

Oral Contraceptive Use and Risk of Early-Onset Breast Cancer in Carriers and Noncarriers of *BRCA1* and *BRCA2* Mutations

Roger L. Milne,¹ Julia A. Knight,⁵ Esther M. John,⁷ Gillian S. Dite,¹ Ronald Balbuena,⁸ Argyrios Ziogas,⁸ Irene L. Andrulis,⁶ Dee W. West,⁷ Frederick P. Li,¹⁰ Melissa C. Southey,² Graham G. Giles,³ Margaret R.E. McCredie,⁴ John L. Hopper,¹ Alice S. Whittemore,⁹
for the Breast Cancer Family Registry

¹Centre for Genetic Epidemiology and ²Department of Pathology, The University of Melbourne; ³Cancer Epidemiology Centre, The Cancer Council Victoria, Carlton, Victoria, Australia; ⁴Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand; ⁵Samuel Lunenfeld Research Institute, Mount Sinai Hospital; ⁶Cancer Care Ontario, Toronto, Ontario, Canada; ⁷Northern California Cancer Center, Union City, California; ⁸Department of Medicine, Division of Epidemiology, University of California, Irvine, California; and ⁹Department of Health Research and Policy, Stanford University, Stanford, California; ¹⁰Dana-Faber Cancer Institute, Boston, Massachusetts

Abstract

Background: Recent oral contraceptive use has been associated with a small increase in breast cancer risk and a substantial decrease in ovarian cancer risk. The effects on risks for women with germ line mutations in *BRCA1* or *BRCA2* are unclear.

Methods: Subjects were population-based samples of Caucasian women that comprised 1,156 incident cases of invasive breast cancer diagnosed before age 40 (including 47 *BRCA1* and 36 *BRCA2* mutation carriers) and 815 controls from the San Francisco Bay area, California, Ontario, Canada, and Melbourne and Sydney, Australia. Relative risks by carrier status were estimated using unconditional logistic regression, comparing oral contraceptive use in case groups defined by mutation status with that in controls.

Results: After adjustment for potential confounders, oral contraceptive use for at least 12 months was associated with

decreased breast cancer risk for *BRCA1* mutation carriers [odds ratio (OR), 0.22; 95% confidence interval (CI), 0.10-0.49; $P < 0.001$], but not for *BRCA2* mutation carriers (OR, 1.02; 95% CI, 0.34-3.09) or noncarriers (OR, 0.93; 95% CI, 0.69-1.24). First use during or before 1975 was associated with increased risk for noncarriers (OR, 1.52 per year of use before 1976; 95% CI, 1.22-1.91; $P < 0.001$).

Conclusions: There was no evidence that use of current low-dose oral contraceptive formulations increases risk of early-onset breast cancer for mutation carriers, and there may be a reduced risk for *BRCA1* mutation carriers. Because current formulations of oral contraceptives may reduce, or at least not exacerbate, ovarian cancer risk for mutation carriers, they should not be contraindicated for a woman with a germ line mutation in *BRCA1* or *BRCA2*. (Cancer Epidemiol Biomarkers Prev 2005;14(2):350-6)

Introduction

A large meta-analysis showed that recent oral contraceptive use was associated with a small increase in breast cancer risk, especially for young women (1). The strength of this association did not differ according to whether or not women reported having at least one first-degree relative with breast cancer. For women known to carry germ line mutations in *BRCA1* and *BRCA2*, the two studies published to date suggest that oral contraceptive use increases breast cancer risk, at least for *BRCA1* mutation carriers (2, 3). For ovarian cancer, there is some evidence to suggest that oral contraceptive use reduces risk for mutation carriers, as in the general population (4),

although the data are inconsistent (5). Nearly all of the studies in the meta-analysis and the studies of mutation carriers included women with at least some exposure to the high-dose hormone formulations used before the mid 1970s, but current clinical decisions are based on low-dose formulations (6). Consequently, mutation carriers and their physicians face difficult decisions regarding the risks and benefits of oral contraceptive use. Here, we present a large population-based case-control study of oral contraceptive use as a risk factor for early-onset breast cancer for Caucasian carriers and non-carriers of mutations in *BRCA1* and *BRCA2*.

Methods

Subjects. We assembled population-based samples of female breast cancer cases and controls from the San Francisco Bay area, California, from Ontario, Canada, and from Melbourne and Sydney, Australia (7). Approval of the study protocol was obtained from relevant ethics committees and written consent was received from all study participants. Each site recruited cases under age 40 years through their regional population-based cancer registries using specific eligibility and sampling criteria. In San Francisco and Ontario, cases were sampled by a two-stage process (8) as described below. In Australia, the study was carried out over two periods: 1992-1995 and 1996-1999, and some case-control analyses from the former period have been previously published (9). Cases ages 35 to 39 years in

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Requests for reprints: John Hopper, Centre for Genetic Epidemiology, The University of Melbourne, Level 2, 723 Swanston Street, Carlton, Victoria 3053, Australia. Phone: 61-3-8344-0697; Fax: 61-3-9349-5815. E-mail: j.hopper@unimelb.edu.au

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San Francisco and ages 36 to 39 years in Ontario were oversampled for characteristics considered indicative of increased genetic susceptibility.

