Oral Contraceptive Use and *BRCA* Penetrance: A Case-Only Study

Patrizia Pasanisi,[1] Guy Hédelin,[2] Jacopo Berrino,[1] Jenny Chang-Claude,[3] Silke Hermann,[3] Michael Steel,[4] Neva Haites,[5] Jacob Hart,[6] Ronit Peled,[7] Lorenzo Gafà,[8] Laura Leggio,[8] Adele Traina,[9] Rosalba Amodio,[9] Maja Primic-Zakelj,[10] Vesna Zadnik,[10] Toomas Veidebaum,[11] Mare Tekkel,[12] and Franco Berrino[1]

[1]Department of Preventive and Predictive Medicine, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy; [2]Department of Epidemiology, Faculty of Medicine of the University of Strasbourg, Strasbourg, France; [3]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [4]Bute Medical School, University of St Andrews, St Andrews, Scotland; [5]Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, Scotland; [6]Loewenstein Rehabilitation Hospital Raanana, Israel Sacler School of Medicine, University of Tel Aviv, Tel Aviv, Israel; [7]Department of Systems Management, Faculty of Health Science, Ben Gurion University of the Negev, BeerSheva, Israel; [8]Italian League Against Cancer, Ragusa Section, Ragusa, Italy; [9]Department of Oncology, Palermo Breast Cancer Registry, Ospedale Civico ''M. Ascoli,'' Palermo, Italy; [10]Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Ljubljana, Slovenia; and [11]Departments of Oncology and Immunology, Estonia and [12]Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia

Abstract

Background: **Women with deleterious mutations in *BRCA* genes are at increased risk of breast cancer. However, the penetrance of the genetic trait may be regulated through environmental factors. This multinational case-only study tested the interaction between oral contraceptive use and genetic susceptibility in the occurrence of breast cancer.**

Methods: **We recruited 3,123 patients diagnosed with breast cancer before the age of 45 years. Participants were classified according to their probability of carrying a *BRCA* mutation on the basis of their family history of breast and ovarian cancer. According to a case-only approach, the frequency of relevant exposures among breast cancer cases with high probability of *BRCA* mutation (''genetic cases'') was compared with the frequency of the same exposures among breast cancer cases with a low probability of *BRCA* mutation (''sporadic cases''). The interaction odds ratios (OR) and 95% confidence intervals (CI) for oral contraceptive use were estimated by unconditional logistic regression, after controlling for potentially confounding variables.**

Results: **The analysis was carried out comparing 382 ''genetic'' and 1,333 ''sporadic'' cases. We found a borderline significant interaction between genetic breast cancer and oral contraceptive use for ever users compared with never users (OR, 1.3; 95% CI, 1.0-1.7). The greatest interaction OR was found for women who started using pill at 18 to 20 years (OR, 1.6; 95% CI, 1.1-2.3).**

Conclusion: **These results suggest that *BRCA* mutation carriers, as well as women with a significant family history of breast and ovarian cancer are more vulnerable to exogenous hormones in oral contraceptives.** (Cancer Epidemiol Biomarkers Prev 2009;18(7):2107–13)

Introduction

Women with deleterious mutations in *BRCA* genes are at increased risk of breast cancer and ovarian cancer, and often develop cancer at a young age. Estimates of the lifetime cumulative risk (penetrance) of breast cancer associated with *BRCA* mutations range from ~80% in studies on high-risk families (1-5), to around 45% in population-based studies (6-12). A sizable proportion of mutation carriers, however, does not develop breast cancer at all or develop it only late in life. Therefore, the penetrance of the genetic trait may be regulated through other genetic or nongenetic factors. The hypothesis of an interaction of genetic and environmental risk factors is supported by the increasing penetrance and declining age at onset over succeeding generations that several authors have described in *BRCA*-positive families (13-16).

This multinational Case Only Study (C.O.S.; refs. 17, 18) aimed to investigate the interaction between genetic susceptibility, nutrition, and environmental factors in the occurrence of breast cancer in young women. We hypothesized that among environmental factors (19, 20) affecting the penetrance of hereditary breast cancer genes, oral contraceptives use may play a significant role (13, 21).

