ORIGINAL RESEARCH

Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers: an international cohort study

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BACKGROUND: Ovarian cancer risk in BRCA1 and BRCA2 mutation carriers has been shown to decrease with longer duration of oral contraceptive use. Although the effects of using oral contraceptives in the general population are well established (approximately 50% risk reduction in ovarian cancer), the estimated risk reduction in mutation carriers is much less precise because of potential bias and small sample sizes. In addition, only a few studies on oral contraceptive use have examined the associations of duration of use, time since last use, starting age, and mutation carriers: an international cohort study.

OBJECTIVE: This study aimed to investigate in more detail the associations of various characteristics of oral contraceptive use and risk of ovarian cancer, to provide healthcare providers and carriers with better risk estimates.

STUDY DESIGN: In this international retrospective study, ovarian cancer risk associations were assessed using oral contraceptives data on 3989 BRCA1 and 2445 BRCA2 mutation carriers. Age-dependent—weighted Cox regression analyses were stratified by study and birth cohort and included breast cancer diagnosis as a covariate. To minimize survival bias, analyses were left truncated at 5 years before baseline questionnaire. Separate analyses were conducted for each aspect of oral contraceptive use and in a multivariate analysis, including all these aspects. In addition, the analysis of duration of oral contraceptive use was stratified by recency of use.

RESULTS: Oral contraceptives were less often used by mutation carriers who were diagnosed with ovarian cancer (ever use: 58.6% for BRCA1 and 53.5% BRCA2) than by unaffected carriers (ever use: 88.9% for BRCA1 and 80.7% for BRCA2). The median duration of use was 7 years for both BRCA1 and BRCA2 carriers who developed ovarian cancer and 9 and 8 years for unaffected BRCA1 and BRCA2 carriers with ovarian cancer, respectively. For BRCA1 mutation carriers, univariate analyses have shown that both a longer duration of oral contraceptive use and more recent oral contraceptive use were associated with a reduction in the risk of ovarian cancer. However, in multivariate analyses, including duration of use, age at first use, and time since last use, duration of oral contraceptive use proved to be the prominent protective factor (compared with <5 years: 5—9 years [hazard ratio, 0.67; 95% confidence interval, 0.40—1.12]; >10 years [hazard ratio, 0.37; 95% confidence interval, 0.19—0.73]; $P_{\text{trend}}=.008$). The inverse association between duration of use and ovarian cancer risk persisted for more than 15 years (duration of >10 years: BRCA1 <15 years since last use [hazard ratio, 0.24; 95% confidence interval, 0.14—0.43]; BRCA1 >15 years since last use [hazard ratio, 0.56; 95% confidence interval, 0.18—0.59]). Univariate results for BRCA2 mutation carriers were similar but were inconclusive because of limited sample size.

CONCLUSION: For BRCA1 mutation carriers, longer duration of oral contraceptive use is associated with a greater reduction in ovarian cancer risk, and the protection is long term.

Key words: BRCA1, BRCA2, epidemiology, multivariate, observational, oral contraceptives, ovarian cancer, retrospective, risk, survival bias.

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reduction in mutation carriers is much less certain and precise because of potential bias and small sample sizes. All previous studies were retrospective and therefore susceptible to survival bias. Only 1 study, as a sensitivity analysis, minimized potential survival bias by restricting the analyses to person-years within the 3 years before study enrollment.6 So far, almost all previous BRCA1 and BRCA2 mutation carrier studies restricted analyses to risk of ovarian cancer and duration of use of oral contraceptives.

To provide carriers with better risk estimates, we wanted to investigate in more detail the association between oral contraceptive use and risk of ovarian cancer. We used retrospective data from the International BRCA1/2 Carrier Cohort Study (IBCCS). Here, we were able to mutually adjust for multiple characteristics of oral contraceptive use to better understand their associations with ovarian cancer risk. To minimize the potential for survival bias, we used a left-truncated approach and conducted full-cohort retrospective analyses (ie, without left truncation) for comparison with the literature.

Materials and Methods

Study group

The IBCCS is a collaborative European study of women carrying a pathogenic or likely pathogenic germline mutation in BRCA1 or BRCA2. Women were eligible if they were between 18 and 80 years of age at recruitment. More than two-thirds of participants were enrolled to 1 of the 3 large ongoing nationwide studies in the United Kingdom and Ireland (Epidemiologic Study of Familial Breast Cancer), France (Gene Etude Prospective Sein Ovaire), and the Netherlands (Hereditary Breast and Ovarian Cancer Research, Netherlands).7 For the current analyses, women with both BRCA1 and BRCA2 mutations were excluded. In addition, women born before 1920 were excluded, because their reproductive years preceded the availability of oral contraceptives.

Data collection

A baseline questionnaire elicited detailed information on known or suspected risk factors for breast and ovarian cancer. Data on preventive surgeries and cancer occurrence were collected from medical records or linkages to cancer and pathology registries (75%) or questionnaires (25%). Participants provided written informed consent, and each study was approved by the relevant institutional ethical committee.

Key findings

For BRCA1 mutation carriers, longer duration of oral contraceptive use is associated with a reduction in ovarian cancer risk, and the protection is long term. Findings for BRCA2 mutation carriers were similar but less definitive given the smaller sample size.