In all sites, controls were identified from the general population living in the catchment area of the regional cancer registry from which cases were drawn and attempts were made to frequency-match controls to the age distribution of cases by 5-year age groups. Eligible cases for this analysis were Caucasian women diagnosed with a first primary invasive breast cancer when aged 18 to 39 years, and eligible controls were Caucasian women without a personal history of invasive breast cancer and aged 18 to 38 years at interview. Race/ethnicity was determined by self-report. Women reporting multiple races/ethnicities or being Hispanic were excluded.

Cases

San Francisco, California. A total of 316 cases of invasive breast cancer diagnosed from 1995 to 1998 in eligible Caucasian women before age 40 years were identified through the Surveillance, Epidemiology and End Results cancer registry, covering nine counties of the Greater San Francisco Bay area.

All 156 cases diagnosed before age 35 were selected. Physician reports on medical or psychological contraindications for contact were obtained for 2 (1%) of these, 5 (3%) were deceased, and 105 (67%) completed the detailed family history questionnaire (given by phone) and the epidemiology questionnaire (given by in-person interview).

Of the 160 cases aged 35 to 39 at diagnosis, 2 (1%) could not be reached due to physician-reported contraindications and 5 (3%) were deceased. Of the 135 (84%) who completed a brief telephone screening interview on personal and family cancer history, 30 cases meeting any of the following inclusion criteria were selected: bilateral breast cancer; previous diagnosis of ovarian or childhood cancer; one or more first-degree relatives with breast, ovarian, or childhood cancer. An additional 4 cases were selected by a random sampling of 5% of those cases not meeting any of the above criteria. Of these 34 selected cases aged 35 to 39 at diagnosis, 29 (85%) completed the detailed family history and epidemiology questionnaires.

Ontario, Canada. A total of 1,119 cases of invasive breast cancer diagnosed from 1996 to 1998 in women before age 40 years were identified through the cancer registry covering the population of the province of Ontario (10). Of these, 20 (2%) patients were deceased at the time the physician was contacted and physicians refused permission to contact 81 (7%) patients.

Information on personal and family cancer history was obtained by mailed questionnaires from 646 (58%) cases. Of these, 394 cases meeting any of the following inclusion criteria were selected: Ashkenazi Jewish; diagnosis before age 36 years; previous diagnosis of breast or ovarian cancer; at least one first- or two second-degree relatives with breast or ovarian cancer; at least one second- or third-degree relative with breast cancer diagnosed before age 36 years, ovarian cancer diagnosed before age 61 years, multiple breast cancer primaries, both breast and ovarian cancer, or male breast cancer; at least three first-degree relatives with any combination of breast, ovarian, colon, prostate, or pancreatic cancer or sarcoma, with at least one diagnosis before age 51 years. Two hundred and ninety-two (74%) of these were selected based on age at diagnosis only. In addition, a random sample of 61 (24%) cases not meeting any of the above criteria was selected from those aged 36 to 39 at diagnosis. Of the 455 cases selected, 313 (69%) returned the mailed epidemiology questionnaire, of whom 278 were Caucasian.

Melbourne and Sydney, Australia. A total of 1,208 cases of invasive breast cancer diagnosed from 1992 to 1998 before the age of 40 years in women living in metropolitan Melbourne and Sydney were identified through the Victorian and New

South Wales cancer registries. All cases were included independent of family history (9, 11). The treating doctor either did not reply for, or refused permission to contact, 112 (9%) cases, 19 (2%) were deceased, and 856 (71%) completed the family history and epidemiology questionnaires by in-person interview, of whom 744 were Caucasian.

Controls

San Francisco, California. Controls were identified by random-digit dialing of telephone numbers in the catchment area from 1999 to 2001. Of 124 eligible Caucasian controls under age 40 selected at random from those identified, 88 (71%) completed a telephone screening interview and 86 (69%) completed the both the family history questionnaire (given by phone) and the epidemiology questionnaire (given by in-person interview), including 80 who were <39 years old at interview.

Ontario, Canada. Controls up to age 69 were identified by random sampling of listed residential telephone numbers for the province of Ontario from 1998 to 2000 (12). Of 504 eligible controls <40 years old selected at random from those identified, 353 (70%) returned the mailed family history and epidemiology questionnaires. Of these, 290 were eligible Caucasians, ages <39 years old at questionnaire completion.

Melbourne and Sydney, Australia. Controls were identified by random sampling from the electoral rolls (electoral registration is compulsory) for the metropolitan areas of Melbourne and Sydney from 1992 to 1999 (9). Of 913 controls sampled, 600 (66%) completed the family history and epidemiology questionnaires by in-person interview. Of these, 445 were eligible Caucasians, ages <39 years old at interview.

Questionnaires. The family history and epidemiology questionnaires that were developed for the Australian Breast Cancer Family Registry (9) and revised and adopted by the Breast Cancer Family Registry (13) were used by all three registries to elicit information on established and suspected risk factors. With respect to oral contraceptive use, these included questions about ever use, age at first use, age at last use, and total duration of use. Questions about most exposures were asked up until 1 year before diagnosis for cases, and up until time of questionnaire completion for controls.