Long-term use of oral contraceptives is an established risk factor for sporadic breast cancer (22). Combined oral contraceptive drugs may also modify the risk of early onset breast cancer, especially in women who started using pill very young (23-27). Oral contraceptives have been found to increase the risk of early-onset breast cancer among *BRCA1* mutation carriers but might protect them against ovarian cancer (21). A case-control

Received 1/9/09; revised 5/11/09; accepted 5/11/09; published OnlineFirst 6/23/09.

Requests for reprints: Patrizia Pasanisi, Department of Preventive and Predictive Medicine, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico Istituto Nazionale dei Tumori, Via Venezian, 1 20133 Milano. Phone: 390223903513; Fax: 390223903516. E-mail: patrizia.pasanisi@istitutotumori.mi.it

doi:10.1158/1055-9965.EPI-09-0024

study involving 1,311 pairs of women with *BRCA* mutations (28) reported that, among *BRCA1* mutation carriers, women who first took oral contraceptives before 1975 (when drugs were likely to contain high doses of hormones), who used them before 30 years of age, or who stayed on them for 5 or more years have a statistically significant increased risk of early onset breast cancer. A retrospective cohort of 1,593 *BRCA* mutation carriers (29) confirmed an increased risk for oral contraceptive users especially for those starting use at 21 to 24 years of age without, however, any difference for calendar time of starting use. Jernstrom and colleagues (30) showed an interaction between teenage oral contraceptive use and *BRCA* carrier status in early-onset breast cancer cases. The same group has recently suggested an association between *BRCA* mutation status, *CYP17* genotype (gene involved in steroid hormone metabolism), and early oral contraceptive use (31).

The aim of the present work is to evaluate the interaction between oral contraceptive use and genetic susceptibility using a case-only approach.

Materials and Methods

Study Population. The C.O.S. study (17, 18) was supported by the European Community. Between January 2001 and April 2004, 3,123 women were recruited from nine centers in seven countries (Estonia, France, Germany, Israel, Italy, Scotland, and Slovenia). Eligible study subjects were women with a breast cancer diagnosis up to the age of 40 y in France, Germany, Italy, and Scotland and, given the small size of countries, up to the age of 45 years in Estonia, Slovenia, and Israel. The number of recruited patients by country is showed in Table 1.

Collaborating centers used different procedures to recruit patients into the study. In Scotland, Israel, and Germany, recruitment was mostly based on hospitals or family clinics; in France, Slovenia, and Estonia, on the local cancer registries; and in Italy, by advertising the study in the media. Such procedures were approved by each center institutional review board. All study subjects received information about the study and provided written consent.

Participants were requested to produce a copy of their pathology report and to fill in self-administered questionnaires on family pedigree and on family history of breast and ovarian cancer (to compute probability of *BRCA* mutation), dietary habits, and other life-style aspects before diagnosis. We also inquired if one or more family members had been tested for *BRCA1* or *BRCA2* mutation, and on the results of the test. However, test results were available in a minority of cases and for the purpose of this analysis their classification was only based on the ''*a priori*'' probability of mutation estimated from the family history.

Two hundred seventy women were excluded from the study either because they lacked a complete family history, age at diagnosis, or information whether they had used oral contraceptive or not.

Case-Only Methodology. The C.O.S. study was based on the collection of a few key information from participants (32). Women were classified according to their probability of carrying a high-penetrance mutation as estimated from their family history of breast and ovarian cancer. The *odds* of a given exposure among breast cancer cases who most likely carry a high-penetrance mutation because of a highly predictive family history (''genetic cases'') were compared with the *odds* computed for breast cancer cases who most likely are not mutation carriers because no other case occurred in an otherwise informative family (''sporadic cases'').

C.O.S. Software. A major requirement of a case-only study is an unbiased classification of ''genetic'' and ''sporadic'' cancers. Several genetic risk assessment methods are available to estimate the probability of *BRCA* mutation in individuals to select them and their families for molecular diagnosis (33). Empirical methods based on the number of breast cancer and ovarian cancer cases in the family, age at diagnosis, and occurrence in subsequent generations, ignore data from unaffected relatives (34-37), and may overestimate the probability of mutation in large families with few affected members. By contrast, methods based on genetic models consider information from all relatives, whether affected or not. Berry et al. (38) and Parmigiani et al. (39) developed a method and a software (BRCAPRO) based on Bayes' theorem that requires data on all first- and second-degree relatives of the proband, and incorporates as prior probabilities incidence rates in the United States population, and allele mutation frequencies and penetrances estimated from studies in families with several breast cancer or ovarian cancer cases (4, 39, 40).