What does this add to what is known?

To date, most studies have examined the association of duration of oral contraceptive use with risk of ovarian cancer, without taking other characteristics of oral contraceptive use into account. For BRCA1 mutation carriers, we have shown that the duration of oral contraceptive use is indeed more important than recency of use or starting age. Moreover, the strong protective effect of long duration of oral contraceptive use persists for a long period. Current results are based on a relatively large sample of BRCA1 and BRCA2 mutation carriers and corrected for potential testing and survival biases.

Why was this study conducted?

The use of combined oral contraceptives is a strong protective factor for ovarian cancer and has been suggested as chemoprevention for BRCA1 and BRCA2 mutation carriers. Previous studies on oral contraceptive use were limited in sample size, and other than duration of use, only a few studies have examined the other characteristics of oral contraceptive use.

Statistical analysis

To estimate hazard ratios (HRs), time-dependent Cox proportional hazards regression models with age as the time-scale were used, stratified for birth cohort and study. To reduce the possible impact of survival bias, analyses were left truncated, restricting the analyses to person-years within 5 years before study enrollment (age at baseline questionnaire). This implies that we started follow-up 5 years before baseline, with women at risk of developing ovarian cancer (so at least 1 ovary in situ: BRCA1 [n=3989] and BRCA2 [n=2445]). For those, who were diagnosed with ovarian cancer during the next 5 years, the mean survival was 3.2 years for BRCA1 mutation carriers and 2.9 years for BRCA2 mutation carriers, ranging from 0 to 5 years. Person-years were calculated up to the diagnosis of ovarian cancer (event of interest), diagnosis of another cancer (with the exception of breast cancer and nonmelanoma skin cancer), risk-reducing salpingo-oophorectomy (RRSO), mutation testing, or baseline questionnaire completion, whichever came first. Because of the retrospective nature of the study and because only person-years before DNA test was included, women were not aware of their mutation during the ages, the person-years, included for analysis. Breast cancer diagnosis was included as a time-dependent covariate. To correct for the potential testing bias, analyses were performed using the extended weighted regression approach described by Antoniou et al.8,9 Cancer cases are more often genetically tested on unaffected women. Therefore, the cancer incidence in a retrospective cohort of mutation carriers is overestimated, and the estimated HRs are underestimated. To correct for this testing bias, ovarian and breast cancer cases and unaffected women were weighted differentially to ensure that age-specific incidence rates implied by

AJOG at a Glance

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the weighted cohort were consistent with known incidence rates for women with a BRCA1 or BRCA2 mutation. Carriers who developed breast or ovarian cancer were underweighted (weights <1), and the unaffected carriers were overweighted (weights >1). In general, the unweighted HR estimates were closer to the null value than the weighted HRs, and the 95% CIs are narrower. For instance, forever vs never use unweighted HRs were 0.72 (95% CI, 0.58–0.90) for BRCA1 and 0.80 (95% CI, 0.55–1.17) for BRCA2 mutation carriers, compared with the weighted HRs of 51 (95% CI, 0.36–0.71) and 0.65 (95% CI, 0.35–1.19) for BRCA1 and BRCA2 mutation carriers.

The effect of familial clustering on estimates of precision was accounted for using robust variance estimation. Trend tests were based on modeling the category-specific mean as a continuous variable. We conducted a separate analysis for duration of use, time since last use, and starting age (ever use, and starting age) (Table 1). Oral contraceptive use was considered time-dependent covariates, compared for each year of observation.

None of the potential confounders (family history, parity number of pregnancies, and menopausal status) changed the HRs for oral contraceptive use and ovarian cancer risk by more than 10%, and therefore, they were excluded from the final models.

Sensitivity analyses were composed of the following: (1) stratified analyses (birth cohort, study, and attained age), (2) left-truncated analyses censored for breast cancer diagnosis, (3) multiple imputations for missing covariate data, and (4) multiple imputations with a random-effects Cox model approach, where we considered study site as a random term. Covariates were imputed 50 times in 5 iterations. Covariates were imputed with multivariate imputation by changed equations, using conditional multiple imputations that follow an iterative procedure. Furthermore, we conducted “full-cohort” retrospective analyses, where the analysis included person-years from birth instead of being left truncated.

All statistical tests were two-sided and a P value of <.05 was considered statistically significant. Trend tests were based on the P value for the continuous variable instead of being left truncated. Analyses were performed using Stata (version 13; StatataCorp, College Station, TX), except for the multiple imputations and mixed model sensitivity analyses for which R (version 4.0.2; R Foundation, Vienna, Austria) was used.