BRCA1 and BRCA2 Mutation Testing. Testing for germ line mutations in *BRCA1* and *BRCA2* for cases was performed and validated by collaborating laboratories at each site (14). For the purpose of this study, a mutation was defined as a protein-truncating or missense mutation classified as deleterious by the Breast Cancer Information Core (15). Controls were not tested for these mutations.

San Francisco, California. Mutation testing was performed using several methods, including two-dimensional gene scanning (16, 17), sequencing by Myriad Genetics (18), and high-throughput heteroduplex detection, a combination of heteroduplex detection (19) and conformation specific gel electrophoresis (20, 21) in which samples are analyzed in a highly multiplexed fashion.

Ontario, Canada. Mutation testing was performed using a protein truncation test covering the complete coding sequence of both genes, as described previously (22, 23). Individuals of Ashkenazi Jewish heritage were initially tested for the three common founder mutations and further testing was conducted only if no founder mutation was found.

Melbourne and Sydney, Australia. Mutation testing was performed on all DNA samples to detect the Ashkenazi founder mutations, protein-truncating mutations (via a DNA-based protein truncation test as described in Hopper et al. (24), and the duplication of exon 13 of *BRCA1* (25). DNA samples from women with two or more first- or second-degree relatives

Table 1. Characteristics of Caucasian women by case-control status and *BRCA1* and *BRCA2* mutation carrier status

	Cases			
	Controls (n = 815) n (%)	<i>BRCA1</i> (n = 47) n (%)	<i>BRCA2</i> (n = 36) n (%)	Noncarriers (n = 1,073)* n (%)
Study location period				
Melbourne and Sydney, 1992-1995	303 (37)	11 (23)	10 (28)	374 (35)
Melbourne and Sydney, 1996-1999	142 (17)	14 (30)	8 (22)	327 (30)
Ontario, 1996-1998	290 (36)	14 (30)	13 (36)	251 (23)
San Francisco, 1995-1998	80 (10)	8 (17)	5 (14)	121 (11)
Reference age (y)				
<30	135 (17)	9 (19)	7 (19)	137 (13)
30-34	276 (34)	20 (43)	14 (39)	448 (42)
35-38	404 (50)	18 (38)	15 (42)	488 (45)
Year of birth				
<1960	172 (21)	19 (40)	13 (36)	492 (46)
1960-1964	359 (44)	15 (32)	14 (39)	427 (40)
≥1965	283 (35)	13 (28)	9 (25)	154 (14)
College graduate	282 (35)	19 (40)	9 (25)	281 (26)
Ever married	660 (81)	39 (83)	28 (78)	941 (88)
Family history [†]	33 (4)	21 (45)	14 (39)	115 (11)
Parous	530 (65)	30 (64)	27 (75)	734 (68)

*Includes 794 cases who tested negative for mutations in both *BRCA1* and *BRCA2*, 18 who tested negative for mutations in one of these genes but were not tested for mutations in the other gene, and 261 who were not tested for mutations in either gene.

[†] Reported history of breast cancer in a first-degree relative; among cases ages 35 to 39, those with a family history were oversampled in San Francisco and Ontario (see Materials and Methods).

affected with breast or ovarian cancer had the coding and flanking intronic regions of *BRCA1* and *BRCA2* sequenced (in-house or by Myriad Genetics). Another randomly selected group of 91 cases was also screened for *BRCA1* mutations via manual sequencing (26).

Statistical Analysis. All exposure variables were truncated at a reference age, defined for cases as age at 1 year before diagnosis of breast cancer and for controls as the age at completion of the epidemiology questionnaire. Oral contraceptive use was defined as use for at least 1 year to reduce contamination of the exposed group due to trivial oral contraceptive use. Unconditional multivariate logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) comparing controls with the three case groups: *BRCA1* mutation carriers, *BRCA2* mutation carriers, and all other cases (referred to as noncarriers). Four sets of analyses were conducted: (a) pooling data from each location/period and fitting effects for potential confounders, (b) stratifying by location/period, (c) stratifying by family history, and (d) stratifying by parity. To adjust for potential confounding, the following covariates were included: location/period (San Francisco, 1995-1998; Ontario, 1995-1998; Australia, 1992-1995; Australia, 1996-1998), reference age (deciles), reported breast cancer in a first-degree relative (yes, no), education (three levels), marital status (ever, never married), born in the country in which the study was conducted (yes, no), age at menarche (<12, 12, 13, ≥14 years), and parity (0, 1, 2, ≥3 full-term pregnancies). These covariates were chosen because they were associated with breast cancer risk in univariate analyses and/or are established risk factors for breast cancer in young women. Year of birth (quintiles) and alternative definitions of family history (any reported breast cancer in a first-degree relative, any reported breast cancer in a second-degree relative, any reported breast cancer in any relative, any reported ovarian cancer in a first-degree relative, any reported ovarian cancer in any relative, any reported breast or ovarian cancer in

any relative, any reported cancer of any type in any relative) were also considered as potential confounders. Pearson's χ^2 test was used to test the assumption that case groups and controls were sampled from populations with equal distributions of demographic characteristics and potential risk factors. *P* values for OR estimates were calculated using the likelihood ratio test. All statistical analyses were done using Stata 8.0 (27) and all statistical tests were two-tailed.