The C.O.S. study was carried out in countries with breast cancer incidence ranging from 50 to 100 per 100,000 women per year (41). In such a context, the application of a Bayesian model requires country-specific assumptions of sporadic breast cancer and ovarian cancer incidence; furthermore, breast cancer incidence has increased over generations, both in the general population (42) and in mutation carriers (13-16) and single age-specific incidence curves, as available from cancer registries, and penetrance curves estimated from

Table 1. Distribution of sporadic and genetic cases as estimated by the C.O.S. software by country

Probability of *BRCA* mutation Country	≥45% genetic cases	<5% sporadic cases	5%-44%	Total no. of cases
Estonia	12	72	98	182
France	18	103	44	165
Germany	32	165	106	303
Israel	77	62	110	249
Italy	184	662	597	1,443
Scotland	26	165	90	281
Slovenia	33	104	93	230

high-risk families, do not accurately describe the disease risk in succeeding generations.

In our study, we developed a computer program (C.O.S. software) to estimate the risk of mutation when incidence and penetrance are increasing over generations. The software is based on the same Bayesian logic as Parmigiani's method (38, 39) but is also able to evaluate third and if necessary fourth degree relatives, and allows incorporation of a hypothetical third *BRCA* gene. To estimate *BRCA* mutation probability, the C.O.S. software requires sex, age or age at death, age at breast cancer or ovarian cancer diagnosis, and age of diagnosis of second or contralateral breast cancer, in each participant's family member. We estimated country-specific general population breast cancer incidence by birth cohort from cause-specific mortality data (43) and population-based cancer survival data (44, 45), using a mathematical model of the relationship between incidence, survival, mortality, and prevalence (46). To estimate breast cancer and ovarian cancer penetrance in those with a deleterious *BRCA* mutation, we used pedigrees from families identified at the Milan National Cancer Institute with a *BRCA* mutation (47). We simulated various age- and birth cohort–specific curves for the incidence of genetic breast cancer and ovarian cancer, and chose a set that produced estimates closest to the observed family histories. We examined the performance of the COS software for Italy in predicting mutations in 131 Italian high-risk families in which direct sequencing or combination of direct sequencing and denaturing high performance liquid chromatography of amplicons found 25 deleterious mutations (17 *BRCA1* and 8 *BRCA2*). Considering a probability of 0.1 and over as indicating a positive prediction, we compared sensitivity, specificity, and area under the receiver operator characteristic curve for the COS and BRCAPRO (Version 4.0) programs. COS had higher sensitivity (76% versus 72%) but lower specificity (48% versus 58%) than BRCAPRO. However, the area under the receiver operator characteristic was numerically better at 0.71 [95% confidence interval (CI), 0.65-0.78] for C.O.S., than the 0.67 (95% CI, 0.60-0.73) for BRCAPRO, suggesting that COS was better able to distinguish between families with and without a deleterious mutation but overestimated the probability of mutation. Also the COS software for Scotland was compared with other genetic models to estimate the probability of *BRCA* mutation, showing higher sensitivity and slightly lower specificity (48).

Lifestyle Questionnaire. The aim of the study was to investigate environmental exposures before breast cancer diagnosis. We used self-administered questionnaire addressing oral contraceptive use, menstrual and reproductive history, active and passive smoking, radiation exposure in childhood, body weight, and physical activity at different ages, usual dietary intake, and some medical conditions. Participants were also instructed to measure their height, weight, and hip and waist circumferences in a standard way.

Referring to oral contraceptive, women were asked about their past and current use, at what age they began using pill and what age they stopped, and about the total duration of use.

The same data entry system was available in different languages and allowed the computation of summary variables useful to statistical analysis. Consistency and validity checks were done at the coordinating center (Department of Preventive and Predictive Medicine of the Milan National Cancer Institute).