**Results**

In the left-truncated analyses of 3989 BRCA1 mutation carriers, 346 women (8.7%) were diagnosed with ovarian cancer at censoring (Table 1). Ovarian cancer cases completed their questionnaire on average 1.8 years (range, 0–5 years) after their ovarian cancer diagnosis. Of the 3642 BRCA1 mutation carriers (91.3%) who were unaffected by ovarian cancer, 2.4% were censored at age of RRSO. Of the 2445 BRCA2 mutation carriers, 106 women (4.3%) were diagnosed with ovarian cancer at censoring. BRCA2 ovarian cancer cases completed their questionnaire on average 2.1 years (range, 0–5 years) after their ovarian cancer diagnosis. Of the 2339 BRCA2 mutation carriers (95.6%) who were unaffected with ovarian cancer, 1.8% were censored at age of RRSO. For both BRCA1 and BRCA2 mutation carriers, compared with ovarian cancer cases, women unaffected with ovarian cancer were younger (BRCA1, 40.5 vs 51.7 years; BRCA2, 43.4 vs 56.9 years) and thus born more recently (birth year 1952–1980: 81.0% vs 43.4% for BRCA1 and 76.7% vs 29.3% for BRCA2). A relatively large proportion was diagnosed with breast cancer before the end of follow-up (BRCA1, 37.9% for those affected with ovarian cancer and 37.9% for those unaffected with ovarian cancer; BRCA2, 33.0% for those affected ovarian cancer and 37.7% for ovarian cancer unaffected).

Oral contraceptives were less often used by women who were diagnosed with ovarian cancer (ever use: 58.6% for BRCA1 and 53.5% for BRCA2) than by unaffected carriers (ever use:88.9% for BRCA1 and 80.7% for BRCA2) (Table 2). The median duration of use was 7 years for both BRCA1 and BRCA2 ovarian cancer cases (interquartile rage (IQR): 3–11 years for BRCA1 and 4–12 years for BRCA2) and 9 years (IQR, 5–13 years) and 8 years (IQR, 5–13 years) for BRCA1 and BRCA2 mutation carriers who were unaffected with ovarian cancer, respectively.

In univariate analyses, only 1 characteristic of oral contraceptive use was taken into account per analysis. Ever oral contraceptive use was associated with a reduction in the risk of ovarian cancer for BRCA1 mutation carriers (HR, 0.51; 95% CI, 0.36–0.71) (Table 2). For BRCA2 mutation carriers, the estimated HR for ever oral contraceptive use and ovarian cancer risk was comparable (HR, 0.65; 95% CI, 0.35–1.19) but not statistically significant. A longer duration of oral contraceptive use was associated with a stronger risk reduction for BRCA1 mutation carriers (HR, 0.92; 95% CI, 0.88–0.96; \( P_{\text{trend}}<0.001 \)): HR of 0.79 (95% CI, 0.53–1.19), 0.54 (95% CI, 0.35–0.85), and 0.32 (95% CI, 0.21–0.50) for durations of <5 years, 5–9 years, and >10 years, respectively. For BRCA2 mutation carriers, again HR estimates were in the same direction, but the associations were not significant (\( P_{\text{trend}}=0.45 \)). For both BRCA1 and BRCA2 mutation carriers, a strong protection was found during oral contraceptive use and within 10 years of oral contraceptive use (current use and <10 years ago \( \text{BRCA1 HR, 0.40 (95% CI, 0.22–0.71); BRCA2 HR, 0.36 (95% CI, 0.14–0.92)} \); 10–19 years ago \( \text{BRCA1 HR, 0.54 (95% CI, 0.36–0.82); BRCA2 HR, 0.58 (95% CI, 0.24–1.42)} \); ≥20 years ago \( \text{BRCA1 HR, 0.61 (95% CI, 0.43–0.87); BRCA2 HR, 0.78 (95% CI, 0.40–1.52)} \); trend \( \text{BRCA1, } P=0.025; \text{BRCA2, } P=0.26 \)). For BRCA1 mutation carriers, the association between ever use of oral contraceptives and risk of ovarian cancer did not show a clear trend according to age at first use of oral contraceptives (≤19 years \( \text{HR, 0.43 (95% CI, 0.28–0.65)} \); 20–23 years \( \text{HR, 0.51;} \text{}}
### TABLE 1
Characteristics of 3989 BRCA1 and 2445 BRCA2 mutation carriers in the left-truncated IBCCS cohort

| Characteristics                      | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------------|-------------------------|-------------------------|
|                                      | OvCa+ (n=3989)          | OvCa− (n=2445)          |
|                                      | n (%)                   | n (%)                   |
| n (%)                                | 346 (8.7)               | 3643 (91.3)             |
| Mean age at start of follow-up (SD), y | 48.4 (8.9)              | 36.4 (11.5)             |
| Mean age at end of follow-up (SD), y | 51.7 (8.9)              | 40.5 (11.4)             |

| Age at end of follow-up, y          | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------------|-------------------------|-------------------------|
|                                      | n (%)                   | n (%)                   |
| <37                                  | 14 (4.1)                | 1413 (38.8)             |
| 37—46                                | 89 (25.7)               | 1202 (33.0)             |
| >47                                  | 243 (70.2)              | 1028 (28.2)             |

| Mean person-years (y/person) (SD)    | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------------|-------------------------|-------------------------|
|                                      | n (%)                   | n (%)                   |
|                                       | 3.2 (1.2)               | 4.2 (1.2)               |