Results

Analyses were based on 1,156 cases (134 from San Francisco, 278 from Ontario, and 744 from Australia) and 815 controls (80 from San Francisco, 290 from Ontario, and 445 from Australia). DNA samples were available for 982 cases (85%), of which 875 (89%) were tested for mutations in both genes, identifying 47 *BRCA1* mutation carriers and 36 *BRCA2* mutation carriers.

Cases differed from controls by study location/period, reference age, year of birth, education, marital status, and family history (all $P \leq 0.001$; Table 1). Controls were more likely to be born in the country where the study was conducted (87% for controls versus 79% for cases, $P < 0.001$). There was no evidence that cases and controls differed by parity ($P = 0.3$). In cases, a greater proportion of *BRCA1* and *BRCA2* mutation carriers reported having at least one first-degree relative affected with breast cancer.

The overall proportion of women who used oral contraceptives for 1 year or more was 66% (SE, 7%) in *BRCA1* mutation carrier cases, 86% (SE, 6%) in *BRCA2* mutation carrier cases, 86% (SE, 1%) in other (noncarrier) cases, and 86% (SE, 1%) in controls (Table 2). The pattern of similar proportions for *BRCA2* mutation carriers, noncarriers, and controls and a lower proportion for *BRCA1* mutation carriers was evident for each study location/period (Table 3). After adjusting for study location/period, reference age, family history, education, marital status, country of birth, age at menarche, and number of full-term pregnancies, there was no evidence that oral contraceptive use was associated with an increase in breast cancer risk, either in carriers, noncarriers, or combined, within any study location/period or when the data were pooled. The inclusion of year of birth as a covariate did not substantially alter OR estimates for any analyses and because it was highly correlated with reference age, year of birth was not included in the final models. Further analyses (not shown) showed that this finding was not changed by including interaction terms for reference age by location/period, family history by location/period, education by location/period, or country of birth by location/period.

For *BRCA1* mutation carriers, use of oral contraceptives for at least 1 year was associated with a decreased risk of breast cancer (OR, 0.22; 95% CI, 0.10-0.49; $P < 0.001$), and this effect was different from that for both noncarriers ($P = 0.009$) and *BRCA2* carriers ($P = 0.04$; Table 2). Comparison with the crude OR estimates indicated that these effects had not been greatly changed by the adjustment for potential confounders, including family history and parity. The age-adjusted odds ratio estimates were all less than unity for each study location/period, although none was statistically significant (Table 3). Both overall, and for groups defined by mutation status, there was no evidence of a dose-response relationship with duration of use, nor of an association with age at first use or time since last use (Table 2).

There was an increased risk for those who had used oral contraceptives during or before 1975. This was evident in all case subgroups, although statistically significant only for noncarriers (Table 2) and when the data were pooled (data not shown). For noncarriers there was a dose-response (OR, 1.52 per year of use during or before 1975; 95% CI, 1.21-1.90; $P < 0.001$). Oral contraceptive use only after 1975 was associated with a small and marginally significant reduced risk for noncarriers (OR, 0.74; 95% CI, 0.55-0.99; $P = 0.05$) and with a

Table 2. Risk of invasive breast cancer associated with oral contraceptive use, by *BRCA1* and *BRCA2* mutation carrier status

	Cases						
	Controls (n = 815)	Mutation carriers				Noncarriers (n = 1,073)*	OR (95% CI) [†]
		<i>BRCA1</i> (n = 47)		<i>BRCA2</i> (n = 36)			
	n (%)	OR (95% CI) [†]	n (%)	OR (95% CI) [†]	n (%)	OR (95% CI) [†]	
Oral contraceptive use							
No [‡]	110 (14)	1.00 (—)	5 (14)	1.00 (—)	152 (14)	1.00 (—)	
Yes	701 (86)	0.22 (0.10-0.49)	31 (86)	1.02 (0.34-3.09)	920 (86)	0.93 (0.69-1.24)	
Duration of use (y)							
<1 or none	110 (14)	1.00 (—)	5 (14)	1.00 (—)	152 (14)	1.00 (—)	
1-4	196 (24)	0.25 (0.09-0.70)	8 (22)	0.97 (0.26-3.56)	202 (19)	0.76 (0.54-1.07)	
5-9	256 (32)	0.22 (0.09-0.58)	14 (39)	1.34 (0.41-4.45)	337 (32)	0.97 (0.70-1.34)	
≥10	248 (31)	0.20 (0.08-0.54)	9 (25)	0.73 (0.20-2.65)	378 (35)	1.02 (0.74-1.41)	
Age at first use (y)							
Nonuser [‡]	110 (14)	1.00 (—)	5 (14)	1.00 (—)	152 (14)	1.00 (—)	
<20	461 (66)	0.26 (0.11-0.62)	26 (84)	1.40 (0.44-4.25)	652 (71)	1.01 (0.75-1.37)	
≥20	240 (34)	0.16 (0.06-0.46)	5 (16)	0.40 (0.10-1.71)	267 (29)	0.76 (0.55-1.06)	
Time since last use (y)							
Nonuser [‡]	110 (14)	1.00 (—)	5 (14)	1.00 (—)	152 (14)	1.00 (—)	
<5	410 (51)	0.16 (0.07-0.40)	10 (29)	0.43 (0.12-1.53)	510 (50)	0.85 (0.63-1.16)	
5-9	148 (18)	0.38 (0.14-1.06)	13 (37)	2.80 (0.77-10.2)	200 (19)	0.96 (0.67-1.36)	
≥10	143 (18)	0.32 (0.09-1.10)	7 (20)	2.01 (0.47-8.60)	166 (16)	0.91 (0.63-1.31)	
Year of first use							
Nonuser [‡]	110 (14)	1.00 (—)	5 (14)	1.00 (—)	152 (14)	1.00 (—)	
≤1975	77 (9)	1.72 (0.41-7.23)	6 (17)	4.18 (0.80-21.9)	228 (21)	3.10 (2.01-4.61)	
>1975	624 (77)	0.18 (0.08-0.42)	25 (69)	0.92 (0.30-2.84)	691 (65)	0.74 (0.55-0.99)	