Statistical Analysis. The statistical analysis aimed to test the interaction between oral contraceptive use and genetic susceptibility. According to a case-only methodology, the frequency of exposure among ''genetic'' cases was compared with the frequency among ''sporadic'' cases. We carried out the basic analysis comparing breast cancer genetic cases (with probability of *BRCA* mutation of $\geq$45%) and sporadic breast cancer cases (with probability of *BRCA* mutation of <5%). We choose these cut off points to guarantee in the genetic group a probability of mutation >80% (83% on average), and in the sporadic group a very low probability of mutation (2% on average).

The means for all continuous variables in patients with high probability of mutation were compared with those of patients with a low probability by using Student's t test. χ^2 test was used to compare frequencies and percentages in relation to probability of mutation. An unconditional logistic regression model was used to compute the interaction odds ratio (OR) and 95% CIs; in our model, the dichotomous dependent variable was the genetic or sporadic nature of the case.

The following covariates were considered as potential confounders according to *a priori* hypotheses: center, age at diagnosis (in quintiles), education (none or primary school, high school, degree, or more), parity (defined as zero, one, two, three, or more), breastfeeding (no, 1-6, 7-12, >12 mo), and age at first live birth (in quintiles).

In Italy, we contacted again all patients whose questionnaires containing missing values on age at starting pill, duration of use, and on potential confounders such as parity, age at first live birth, and breast feeding. As missing values on confounding factors may bias the results, we also produced a statistical analysis restricted to the Italian series of patients, 96% of whom had complete information. A P value of <0.05 was taken to be significant. All statistical tests were two sided. The analyses were carried out using the STATA 8.0. statistical package.

Results

Table 1 describes the distribution of cases by countries and probability of mutation. We analyzed key information from 1,715 C.O.S. women, 382 classified as genetic cases (probability of mutation, $\geq$45%) and 1,333 classified as sporadic cases (probability of mutation, <5%).

Characteristics of the study population and comparison of genetic and sporadic cases are reported in Table 2. Genetic cases were significantly younger and more educated; they showed a higher frequency of nulliparity and, among parous women, of those with three or more children. There were no statistically significant difference in mean age at menarche, age at first live birth, months of breast feeding, and usual body mass index. Oral contraceptive has been used by 74.9% of the genetic

Table 2. Main analysis: distribution of exposures under study in genetic and sporadic cases

		Genetic cases	Sporadic cases	*P**
Age at diagnosis mean ± SD		34.2 ± (4.4)	36.4 ± (3.1)	<0.01
Age at diagnosis (quintiles)	% 16-33	39.8	16.7	
	34-35	15.7	18.8	
	36-37	21.5	23.6	
	38-39	15.9	32.3	0.00 †
	40-45 ‡	7.1	8.6	
Education	% low	28.3	31.1	
	high	40.3	45.6	
	degree or more	31.4	23.3	0.01
Menarche mean age ± (SD)		12.5 ± (1.4)	12.6 ± (1.4)	0.62
Pregnancy	% never	24.4	19.6	
	ever	75.6	80.4	0.04
Parous, by no. of children	% 1	37.3	34.9	
	2	42.1	49.6	
	3+	20.6	15.5	0.01
Average age at 1st live birth ± (SD)		25.8 ± (4.4)	25.7 ± (4.6)	0.65
Breastfeeding (parous women)	% no	20.7	21.3	
	1-6 mo	39.9	40.1	
	7-12 mo	22.2	20.4	
	13+ mo	17.2	18.2	0.95
Mean months of breast feeding ± (SD)		6.9 ± (7.6)	7.0 ± (8.4)	0.80
Oral contraceptive	% never	25.1	28.4	
	ever	74.9	71.6	0.20
Ever users, mean age at first use ± (SD)		21.3 ± (4.7)	22.1 ± (5.3)	0.04
	% under 20	58.0	49.9	0.02
Mean duration of use (mo) ± (SD)		69.3 ± (56.5)	74.0 ± (59.3)	0.30
Usual BMI before diagnosis mean ± (SD)		22.1 ± (3.4)	22.4 ± (3.3)	0.10

Abbreviation: BMI, body mass index.
*P of differences using Student's t test for continuous variables and χ^2 test for frequencies and percentages comparison.
† P of comparison excluding age group 40-45 y.
‡ Only Estonia, Israel, and Slovenia contributed to this category.

cases and by 71.6% of the sporadic cases. Among women who used oral contraceptive, the age at start was slightly earlier and the average duration of use was slightly shorter in genetic than in sporadic cases.