Censored for the following:

| Event                                | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------------|-------------------------|-------------------------|
| Ovarian cancer                       | 346 (100.0)             | 0 (0.0)                 |
| DNA test or baseline questionnaire   | 0 (0.0)                 | 3521 (96.6)             |
| Other cancer                         | 0 (0.0)                 | 41 (1.1)                |
| Bilateral RRSO                       | 0 (0.0)                 | 81 (2.2)                |

| Year at end of follow-up             | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------------|-------------------------|-------------------------|
|                                      | n (%)                   | n (%)                   |
| 1990—2000                            | 137 (39.6)              | 1122 (30.8)             |
| 2001—2005                            | 133 (38.4)              | 1354 (37.2)             |
| 2006—2012                            | 76 (22.0)               | 1167 (32.0)             |

| Birth year                            | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------------|-------------------------|-------------------------|
|                                      | n (%)                   | n (%)                   |
| 1920—1944                            | 87 (25.1)               | 292 (8.0)               |
| 1945—1951                            | 109 (31.5)              | 401 (11.0)              |
| 1952—1980                            | 150 (43.4)              | 2950 (81.0)             |

| Study™                               | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------------|-------------------------|-------------------------|
|                                      | n (%)                   | n (%)                   |
| EMBRACE                               | 129 (8.8)               | 1183 (90.2)             |
| GENEPSO                              | 64 (6.9)                | 865 (93.1)              |
| Other™                               | 153 (8.8)               | 1595 (91.3)             |

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| Characteristics | BRCA1 mutation carriers | BRCA2 mutation carriers |
|-----------------|------------------------|------------------------|
|                 | N=3989                 | N=2445                 |
| Breast cancer   |                        |                        |
| No              | 215 (62.4)             | 2255 (61.9)            |
| Yes             | 131 (37.9)             | 1388 (37.9)            |
| Number of ovarian cancers among first- and second-degree relatives | | |
| 0               | 132 (51.8)             | 1877 (64.0)            |
| 1               | 90 (35.3)              | 752 (25.6)             |
| ≥2              | 33 (12.9)              | 305 (10.4)             |
| Missing         | 91                     | 708                    |
| Cancer type unknown | 0                    | 27                     |

Data are presented as number (percentage), unless otherwise indicated.

BRCA, breast cancer; CNIO, Spanish National Cancer Center; DKFZ, German Consortium for Translational Cancer Research; EMBRACE, Epidemiological Study of Familial Breast Cancer; GC-HBDC, German Consortium of Hereditary Breast and Ovarian Cancer; GENEPSO, Gene Etude Prospective Sein Ovaire; HCSC, Health Care Service Corporation; HEBON, Hereditary Breast and Ovarian Cancer Research Group Netherlands; HSP, Henoch-Schönlein purpura; IBCCS, International Carrier Cohort Study; INHERIT, Interdisciplinary Health Research International Team on Breast Cancer susceptibility; MODSQUAD, Modifier Study of Quantitative Effects on Disease; MUV, Medical University of Vienna; NIO, National Institute of Oceanography; OvCa, ovarian cancer; RRso, risk-reducing salpingo-oophorectomy; SD, standard deviation.

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| Variable                        | BRCA1 mutation carriers | BRCA2 mutation carriers |
|--------------------------------|-------------------------|-------------------------|
|                                | OvCa +, n (%)          | OvCa −, n (%)          | Weighted,\(^{a,b}\) HR (95% CI)  |
| Oral contraceptive use        |                        |                        |                                  |
| Never (<6 mo)                  | 133 (41.4)             | 659 (19.1)             | 1.00                              |
| Ever                           | 188 (58.6)             | 2788 (88.9)            | 0.51 (0.36—0.71)                  |
| Ever, starting age unknown    | 11                     | 125                    | 4 (4.6)                           |
| Missing                        | 14                     | 71                     | 3                                  |
| Calendar year at start         |                        |                        |                                  |
| Never (<6 mo)                  | 133 (41.4)             | 659 (19.1)             | 1.00                              |
| ≤1975                          | 114 (35.5)             | 684 (19.8)             | 0.45 (0.33—0.62)                  |
| >1975                          | 74 (23.1)              | 2104 (61.0)            | 0.56 (0.35—0.88)                  |
| Ever, starting year unknown   | 11                     | 125                    | 4                                  |
| Missing                        | 14                     | 71                     | 3                                  |
| Total duration of use          |                        |                        |                                  |
| Never (<6 mo)                  | 133 (43.0)             | 659 (20.2)             | 1.00                              |
| <5 y                           | 67 (21.7)              | 616 (18.9)             | 0.79 (0.53—1.19)                  |
| 5—9 y                          | 53 (17.2)              | 867 (26.6)             | 0.54 (0.35—0.85)                  |
| ≥10 y                          | 56 (18.2)              | 1121 (34.4)            | 0.32 (0.21—0.50)                  |
| Ever, no period specific data | 23                     | 309                    | 6                                  |
| Missing                        | 14                     | 71                     | 3                                  |
| Trend                          | \(P = 2.0 \times 10^{-4}\) |                       | \(P = .449\)                      |
| Time since last use            |                        |                        |                                  |
| Never (<6 mo)                  | 133 (43.0)             | 659 (20.2)             | 1.00                              |
| <10 y                          | 29 (9.4)               | 1478 (45.3)            | 0.40 (0.22—0.71)                  |
| 10—19 y                        | 60 (19.4)              | 648 (19.9)             | 0.54 (0.36—0.82)                  |
| ≥20 y                          | 87 (28.2)              | 478 (14.7)             | 0.61 (0.43—0.87)                  |
| Ever, no period specific data | 23                     | 309                    | 6                                  |
| Missing                        | 14                     | 71                     | 3                                  |
| Trend                          | \(P = .025\)           |                       | \(P = .258\)                      |
TABLE 2
The oral contraceptive “univariate” association between aspects of oral contraceptive use and risk of ovarian cancer for 3989 BRCA1 and 2445 BRCA2 mutation carriers (continued)