*Includes 794 cases who tested negative for mutations in both *BRCA1* and *BRCA2*, 18 who tested negative for mutations in one of these genes but were not tested for mutations in the other gene, and 261 who were not tested for mutations in either gene.

[†]OR (adjusted for study location/period, reference age, family history, education, marital status, country of birth, age at menarche, and number of full-term pregnancies) and corresponding 95% CI.

[‡]Never used oral contraceptives or used for <1 year.

different ($P = 0.006$) and substantially reduced risk for *BRCA1* mutation carriers (OR, 0.18; 95% CI, 0.08-0.42; $P < 0.001$). These findings were observed independently of year of birth. Corresponding OR estimates when year of birth was also included in the models were 1.73 (95% CI, 1.35-2.23) per year of use during or before 1975 for noncarriers, 0.89 (95% CI, 0.60-1.31) for any use after 1975 for noncarriers, and 0.25 (95% CI, 0.08-0.79) for use after 1975 in *BRCA1* mutation carriers.

The age-adjusted associations between oral contraceptive use and breast cancer were no different for parous versus

nonparous women nor did they differ between women with, versus women without, a family history (Table 4). In particular, after adjusting for study location/period, age, education, marital status, country of birth, age at menarche, and number of full-term pregnancies, *BRCA1* mutation carriers with no affected first-degree relatives were at decreased risk for first use after 1975 (OR, 0.13; 95% CI, 0.05-0.34; $P < 0.001$). Adjustment for family history, by all definitions considered, made no substantive difference to any results. For *BRCA1* carriers the OR estimates for ever use remained within the range of 0.2 to 0.3

Table 3. Age-adjusted risk of invasive breast cancer associated with oral contraceptive use for at least 12 months, by *BRCA1* and *BRCA2* mutation carrier status and study location/period

	Cases						
	Controls (n = 815)	Mutation carriers				Noncarriers (n = 1,073)*	OR (95% CI) [†]
		<i>BRCA1</i> (n = 47)		<i>BRCA2</i> (n = 36)			
	n (%)	OR (95% CI) [†]	n (%)	OR (95% CI) [†]	n (%)	OR (95% CI) [†]	
Oral contraceptive use[‡]							
Melbourne and Sydney, 1992-1995							
No	36 (12)	1.00 (—)	1 (10)	1.00 (—)	40 (11)	1.00 (—)	
Yes	267 (88)	0.54 (0.11-2.69)	9 (90)	1.16 (0.14-9.81)	334 (89)	1.12 (0.69-1.82)	
Melbourne and Sydney, 1996-1999							
No	25 (18)	1.00 (—)	1 (13)	1.00 (—)	38 (12)	1.00 (—)	
Yes	117 (82)	0.37 (0.11-1.24)	7 (87)	1.63 (0.18-14.6)	289 (88)	1.33 (0.74-2.38)	
Ontario, 1996-1998							
No	35 (12)	1.00 (—)	2 (15)	1.00 (—)	35 (14)	1.00 (—)	
Yes	251 (88)	0.29 (0.09-0.95)	11 (85)	0.69 (0.14-3.37)	215 (86)	0.83 (0.49-1.39)	
San Francisco, 1995-1998							
No	14 (18)	1.00 (—)	1 (20)	1.00 (—)	39 (32)	1.00 (—)	
Yes	66 (82)	0.27 (0.06-1.32)	4 (80)	1.06 (0.10-11.5)	82 (68)	0.46 (0.22-0.95)	

*Includes 794 cases who tested negative for mutations in both *BRCA1* and *BRCA2*, 18 who tested negative for mutations in one of these genes but were not tested for mutations in the other gene, and 261 who were not tested for mutations in either gene.

[†]Age-adjusted OR and corresponding 95% CI; for analyses for *BRCA1* and *BRCA2* mutation carriers categories of reference age were collapsed so that at least one case was included in each category.

[‡]Use for at least 1 year.