We examined the interaction between oral contraceptive and genetic susceptibility by a multiple logistic regression model (Table 3). The adjusted interaction OR of breast cancer comparing ever users with women who had never used oral contraceptive was 1.3 (95% CI, 1.0-1.7). Table 3 reports the interaction OR of genetic breast cancer for each quartile of age at start using pill. This analysis by age at first use included the 1,515 participants with complete data. The higher risk was for women who started using oral contraceptive at age 18-20 (interaction OR, 1.6; 95% CI, 1.1-2.3), but women who started before the age of 18 years were not at increased risk (interaction OR, 1.1; 95%CI, 0.6-1.8). Women probably carrying a *BRCA* mutation who began taking pill after the age of 25 years were not at increased risk (interaction OR, 1.0; 95% CI, 0.6-1.4). Due to missing values, adjustment for reproductive variables was possible only for a subset of 1,457 cases. Results however showed only trivial changes (interaction OR, 1.3; 95% CI, 1.0-1.8 comparing ever versus never users).

Table 3. Interaction ORs for oral contraceptive use

Oral contraceptive use	n	OR* (95% CI)
Never	475	1.0 (Reference)
Ever use	1,240	1.3 (1.0-1.7)
Age at start pill (y)		
12-17	164	1.1 (0.6-1.8)
18-20	375	1.6 (1.1-2.3)
21-24	225	1.4 (0.9-2.1)
25+	276	1.0 (0.6-1.4)
Test for global null hypothesis		P = 0.05
Test for trend		P = 0.18

These ORs express how much larger (or smaller) is the relative risk associated with an exposure in women with high probability of BRCA mutations with respect to women with a low probability.
*Adjusted for age at diagnosis, country, and education.

C.O.S. participants took oral contraceptive for an average of 6 years (72.8 months) without significant difference between genetic and sporadic cases (P = 0.30; Table 2). The analysis on duration of oral contraceptive use showed an interaction OR slightly higher for short duration of use (≤5 years) than for longer duration, but the difference was not statistically significant (P = 0.32; data not shown).

Italian Subset Analysis. This analysis include 846 Italian C.O.S. participants, 184 genetic, and 662 sporadic cases.

The interaction OR of breast cancer comparing ever versus never users oral contraceptive after controlling for age at diagnosis, education, parity, age at first live birth, and months of breast feeding was 1.4 (95% CI, 0.9-2.0; Table 4). Table 4 reports the interaction OR of genetic breast cancer for the same categories of age at start using oral contraceptives of the main analysis. The interaction OR was higher for women starting at the age 18-20 (interaction OR, 2.0; 95% CI, 1.2-3.3), but women starting in their early teens were not at increased risk. However, the trend of decreasing OR for increasing age of starting oral contraceptive use was statistically significant. There

Table 4. Italian subset analysis: interaction ORs for oral contraceptive use

Oral contraceptive use	*n*	OR (95% CI)
Never	280	1.0 (Reference)
Ever use	566	1.4 (0.9-2.0)
Age at start pill (y)		
12-17	44	1.0 (0.4-2.4)
18-20	182	2.0 (1.2-3.3)
21-24	131	1.4 (0.8-2.4)
25+	209	1.0 (0.6-1.7)
Test for global null hypothesis		$P = 0.04$
Test for trend		$P = 0.02$

Adjusted for age at diagnosis, education, parity, age at first live birth, and breastfeeding.

was no difference according to the duration of oral contraceptive use (data not shown).

Discussion

The multinational C.O.S. study on gene-environment interaction in the occurrence of breast cancer in young women was designed to test several specific hypotheses based on the available knowledge on the function of *BRCA1* and *BRCA2* proteins, namely their role in DNA repair and their role in controlling the effect of estrogen exposure (49). C.O.S. secondary aim was the development of primary preventive recommendations for high-risk families.