| Variable | BRCA1 mutation carriers | BRCA2 mutation carriers |
|----------|-------------------------|-------------------------|
|          | OvCa+, n (%) | OvCa−, n (%) | Weighted, a, b HR (95% CI) | OvCa+, n (%) | OvCa−, n (%) | Weighted, a, b HR (95% CI) |
| Starting age |                      |                      |                      |                      |                      |                      |
| Never (<6 mo) | 133 (41.4) | 659 (19.1) | 1.00 | 46 (46.5) | 426 (19.3) | 1.00 |
| ≤19 y | 62 (19.3) | 1753 (50.9) | 0.43 (0.28–0.65) | 20 (20.2) | 1030 (46.7) | 1.02 (0.43–2.42) |
| 20–23 y | 58 (18.1) | 615 (17.8) | 0.51 (0.33–0.78) | 12 (12.1) | 461 (20.9) | 0.49 (0.20–1.23) |
| >23 y | 68 (21.2) | 420 (12.2) | 0.63 (0.41–0.97) | 21 (21.2) | 291 (13.2) | 0.60 (0.29–1.21) |
| Ever, starting age unknown | 11 | 125 | | 4 | 87 | |
| Missing | 14 | 71 | | 3 | 44 | |
| Trend | P = .154 | | | P = .114 | |

BRCA, breast cancer gene; CI, confidence interval; EMBRACE, Epidemiological Study of Familial Breast Cancer; GENEPSO, Gene Etude Prospective Sein Ovaire; HR, hazard ratio; OvCa, ovarian cancer.

a Weighted: to account for the oversampling of affected individuals (breast and ovarian cancer); b Unweighted results: never or ever use.

Table 1. How the difference in the effect size was not significant for both cohorts. Analyses stratified for birth cohort were limited to examine if this could be explained by recent use. Study-specific analyses (univariate, unweighted) suggested that the univariate associations were not significant.
TABLE 3
The associations of duration, recency, and starting use of oral contraceptives and risk of ovarian cancer for BRCA1 mutation carriers

| Variable                              | OvCa++, n (%) | OvCa–, n (%) | Oral contraceptive univariate, HR (95% CI) | Oral contraceptive multivariate, HR (95% CI) |
|---------------------------------------|---------------|--------------|------------------------------------------|-------------------------------------------|
| **Mutually adjusted**                 |               |              |                                          |                                           |
| Oral contraceptive never use         | 133 (43.0)    | 659 (20.2)   | 1.15 (0.40–3.34)                         |                                           |
| **Total duration of use, y**          |               |              |                                          |                                           |
| <5y                                   | 67 (21.7)     | 616 (18.9)   | 1.00                                     | 1.00                                      |
| 5–9y                                  | 53 (17.2)     | 867 (26.6)   | 0.69 (0.43–1.09)                         | 0.67 (0.40–1.12)                          |
| ≥10y                                  | 56 (18.2)     | 1121 (34.4)  | 0.40 (0.25–0.65)                         | 0.37 (0.19–0.73)                          |
| Trend                                 |               |              |                                          |                                           |
| **Time since last use, y**            |               |              |                                          |                                           |
| <10y                                  | 29 (9.4)      | 1478 (45.3)  | 1.00                                     | 1.00                                      |
| 10–19y                                | 60 (19.4)     | 648 (19.9)   | 1.35 (0.77–2.37)                         | 0.96 (0.50–1.83)                          |
| ≥20y                                  | 87 (28.2)     | 478 (14.7)   | 1.50 (0.85–2.66)                         | 0.79 (0.35–1.78)                          |
| Trend                                 |               |              |                                          |                                           |
| **Starting age, y**                   |               |              |                                          |                                           |
| ≤19y                                  | 58 (18.8)     | 1632 (50.0)  | 1.00                                     | 1.00                                      |
| 20–23y                                | 51 (16.5)     | 580 (17.8)   | 1.07 (0.68–1.70)                         | 0.98 (0.61–1.58)                          |
| >23y                                  | 67 (21.7)     | 392 (12.0)   | 1.51 (0.91–2.50)                         | 1.15 (0.65–2.04)                          |
| Trend                                 |               |              |                                          |                                           |
| **Stratified for recency of use**     |               |              |                                          |                                           |
| Never (<6 mo)                         | 133 (43.0)    | 659 (20.2)   | 1.00                                     |                                           |
| <15y since last use                   |               |              |                                          |                                           |
| <5y                                   | 10 (3.2)      | 288 (8.8)    | 1.21 (0.55–2.68)                         |                                           |
| 5–9y                                  | 16 (5.2)      | 580 (17.8)   | 0.61 (0.30–1.24)                         |                                           |
| ≥10y                                  | 25 (8.1)      | 956 (29.3)   | 0.24 (0.14–0.43)                         |                                           |
| Trend                                 |               |              |                                          |                                           |
| >15y since last use                   |               |              |                                          |                                           |
| <5y                                   | 57 (18.5)     | 328 (10.1)   | 0.72 (0.48–1.07)                         |                                           |
| 5–9y                                  | 37 (12.0)     | 287 (8.8)    | 0.47 (0.29–0.76)                         |                                           |
| ≥10y                                  | 31 (10.0)     | 165 (5.1)    | 0.56 (0.18–0.95)                         |                                           |
| Trend                                 |               |              |                                          |                                           |
| **Ever, starting age unknown**        | 23            | 309          |                                          |                                           |
| **Missing**                           | 14            | 71           |                                          |                                           |