Table 4. Risk of invasive breast cancer associated with year of first use of oral contraceptives, by *BRCA1* and *BRCA2* mutation carrier status, first-degree family history of breast cancer, and parity

	Cases						
	Controls (n = 815)	Mutation carriers				Noncarriers (n = 1,073)*	
		<i>BRCA1</i> (n = 47)		<i>BRCA2</i> (n = 36)		n (%)	OR (95% CI) [†]
n (%)	OR (95% CI) [†]	n (%)	OR (95% CI) [†]				
Year first used oral contraceptives							
Women with no affected first-degree relatives							
Nonuser [‡]	106 (14)	11 (42)	1.00 (—)	2 (9)	1.00 (—)	127 (13)	1.00 (—)
≤1975	73 (9)	5 (19)	1.61 (0.43-6.05)	3 (14)	3.07 (0.46-20.5)	202 (21)	3.23 (2.10-4.96)
>1975	595 (77)	10 (38)	0.16 (0.06-0.39)	17 (77)	1.34 (0.30-5.93)	627 (66)	0.79 (0.58-1.08)
Women with an affected first-degree relative							
Nonuser [‡]	4 (12)	5 (24)	1.00 (—)	3 (21)	1.00 (—)	24 (21)	1.00 (—)
≤1975	4 (12)	1 (5)	0.22 (0.01-3.94)	3 (21)	2.08 (0.15-29.6)	26 (23)	1.37 (0.21-8.71)
>1975	25 (76)	15 (71)	0.42 (0.08-2.10)	8 (57)	0.49 (0.07-3.62)	64 (56)	0.25 (0.06-0.99)
Nulliparous women							
Nonuser [‡]	51 (18)	8 (47)	1.00 (—)	3 (33)	1.00 (—)	53 (16)	1.00 (—)
1975	15 (5)	0 (0)	—	2 (22)	2.81 (0.28-27.7)	48 (14)	3.99 (1.73-9.17)
>1975	219 (77)	9 (53)	0.27 (0.10-0.76)	4 (44)	0.20 (0.04-1.01)	237 (70)	0.97 (0.60-1.57)
Parous women							
Nonuser [‡]	59 (11)	8 (27)	1.00 (—)	2 (7)	1.00 (—)	99 (14)	1.00 (—)
≤1975	62 (12)	6 (20)	0.88 (0.27-2.84)	4 (15)	2.52 (0.42-15.0)	180 (25)	2.40 (1.47-3.90)
>1975	405 (77)	16 (53)	0.27 (0.11-0.67)	21 (78)	1.46 (0.33-6.43)	454 (62)	0.60 (0.41-0.87)

*Includes 794 cases who tested negative for mutations in both *BRCA1* and *BRCA2*, 18 who tested negative for mutations in one of these genes but were not tested for mutations in the other gene, and 261 who were not tested for mutations in either gene.

[†]Age-adjusted OR and corresponding 95% CI; categories of age were collapsed where necessary so that at least one case was included in each category.

[‡]OR adjusted for study location/period, reference age (with categories collapsed where necessary so that at least one case was included in each category), family history (where appropriate), education, marital status, country of birth, age at menarche, and number of full-term pregnancies (where appropriate) and corresponding 95% CI.

[§]Never, or use for <1 year.

after adjustment for each of the following family history variables: any reported breast cancer in a first-degree relative, any reported breast cancer in a second-degree relative, any reported breast cancer in any relative, any reported ovarian cancer in a first-degree relative, any reported ovarian cancer in any relative, any reported breast or ovarian cancer in any relative, any reported cancer of any type in any relative. The same applied when we excluded probands with any reported family history of breast or ovarian cancer. Analyses were also repeated, excluding all women with reference age 34 to 38 years (some cases in this age group had been oversampled for family history in San Francisco and Ontario). Results were consistent with those reported above; the OR estimate associated with ever use for *BRCA1* carriers was 0.12 (95% CI, 0.04-0.38; $P < 0.001$).

These analyses were repeated after excluding 279 cases who had not been tested for mutations in both *BRCA1* and *BRCA2*, and there were no substantive differences in the estimated ORs for the noncarriers (e.g., oral contraceptive use for at least 1 year: OR, 1.04; 95% CI, 0.75-1.45, compared with OR, 0.93; 95% CI, 0.69-1.24; use during or before 1975: OR, 1.46 per year of use; 95% CI, 1.16-1.84, compared with OR, 1.52; 95% CI, 1.21-1.90; see Table 2).

All analyses were also repeated defining contraceptive users as those who reported any use (i.e., including use for <1 year), and there were no substantive differences in inference. In particular, the estimated OR for any oral contraceptive use was 0.30 (95% CI, 0.12-0.79) for *BRCA1* mutation carriers and 0.84 (95% CI, 0.59-1.20) for noncarriers. In noncarriers, the estimated OR by year of first use were 2.81 (95% CI, 1.77-4.46) and 0.70 (95% CI, 0.49-1.00) for first use during or before 1975 and for first use after 1975, respectively.

Discussion

This population-based study found that the use of high-dose formulations of oral contraceptives used before the mid 1970s was associated with increased risk of early-onset breast cancer.

There was no evidence, however, that use of *current* low-dose oral contraceptive formulations was associated with *increased* risk of breast cancer either for carriers or noncarriers of mutations in *BRCA1* or *BRCA2*. For *BRCA1* mutation carriers, the use of current oral contraceptives formulations for at least 1 year was associated with a substantially reduced risk that was highly statistically significant, and this association did not seem to depend on duration of use, time since last use, or age at first use.