In a case-only study, an interaction OR significantly different from one indicates a gene-environment interaction, i.e., that the factor under study affects the incidence of genetic cancer by a greater (or lesser) magnitude than the incidence of sporadic cancer. The major contribution of the present study is that the relative risk of oral contraceptive use is greater for women with high probability of *BRCA* mutation than for women with a low probability.

This positive interaction was expected, because among the multiple functions of *BRCA* gene products, there is the regulation of estrogen signaling (50-52). We therefore corroborated one of the C.O.S. *a priori* hypothesis that oral contraceptives may increase breast cancer risk with a greater effect in presence of *BRCA* mutation. Women with a genetic predisposition may be more vulnerable to exogenous hormones. The Narod and collegues' case-control study (28) involving 1,311 pairs of women with *BRCA1* or *BRCA2* mutations reported that, among *BRCA1* mutation carriers but not among *BRCA2* mutation carriers, women who first took oral contraceptives before 1975, who used them before age 30 years, or who stayed on them for 5 or more years have a statistically significant increased risk of early onset breast cancer. The Brohet and collegues' retrospective cohort (29) confirmed the association with an increasing trend with the duration of use and the greater risk for women starting use before the age of 25 years. Those investigations, however, was not designed to analyze whether oral contraceptive risk is greater among carriers or non carriers. In the C.O.S. study, almost all the patients started using oral contraceptives after 1975 and the risk of carriers was increased with respect to noncarriers. The risk associated with oral contraceptive use in mutation carriers may be greater than our estimate because women with positive family history may be recommended not to use oral contraceptives or may decide to stop their use when a relative develops breast cancer. This may cause an underestimation of the interaction OR measured in a case-only study.

The relationship between oral contraceptive and genetic breast cancer was greater in selected subgroups. When we examined the risk by quartile of age at start using pill, the higher interaction OR was observed for women who started between 18 to 20 years of age (OR, 1.6; 95%CI, 1.1-2.3). Among women who started earlier (before 18 years) there was no difference between genetic and sporadic cases both in the main analysis and in the Italian subset. The interaction with genetic susceptibility may change with age on the basis of different hormonal responses or pathologic conditions. We have to consider that oral contraceptive pill before the age of 18 years is frequently prescribed for reasons other than avoidance of pregnancy, such as to reduce irregularity in menstrual cycle after menarche, or to reduce pain, acne and hirsutism, or for polycystic ovary. These conditions may be associated with breast cancer risk and hormonal treatments might contribute to reduce the risks.

The results, however, suggest that the excess risk of probable mutation carriers with respect to noncarriers is not apparent until age 18 to 20 years and after that decreases with increasing age at start. There may be no excess risk in women starting oral contraceptive use at age 25 years or later as previously shown by Narod and collegues (28).

The strength of our study is the case-only design. It allows to express how greater is the association of the environmental exposure with genetic cancers than with sporadic cancers, which is the statistical interaction between the exposure and the genetic trait. Referring to the classification of cases, the estimated average probability of high probability group—the genetic cases—was 83%; the average probability of mutation of the low probability group—the sporadic cases—was 2%. This implies that 17% of patients classified as genetic may have been false positive, and that 2% of cases classified as sporadic false negative, i.e., actually carriers of *BRCA* mutation. Such misclassification implies an underestimation of the interaction OR and the risks associated with oral contraceptive exposures for *BRCA1* or *BRCA2* mutation carriers are likely somewhat higher. Genetic test results were available for 143 cases, 52 positive, and 91 negative. History of oral contraceptive use was most frequent among the former with an age adjusted interaction OR of 6.1 (95% CI, 1.2-30.9), suggesting that the overall results of the study underestimated the effect.

We also tested the relationship with oral contraceptive use comparing the intermediate mutation probability group (5-44%) *versus* the low probability group (<5%). The interaction OR was 1.0 (95% CI, 0.8-1.3), suggesting a fairly high specificity of our classification.