BRCA, breast cancer gene; CI, confidence interval; EMBRACE, Epidemiological Study of Familial Breast Cancer; GENEPSO, Gene Etude Prospective Sein Ovaire; HR, hazard ratio; OvCa, ovarian cancer.

a Distribution of variables at end of follow-up; b Weighted: to account for the oversampling of affected individuals (breast and ovarian cancer); c Intrinsically stratified on study (EMBRACE, GENEPSO, other) and birth cohort (1920–1946, 1947–1954, 1955–1980). Clustered on family membership; d In addition: mutually adjusted for duration, time since, and age at start of oral contraceptive use; e Trend tests were based on the P value of the category-specific mean as a continuous variable of ever oral contraceptive users.

Schrijver et al. Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers. Am J Obstet Gynecol 2021.
The full-cohort approach included person-years from birth, adding 829 BRCA1 and 399 BRCA2 mutation carriers, where 209 and 68 of whom, respectively, were diagnosed with ovarian cancer. The average time between ovarian cancer diagnosis and enrollment was 5.4 years (range, 0–36 years) for BRCA1 and 5.8 years (range, 0–30 years) for BRCA2 mutation carriers (19% were enrolled >10 years following diagnosis). For both BRCA1 and BRCA2 mutation carriers, results of full-cohort analyses were consistent, but associations were slightly attenuated compared with those from left-truncated analyses (Supplemental Table 2 and Supplemental Table 3).

**Discussion**

**Principal findings**

Based on data for 3989 BRCA1 mutation carriers, we found a clear inverse association between oral contraceptive use and ovarian cancer risk. Whereas both a longer duration and more recent use of oral contraceptives showed greater inverse associations with ovarian cancer, duration of use was the prominent protective factor in multivariate analyses. The reduction with a longer duration of oral contraceptive use was still present more than 15 years after stopping. For BRCA2 mutation carriers (n=2445), the HR estimates were consistent, but CIs were wide.

**Results in the context what is already known**

To date, 4 retrospective studies have investigated the association between oral contraceptive use and ovarian cancer risk stratified by gene mutation, and only 1 conducted left-truncated analyses. The study of McLaughlin et al included a subset of the participants in Kotsopoulos et al and the study of Antoniou et al included a subset of the carriers included in this study. For both BRCA1 and BRCA2 mutation carriers, 2 independent studies have reported a stronger risk reduction with longer duration of use of oral contraceptives, but these authors did not consider other aspects of oral contraceptive use. Kotsopoulos et al found strong risk reductions after short durations of use for both BRCA1 and BRCA2 mutation carriers (BRCA1, 1–<3 years [odds ratio (OR), 0.56; 95% CI, 0.41–0.75]; BRCA2, 3–<5 years [OR, 0.42; 95% CI, 0.22–0.83]). In contrast, we found modest, not significant, risk reductions for less than 5 years of use (HR, 0.79 [95% CI, 0.53–1.19] and 0.87 [95% CI, 0.42–1.80], respectively). For BRCA2 mutation carriers, we found only a significantly reduced risk for a duration of 5 to 9.99 years, but there was no evidence for a trend (P=.45). With the exception of “ever use” and “duration of use,” the oral contraceptive aspects “age at start,” “calendar year at start,” and “time since last use” were investigated only by Antoniou et al, a subset of our study. The study of Antoniou et al included 2281 BRCA1 mutation carriers, 201 diagnosed with ovarian cancer, and 1038 BRCA2 mutation carriers, 52 diagnosed with ovarian cancer. In both analyses, we found decreasing risks of ovarian cancer with longer durations of oral contraceptive use and more recent oral contraceptive use for BRCA1 mutation carriers. However, in this study, after mutual adjustment of these related aspects of oral contraceptive use, only duration of use remained significantly associated with ovarian cancer risk. The power of the previous study was too limited to explore mutual adjustments.

In the general population, oral contraceptive use is associated with a reduced risk of ovarian cancer, and the reduction in risk of ovarian cancer is stronger for longer durations of oral contraceptive use. In addition, relative risks of ovarian cancer remained low for a prolonged period after stopping oral contraceptive use and only attenuated 20 years after stopping. In our BRCA1 analysis of duration of use within categories of recency of use, oral contraceptive–associated risk reductions persisted for a long period. Whether the risk reduction attenuated over time could not be confirmed for BRCA1 mutation carriers but was not ruled out. For BRCA2 mutation carriers, a similar analysis was not possible because of the small sample size.