In a previous study, the association between oral contraceptive use and breast cancer risk was assessed by a comprehensive meta-analysis of an estimated 90% of the relevant data worldwide collected up to the early 1990s (1). Many of the studies combined in the meta-analysis included subjects who took the high-dose oral contraceptive formulations available before the mid 1970s. A slightly elevated risk was found for women of all ages who either were current users or who had used oral contraceptives within the past 9 years. Analyses of different aspects of oral contraceptive use, after taking into account current and recent use, showed no independent associations for duration of use, age at first use, dose, or hormone type. Age-specific analyses suggested that risk was doubled for young women who had used oral contraceptives within the past 5 years and who were <20 years old at first use, and this effect on risk was less for cancers with a later age at diagnosis. The findings of the present study of a substantially increased risk of breast cancer before the age of 40 years in noncarriers who first used oral contraceptives during or before 1975, but no increased risk and perhaps even a decreased risk for first use post-1975, are not inconsistent with the meta-analysis. Of the studies published since the meta-analysis, one supported an increased risk from ever or recent oral contraceptive use in young women (28), driven by an 8-fold increased risk associated with use of preparations with high progestin content. None of the other studies found evidence for an association between oral contraceptive use and breast cancer (29-31).

We are aware of only two published studies on the relationship between oral contraceptive use and breast cancer risk for women known to carry a germ line mutation in *BRCA1* or *BRCA2*. A study of 1,311 case-control pairs of

living mutation carriers identified from multiple-case families (2) found a small increased breast cancer risk (OR, 1.2; 95% CI, 1.0-1.4; $P = 0.03$) for *BRCA1* mutation carriers who had ever used oral contraceptives. Interestingly, this effect was most evident for cases diagnosed before 1980 (OR, 2.0; 95% CI, 1.2-3.4; $P = 0.01$), and for those who first used oral contraceptives before 1975 (OR, 1.4; 95% CI, 1.2-2.8; $P < 0.001$). More than 50% of the cases who used oral contraceptives had first used them before 1975, so although the effect for those who only used oral contraceptives since 1975 was not reported, it must have been close to unity. This is supported by the observation that, whereas the average cumulative duration of use before 1975 was greater for cases than controls (1.2 years versus 0.9 years, respectively; $P = 0.003$), the average cumulative use after 1975 did not differ between cases and controls (2.7 years versus 2.6 years, respectively; $P = 0.7$). No effect was observed for *BRCA2* mutation carriers. As noted by Narod et al. (2), their use of prevalent rather than incident cases could have resulted in biased risk estimates if oral contraceptive use were associated with breast cancer survival. Specifically, if oral contraceptive use or some associated factor improves cancer survival then their estimates could have been biased upward.

A small population-based cases-only study of young Ashkenazi patients with breast cancer compared oral contraceptive use in 14 founder mutation carriers and 36 noncarriers (3) and suggested cautiously that long-term use before a first full-term pregnancy may be associated with a greater increased risk of breast cancer for mutation carriers than noncarriers. There was no difference between mutation carriers and noncarriers in the proportion of cases who used oral contraceptives for more than 12 months ($P = 0.2$).

In another study, the female relatives of women diagnosed with breast cancer in the 1950s were followed up in the early 1990s (6). The only evidence for an increased risk was for the sisters and daughters who used oral contraceptives before 1975, and this risk seemed to be greater for women with a stronger family history of breast cancer. None of the subjects had been tested for mutations in *BRCA1* or *BRCA2*, and it is likely that less than half of the women in that category would have been *BRCA1* and *BRCA2* mutation carriers (32).

One possible limitation of the present study is that some cases were not tested for mutations in both *BRCA1* and *BRCA2*, but this is unlikely to have influenced our major findings for noncarriers. Of the 1,156 cases, 877 (76%) were tested for mutations in both genes, identifying 83 mutation carriers (10%). Given that there was some preferential testing for those whose family history suggested they were more likely to be mutation carriers, in terms of selection for and extent of testing, we would predict that no more than 10%, or about 28 of the 279 "noncarrier" cases not tested for mutations in both genes, would carry unidentified mutations. That is, only 3% of the 1,073 noncarrier cases may have been misclassified. When we repeated our analyses omitting the cases not tested for mutations in both *BRCA1* and *BRCA2*, we found no substantive change in odds ratio estimates or inferences for noncarriers.

The major findings (increased risk associated with use during or before 1975, reduced risk in *BRCA1* mutation carriers for first use after 1975, no increased risk otherwise) were not influenced by definition of use (ever or at least 1 year). Although there were differences in the mode of administration of the questionnaire between, but not within, the four study location/periods, the major findings were consistent across these subgroups (see Table 3), and independent of year of birth.

