The odds ratios for ovarian cancer were 0.9 (95 percent confidence interval, 0.4 to 2.1), 0.4 (95 percent confidence interval, 0.2 to 1.2), and 0.3 (95 percent confidence interval, 0.1 to 0.7) for oral-contraceptive use for less than three years, three to less than six years, and six or more years, respectively ($P=0.02$).

Among the 63 patients who had had breast cancer in addition to ovarian cancer, the average duration of oral-contraceptive use was five years, as compared with four years among those who had not had breast cancer. The average duration of oral-contraceptive use was six years among the 29 control women who had had breast cancer and among those who had not had breast cancer.

DISCUSSION

In this multicenter case-control study, the use of oral contraceptives was associated with a significant reduction in the risk of ovarian cancer among women with a mutation in the *BRCA1* or *BRCA2* gene. The reduction in risk was 20 percent for up to three years of use, rising to 60 percent for six or more years of use.

The magnitude of the protective effect of oral contraceptives in carriers of *BRCA1* and *BRCA2* mutations is consistent with that previously found in the general population. In a meta-analysis of 12 case-control studies of oral-contraceptive use and the risk of ovarian cancer in the United States,⁹ the risk decreased with increasing length of oral-contraceptive use. In the six population-based studies, the risk reduction was 34 percent for those who had ever used oral contraceptives and 70 percent for those with six or more years of use. In the six hospital-based studies, the corresponding risk reductions were 30 percent and 45 percent, respectively.

The strengths of the present study are that the cases of ovarian cancer were identified through a large international consortium, all patients with ovarian cancer were confirmed carriers of mutations, and the control group consisted of sisters of the patients. We think the smaller size of the control group is counterbalanced by the similarity of the control women to the patients, because by definition they shared the same family history, were members of the same ethnic group, and were from the same geographic region.

Ashkenazi Jewish women were somewhat overrepresented among the patients and French-Canadian women among the controls. These differences reflect the average family size of women from the two ethnic groups, rather than the willingness of the sis-

ters of the patients to participate. On average, a Jewish woman had 1.2 sisters, and a French-Canadian woman had 4.5 sisters. In other respects, the patients and control women were well matched.

The ideal control group for this study might be sisters of the patients who still had both their ovaries and who carried the same mutation but in whom ovarian cancer had not developed by the age at which it was diagnosed in their sisters. Unfortunately, we could not identify sufficient numbers of control women with these characteristics, and we therefore extended the control group to include all unaffected living sisters of the patients. Nevertheless, more of the sisters with and without mutations in *BRCA1* or *BRCA2* than patients had used oral contraceptives. The extent of misclassification introduced by the inclusion of sisters without mutations is likely to be minimal, given the similarity of the results of the analysis based on all control women and on only sisters with mutations. Furthermore, if the use of oral contraceptives protects against ovarian cancer, then a higher proportion of women with mutations who did not have ovarian cancer would have been expected to have taken oral contraceptives. This was true: 77 percent of the control women with mutations had taken oral contraceptives, as compared with 64 percent of those without mutations.

Our study included control women who had undergone oophorectomy. Fewer of these women might have taken oral contraceptives than expected if the oophorectomy was performed before menopause. However, there was little difference in the frequency of use of oral contraceptives between control women who had had their ovaries removed and those who had not. Selection bias of this type should lead to underestimation of the magnitude of the risk reduction associated with oral-contraceptive use.

Adjustment for parity, the presence or absence of tubal ligation, and ages at the delivery of a first and last child did not influence the protective effect of oral-contraceptive use. Increasing parity appears to be protective against hereditary ovarian cancer, as it is for ovarian cancer in the general population.⁹ There are no other known risk factors for ovarian cancer that are likely to have been confounders in the present study.

A limitation of this study is that it included only living women with ovarian cancer as case patients. This was true because of the difficulty of ascertaining whether deceased patients had carried mutations and of obtaining an accurate history of contraceptive use in interviews with surrogates. If oral-contraceptive use is associated with a higher case fatality rate for ovarian cancer, then this selection strategy will exaggerate the protective effect of oral contraceptives. On average, the women in our study stopped using oral contraceptives 17 years before the diagnosis of ovarian cancer, and only 12 women had taken an

oral contraceptive agent during the 5-year period before diagnosis.