**Clinical and research implications**

Although oral contraceptive use might be considered a preventive approach for developing ovarian cancer, its use in BRCA1 and BRCA2 mutation carriers needs to be weighed against the possible association of oral contraceptive use with increased risk of breast cancer. However, the inverse association with ovarian cancer is stronger than the possible positive association with breast cancer risk. The cumulative risk of breast cancer is 43% (95% CI, 39–49; BRCA1) and 35% (95% CI, 29–41; BRCA2) at age 50 years, when the cumulative of ovarian cancer is 8% (95% CI, 6–12; BRCA1) and 0% (95% CI, 0–2; BRCA2). Consequently, in the years before ovarian cancer incidence starts to rise for mutation carriers, the beneficial effect of oral contraceptive use on ovarian cancer risk will likely not outweigh the potential increased risk of oral contraceptive use on breast cancer risk. In addition, in many Western countries to date, most BRCA1 and BRCA2 carriers (70%–75%) opt for RRSO around age 40 years, when childbearing is completed; however, the uptake of a risk-reducing mastectomy is low (35%–44%) and varies widely among countries. In addition, further research on the absolute effects of the associations of oral contraceptive use with breast and ovarian cancer weighted with the current practice of risk-reducing surgery is needed.

**Strengths and limitations**

Limitations of retrospective studies in BRCA1/2 mutation carriers include the potential testing and survival biases because of the inclusion of prevalent cases. BRCA1 and BRCA2 mutation carriers tested in clinics were not randomly sampled with respect to their disease status. Generally, the first woman in the family who is tested has a personal history of breast or ovarian cancer. Most carriers were selected from high-risk families qualifying for genetic testing, resulting in an oversampling of women with breast and ovarian cancer. To correct for the potential testing bias, we used the extended weighted approach developed by Antoniou.
et al. in women who were differentially weighted according to whether they had breast or ovarian cancer or were unaffected, to ensure that age-specific incidence rates implied by the weighted cohort were consistent with known incidence rates for BRCA1 and BRCA2 mutation carriers. Because reliable weight calculations were impossible to obtain because of the subgroup sample size, subanalyses on birth cohort and study were unweighted. However, the results of unweighted analyses were informative, giving a direction for further research.

Survival bias might occur if oral contraceptive use is associated with survival after ovarian cancer diagnosis. Studies in the general population have suggested that oral contraceptive use before a diagnosis of ovarian cancer is associated with better outcomes. A meta-analysis has shown that the greatest difference in survival was associated with duration of use of oral contraceptives of over 5 years within the last 20 years of use. However, studies of BRCA1 and BRCA2 mutation carriers are lacking. If oral contraceptive use has a similar effect on ovarian cancer survival in BRCA1 and BRCA2 mutation carriers, HR estimates based on retrospective studies would be biased toward the null hypothesis of no association. Consistent with the results of our left-truncated analysis, associations between oral contraceptive use and ovarian cancer risk were somewhat stronger than the associations in the full-retrospective analyses for both BRCA1 and BRCA2 mutation carriers. Because the prognosis of ovarian cancer might be poor, a left truncation at 3 years would be even better. However, the number of ovarian cancer cases would drop from 346 to 245 for BRCA1 and from 106 to 64 for BRCA2.

Data on specific oral contraceptive formulation used were not available. Analyses stratified on calendar year of starting oral contraceptive use (HR estimates varied between 0.45 and 0.73) (Table 1) and study or country (HR estimates varied between 0.43 and 0.82) have shown comparable HRs among strata, with overlapping CIs.

A prospective analysis based on incident ovarian cancer cases after DNA testing would, in principle, eliminate testing and survival bias completely. However, such studies are challenging given the high uptake of RRSO after genetic testing. This results in a short duration of prospective follow-up and increased chance of informative censoring.

Conclusions

For BRCA1 mutation carriers, oral contraceptive use was associated with a reduction in ovarian cancer risk. The risk was more strongly reduced with longer durations of oral contraceptive use, and risk reductions persisted for a long period. The findings for BRCA2 mutation carriers were similar, but sample size was limited to make definitive conclusions.

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## SUPPLEMENTAL TABLE 1
The association between oral contraceptive use and risk of ovarian cancer, by attained age for 3989 BRCA1 mutation carriers

| Variable | Attained age of <50 y (n=3268) | Attained age of >50 y (n=958) |
|----------|-------------------------------|-------------------------------|
|          | OvCa+, n (%)<sup>a</sup> | OvCa-, n (%)<sup>a</sup> | HR (95% CI)<sup>b,c</sup> | OvCa+, n (%)<sup>c</sup> | OvCa-, n (%)<sup>c</sup> | HR (95% CI)<sup>b,c</sup> |
| n (%)    | 150 (4.6) | 3118 (95.4) |  | 196 (20.5) | 762 (79.5) |  |
| Mean age at end of follow-up (SD), y | 43.6 (4.6) | 37.3 (8.5) |  | 57.9 (5.9) | 57.2 (6.3) |  |

**Age at end of follow-up, y**

|       | <45 | 45—64 | >65 |
|-------|-----|-------|-----|
|       | 77  (51.3) | 2402 (77.0) | 0 (0.0) |
| 45—64 | 73  (48.7) | 716 (23.0) | 165 (84.2) |
| >65   | 0   (0.0) | 0 (0.0) | 31 (15.8) |