A further possible limitation of the present study is that inferences for mutation carriers were made under the assumption that patterns of oral contraceptive use are similar in mutation carriers and noncarriers in the general population. Carrier status was unknown at the time of questionnaire completion. It is possible that women with a family history,

who are more likely to carry a germ line mutation in *BRCA1* or *BRCA2*, may also be less likely to use oral contraceptives. Contrary to popular belief, though, population-based mutation carrying cases do not typically have a strong family history of breast or ovarian cancer, at least not of the type seen in the families used by linkage studies to find *BRCA1* and *BRCA2* or in the families referred to genetics clinics who are considered eligible for mutation testing (33). In this study, as in others, less than half (21 of 47) of the women with a *BRCA1* mutation had a first-degree relative with breast cancer (Table 4).

For *BRCA1* mutation carriers, the protective effect associated with use of current formulations of oral contraceptives was observed for women with no first-degree family history (Table 4), and for women with no breast or ovarian cancer in any relative. Furthermore, the effects associated with oral contraceptive use were unchanged after adjustment for "family history" no matter what definition was used. The same results were seen when analyses were restricted to women with reference age <34 years, who had all been sampled irrespective of family history.

Similarly, it could be argued that parity confounds the observed effects with contraceptive use, but Table 4 shows that the effects for parous women are almost identical to those observed for nulliparous women. Table 2 shows crude numbers, from which crude OR estimates can be calculated and seen to be little different from the adjusted OR estimates. That is, adjustment for family history and parity did not substantially alter the OR estimates.

If our finding of a stronger protective effect of use of current formulations of oral contraceptives on breast cancer risk for *BRCA1* mutation carriers compared with *BRCA2* mutation carriers and noncarriers were true, it would be of substantial biological and clinical significance. It is known that the age-specific cumulative risks of breast cancer differ between *BRCA1* and *BRCA2* mutation carriers. A recent meta-analysis of breast and ovarian cancer risks for *BRCA1* and *BRCA2* mutation carriers, based on population-based studies of the female relatives of mutation-carrying incident cases of breast or ovarian cancer (33), found that the multiplicative effect on breast cancer risk associated with having a *BRCA1* mutation decreased with age (P for trend = 0.001) from >30-fold in women <40 years old to ~10-fold in women >60 years old. This estimate was derived from analysis of 289 mutation-carrying families. In contrast, the increased risk for women with a *BRCA2* mutation estimated from 221 families was on average ~11-fold and there was no evidence that it was higher at younger ages.

The observation that the effect on breast cancer risk for *BRCA1* mutation carriers, relative to noncarriers, decreases with age may reflect differences in the age-specific sensitivity of the breast to ovarian hormones in these genetically at-risk women. There is well-described epidemiologic, experimental, and clinical evidence that ovarian hormones play a major role in the development and progression of female hormone-dependent cancers. For example, cumulative exposure to ovarian hormones is associated with increased breast cancer risk (34), and postmenopausal women on hormone replacement therapy containing progestin have increased breast cancer risk (35). Oophorectomy confers protection against breast cancer in mutation carriers (36), demonstrating that exposure to ovarian hormones is required for at least part of the increased breast cancer risk for a woman with a mutation in *BRCA1*. The mechanisms of *BRCA1* interacting with ovarian hormone signaling pathways, however, are not known. *BRCA1* can inhibit transcriptional activity of estrogen receptor- α (37), but there is evidence that these *in vitro* findings are not applicable to the normal breast (38). There are no data on the sensitivity of the normal breast to the proliferative effects of the ovarian axis at different ages nor is the hormone sensitivity of the normal breast in *BRCA1* mutation carriers, compared with noncarriers, understood.

Oral contraceptive use is associated with altered circulating ovarian hormone levels that lead to inhibition of ovulation, and for women without a genetic predisposition it is associated with increased breast cell proliferation (39, 40). In the normal breast of women with a mutation in *BRCA1* or *BRCA2* there is a profound attenuation of estrogen-sensitive protein expression leading to reduced progesterone receptor levels by mechanisms that seem to differ between *BRCA1* and *BRCA2* mutation carriers (37). High progestin potency in oral contraceptives is associated with substantially increased risk of breast cancer (28). Therefore, the reduction in progesterone receptor expression in *BRCA1* mutation carriers (38) may result in reduced sensitivity to the proliferative effects of progestins derived from oral contraceptives and may provide a potential mechanism for the greater reduction in breast cancer risk for *BRCA1* mutation carriers.

In summary, this is the first, large, population-based study specifically addressing breast cancer risk in *BRCA1* and *BRCA2* mutation carriers and noncarriers. We found no evidence that use of current low-dose oral contraceptive formulations increases risk of early-onset breast cancer, regardless of *BRCA1* or *BRCA2* mutation status. Our data suggest that risk may be reduced substantially for *BRCA1* mutation carriers. This finding did not seem to be explained by potential confounding due to family history—it was clearly evident in women with no family history—nor by any differences in age or year of birth distribution between cases and controls. These findings need to be assessed by other similar studies. Given that current formulations of oral contraceptives may reduce, or at least not exacerbate, risk of ovarian cancer for mutation carriers (4, 5, 41), our data suggest they should not be contraindicated for women with germ line mutations in *BRCA1* or *BRCA2*.

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Oral Contraceptive Use and Risk of Early-Onset Breast Cancer in Carriers and Noncarriers of *BRCA1* and *BRCA2* Mutations

Roger L. Milne, Julia A. Knight, Esther M. John, et al.

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