Knowledge of breast cancer susceptibility genes, along with the introduction of predictive genetic testing, has made it possible to identify women at increased risk for inherited breast and ovarian cancer. Options currently available for these women include surveillance programs aimed at early detection, prophylactic bilateral mastectomy, and prophylactic oophorectomy,

whereas nonsurgical primary prevention options are not yet firmly established. Oral contraceptive use has been considered as a preventive measure against ovarian cancer in *BRCA* mutation carriers. However, the effect of oral contraceptive use on ovarian cancer in *BRCA* mutation carriers is still unclear (53). Narod and collegues (54-56) reported a protective effect of oral contraceptives on the risk of ovarian cancer among *BRCA1* or *BRCA2* carriers, but Modan and collegues (57) did not find any effect.

Whatever the effect on ovarian cancer, C.O.S. results suggest that it would be prudent to avoid starting oral contraception before the age of 25 years. Further studies are warranted to clarify the modifying effect of age in the interaction between oral contraceptive use and *BRCA* penetrance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

References

1. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. J Natl Cancer Inst 1999;91:1310–6.
2. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 2002;94:1365–72.
3. Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1993;52:678–701.
4. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676–89.
5. Narod S, Ford D, Devilee P, et al. Breast Cancer Linkage Consortium. Genetic heterogeneity of breast-ovarian cancer revisited. Am J Hum Genet 1995;57:957–8.
6. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 2000;83:1301–8.
7. Bonadona V, Sinilnikova OM, Chopin S, et al. Contribution of BRCA1 and BRCA2 germ-line mutations to the incidence of breast cancer in young women: results from a prospective population-based study in France. Genes Chromosomes Cancer 2005;43:404–13.
8. Hopper JL, Southey MC, Dite GS, et al. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomarkers Prev 1999;8:741–7.
9. Loman N, Bladstrom A, Johannsson O, Borg A, Olsson H. Cancer incidence in relatives of a population-based set of cases of early-onset breast cancer with a known BRCA1 and BRCA2 mutation status. Breast Cancer Res 2003;5:R175–86.
10. Peto J, Collins N, Barfoot R, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 1999;91:943–9.
11. Risch HA, McLaughlin JR, Cole DE, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006;98:1694–706.
12. Thorlacius S, Struewing JP, Hartge P, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet 1998;352:1337–9.
13. Narod SA. Modifiers of risk of hereditary breast cancer. Oncogene 2006;25:5832–6.
14. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117–30.
15. Chang-Claude J, Becher H, Eby N, Bastert G, Wahrendorf J, Hamann U. Modifying effect of reproductive risk factors on the age at onset of breast cancer for German BRCA1 mutation carriers. J Cancer Res Clin Oncol 1997;123:272–9.
16. Narod SA, Goldgar D, Cannon-Albright L, et al. Risk modifiers in carriers of BRCA1 mutations. Int J Cancer 1995;64:394–8.
17. Berrino F, Pasanisi P, Berrino J, Curtosi P, Bellati C. A European case-only study on familial breast cancer. IARC Sci Publ 2002;156:63–5.
18. Pasanisi P, Berrino J, Fusconi E, Curtosi P, Berrino F. A European Case-Only Study (COS) on familial breast cancer. J Nutr 2005;135:3040–1S.
19. Kotsopoulos J, Narod SA. Towards a dietary prevention of hereditary breast cancer. Cancer Causes Control 2005;16:125–38.
20. Nkondjock A, Ghadirian P. Epidemiology of breast cancer among BRCA mutation carriers: an overview. Cancer Lett 2004;205:1–8.
21. Bermejo-Perez MJ, Marquez-Calderon S, Llanos-Mendez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. Int J Cancer 2007;121:225–31.
22. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Breast cancer. In Combined Estrogen-Progesteron Contraceptives and Combined Estrogen-Progesteron Menopausal Therapy. IARC Monographs n 91. Lyon: IARC Press; 2007. p. 50–5.
23. Henderson BE, Feigelson HS. Hormonal carcinogenesis. Carcinogenesis 2000;21:427–33.
24. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol 2001;2:133–40.
25. Kumle M, Weiderpass E, Braaten T, Persson I, Adami HO, Lund E. Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Cancer Epidemiol Biomarkers Prev 2002;11:1375–81.
26. Olsson H, Moller TR, Ranstam J. Early oral contraceptive use and breast cancer among premenopausal women: final report from a study in southern Sweden. J Natl Cancer Inst 1989;81:1000–4.
27. Velentgas P, Daling JR. Risk factors for breast cancer in younger women. J Natl Cancer Inst Monogr 1994;16:15–24.
28. Narod SA, Dube MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002;94:1773–9.
29. Brohet RM, Goldgar DE, Easton DF, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, the IBCCS Collaborating Group 813. J Clin Oncol 2007;25:3831–6.
30. Jernstrom H, Loman N, Johannsson OT, Borg A, Olsson H. Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. Eur J Cancer 2005;41:2312–20.
31. Henningson M, Johansson U, Borg A, Olsson H, Jernstrom H. CYP17 genotype is associated with short menstrual cycles, early oral contraceptive use and BRCA mutation status in young healthy women. Mol Hum Reprod 2007;13:231–6.
32. Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia: Lippincott; 1998.
33. Antoniou AC, Easton DF. Models of genetic susceptibility to breast cancer. Oncogene 2006;25:5898–905.
34. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994;73:643–51.
35. Federico M, Maiorana A, Mangone L, et al. Identification of families with hereditary breast and ovarian cancer for clinical and mammographic surveillance: the Modena Study Group proposal. Breast Cancer Res Treat 1999;55:213–21.
36. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol 2002;20:1480–90.
37. Shattuck-Eidens D, Oliphant A, McClure M, et al. BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA 1997;278:1242–50.
38. Berry DA, Parmigiani G, Sanchez J, Schildkraut J, Winer E. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. J Natl Cancer Inst 1997;89:227–38.
39. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 1998;62:145–58.
40. Andersen TI. Genetic heterogeneity in breast cancer susceptibility. Acta Oncol 1996;35:407–10.