It is important to establish whether the risk of breast cancer in women with *BRCA1* or *BRCA2* mutations is influenced by oral-contraceptive use, especially if oral contraceptives are to be recommended to healthy carriers as chemopreventive agents. Oral-contraceptive use has been associated with a small increase in the risk of breast cancer in young⁹ and older¹⁰ women. In a large meta-analysis, current use of oral contraceptives was associated with a relative risk of 1.2 for breast cancer, and past use was associated with a relative risk of 1.1. However, there was no increased risk in the subgroup of women with a family history of breast cancer (defined as having a mother or sister affected). In one study of Jewish women with breast cancer, the frequency of long-term oral-contraceptive use was higher among women who had a *BRCA1* or *BRCA2* mutation than among women without a mutation.¹¹ We found no difference in the history of oral-contraceptive use between women who had had breast cancer and those who had not, but our study was not specifically designed to evaluate this issue.

Our data suggest that the administration of an oral contraceptive agent should be considered as part of a program of prevention for women with *BRCA1* or *BRCA2* mutations who have not had ovarian cancer. However, our data do not allow us to address the specific formulation to be recommended or the age at which treatment should begin.

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APPENDIX

Other members of the Hereditary Ovarian Cancer Clinical Study Group are as follows: Montreal: W. Foulkes, P. Tonin, J. Rosenblatt, P. Ghadirian, C. Perret, A.-M. Mes-Masson, and B. Godard; Toronto: B. Rosen, D. Cole, J. McLaughlin, J. Murphy, L. Bradley, I. Fan, J. Abrahamson, and E. Warner; Philadelphia: T. Rebbeck, B. Weber, F. Couch, M. Daly, A. Godwin, and J. Wagner-Costalos; Washington, D.C.: C. Lerman and B. Peshkin; Durham, N.C.: A. Futreal and J. Lancaster; Chicago: O. Olopade and S. Cummings; Salt Lake City: L. Cannon-Albright and L. Steele; Boston: J. Garber and N. Tung; Omaha, Nebr.: H. Lynch, J. Lynch, C. Snyder, and C. Durham; Los Angeles: B. Karlan; New Hyde Park, N.Y.: D. Smotkin; New York: A. Fields, D. Russo, and K. Antman; Cambridge, United Kingdom: D. Ford and D. Easton; Lyons, France: G. Lenoir, O. Serova, and S. Mazoyer; Rotterdam, the Netherlands: E. Meijers-HeijBoer and L. Verhoog; Manchester, United Kingdom: F. Laloo; Lund, Sweden: O. Johannsson and A. Borg; and Oslo, Norway: P. Moller.

REFERENCES

1. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in *BRCA1*-mutation carriers. *Lancet* 1994;343:692-5.
2. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. *Am J Hum Genet* 1998;62:676-89.
3. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in *BRCA1*-mutation carriers. *Am J Hum Genet* 1995;56:265-71.

4. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. *JAMA* 1997;277:997-1003.
5. Whittemore AS, Harris R, Itmyre J, Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;136:1184-203.
6. Franceschi S, Parazzini F, Negri E, et al. Pooled analysis of 3 European case-control studies of epithelial ovarian cancer. III. Oral contraceptive use. *Int J Cancer* 1991;49:61-5.
7. Hogervorst FB, Cornelis RS, Bout M, et al. Rapid detection of BRCA1 mutations by the protein truncation test. *Nat Genet* 1995;10:208-12.
8. Tonin P, Weber B, Offit K, et al. Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families. *Nat Med* 1996;2:1179-83.
9. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996;347:1713-27.
10. Risch HA, Howe GR. Menopausal hormone usage and breast cancer in Saskatchewan: a record-linkage cohort study. *Am J Epidemiol* 1994;139:670-83.
11. Ursin G, Henderson BE, Haile RW, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? *Cancer Res* 1997;57:3678-81.