41. Parkin D, Whelan SL, Ferlay J. Cancer Incidence in Five Continents. IARC Scientific Publication n.155. Lyon: IARC Press; 2002.
42. Capocaccia R, Verdecchia A, Micheli A, Sant M, Gatta G, Berrino F. Breast cancer incidence and prevalence estimated from survival and mortality. Cancer Causes Control 1990;1:23–9.
43. Verdecchia A, Capocaccia R, Egidi V, Golini A. A method for the estimation of chronic disease morbidity and trends from mortality data. Stat Med 1989;8:201–16.
44. Berrino F, Capocaccia R, Esteve J, et al. Survival of cancer patients in Europe: the EUROCARE-2 Study. IARC Scientific Publications N 151. Lyon: IARC Press; 1999.
45. Berrino F, Capocaccia R, Coleman P, et al. Survival of Cancer patients in Europe: the EUROCARE-3 Study. Ann Oncol 2003;14(S_5):9–155.
46. De Angelis G, De Angelis R, Frova L, Verdecchia A. MIAMOD: a computer package to estimate chronic disease morbidity using mortality and survival data. Comput Methods Programs Biomed 1994;44:99–107.
47. Radice P. Mutations of BRCA genes in hereditary breast and ovarian cancer. J Exp Clin Cancer Res 2002;21:9–12.
48. Roudgari H, Miedzybrodzka ZH, Haites NE. Probability estimation models for prediction of BRCA1 and BRCA2 mutation carriers: COS compares favorably with other models. Fam Cancer 2007;7: 199–212.
49. Tan DS, Marchio C, Reis-Filho JS. Hereditary breast cancer: from molecular pathology to tailored therapies. J Clin Pathol 2008;61: 1073–82.
50. Fan S, Wang J, Yuan R, et al. BRCA1 inhibition of estrogen receptor signaling in transfected cells. Science 1999;284:1354–6.
51. Monteiro AN. BRCA1: the enigma of tissue-specific tumor development. Trends Genet 2003;19:312–5.
52. Welcsh PL, King MC. BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. Hum Mol Genet 2001;10:705–13.
53. Friedman LC, Kramer RM. Reproductive issues for women with BRCA mutations. J Natl Cancer Inst Monogr 2005;34:83–6.
54. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 1998;339:424–8.
55. Narod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet 2001;357:1467–70.
56. Narod SA, Sun P, Risch HA. Ovarian cancer, oral contraceptives, and BRCA mutations. N Engl J Med 2001;345:1706–7.
57. Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med 2001; 345:235–40.