**Oral contraceptive use**

|               | Never (<6 mo) | Ever | Ever, starting age unknown | Missing | Trend<sup>d</sup> |
|---------------|---------------|------|---------------------------|---------|-----------------|
|               | 50 (34.7)     | 94   (65.3) | 0                        | 6       | P<0.0001        |
| <5 y          | 36 (25.7)     | 28   (20.0) | 0 (0.0)                  | 4       | P=2.8E-04       |
| 5—9 y         | 32 (22.0)     | 800  (82.5) | 0 (0.0)                  | 6       | P=.471          |
| ≥10 y         | 26 (18.6)     | 1013 (95.3) | 0 (0.0)                  | 6       |                 |
| Ever, no period specific data | 4 | 261 | 19 | 62 | |
| Missing       | 6 | 53 | 8 | 22 | |

|               | OvCa+, n (%)<sup>c</sup> | OvCa-, n (%)<sup>c</sup> | HR (95% CI)<sup>b,c</sup> |
|---------------|---------------------------|---------------------------|---------------------------|
| Never (<6 mo) | 83 (46.9)                 | 251 (35.9)                | 1.00                      |
| <5 y          | 31 (18.3)                 | 135 (19.9)                | 0.62 (0.38—1.02)          |
| 5—9 y         | 25 (14.8)                 | 119 (17.6)                | 0.77 (0.45—1.33)          |
| ≥10 y         | 30 (17.8)                 | 173 (25.5)                | 0.52 (0.31—0.86)          |
| Ever, no period specific data | 19 | 64 |  |  |
| Missing       | 8 | 22 |  |  |

Data are presented as number (percentage), unless otherwise indicated.

CI, confidence interval; EMBRACE, Epidemiological Study of Familial Breast Cancer; GENEPSO, Gene Etude Prospective Sein Ovaire; HR, hazard ratio; OvCa, ovarian cancer.

<sup>a</sup> Distribution of variables at end of follow-up; <sup>b</sup> Weighted: to account for the oversampling of affected individuals (breast and ovarian cancer); <sup>c</sup> Intrinsically stratified on study (EMBRACE, GENEPSO, other) and birth cohort (1920—1946, 1947—1954, 1955—1980). Clustered on family membership; <sup>d</sup> Trend tests were based on the P value of the category-specific mean as a continuous variable of ever oral contraceptive users.

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### SUPPLEMENTAL TABLE 2
Characteristics of 4818 **BRCA1** and 2844 **BRCA2** mutation carriers in the full-retrospective IBCCS

| Characteristic                        | BRCA1 mutation carriers | BRCA2 mutation carriers |
|---------------------------------------|-------------------------|-------------------------|
|                                       | OvCa+ | OvCa− | OvCa+ | OvCa− |
| n (%)                                 | n     | (%)   | n     | (%)   |
| Mean age at end of follow-up (SD)     | 50.2  | (8.8) | 40.6  | (11.1) |
| Age at end of follow-up               |       |       |       |       |
| <37 y                                 | 30 (5.4) | 1619 (38.0) | 7 (4.0) | 779 (29.2) |
| 37—46 y                               | 163 (29.4) | 1447 (33.9) | 22 (12.6) | 910 (34.1) |
| >47 y                                 | 362 (65.2) | 1197 (28.1) | 145 (83.3) | 981 (36.7) |
| Mean person-years (y/person) (SD)     | 50.2  | (8.8) | 40.6  | (11.1) |
| Censored for                          |       |       |       |       |
| Ovarian cancer                        | 555 (100.0) | 0 (0.0) | 174 (100.0) | 0 (0.0) |
| DNA test or baseline questionnaire    | 0 (0.0) | 3781 (88.7) | 0 (0.0) | 2357 (88.3) |
| Other cancer                          | 0 (0.0) | 165 (3.9) | 0 (0.0) | 127 (4.8) |
| Bilateral RRSO                        | 0 (0.0) | 317 (7.4) | 0 (0.0) | 186 (7.0) |
| Year at end of follow-up              |       |       |       |       |
| 1958—1989                             | 68 (12.3) | 121 (2.8) | 20 (11.5) | 86 (3.2) |
| 1990—2000                             | 257 (46.3) | 1500 (35.2) | 72 (41.4) | 554 (20.8) |
| 2001—2005                             | 152 (27.4) | 1472 (34.5) | 88 (42.9) | 1037 (38.8) |
| 2006—2012                             | 78 (14.1) | 1170 (27.5) | 62 (32.0) | 993 (37.2) |
| Birth year                            |       |       |       |       |
| 1920—1941                             | 143 (25.8) | 295 (6.9) | 79 (45.4) | 244 (9.1) |
| 1942—1950                             | 189 (34.1) | 579 (13.6) | 50 (28.7) | 417 (15.6) |
| 1951—1992                             | 223 (40.2) | 3389 (79.5) | 45 (25.9) | 2009 (75.2) |
| Studya                                |       |       |       |       |
| EMBRACE                                | 187 (12.0) | 1373 (88.0) | 90 (6.6) | 1265 (93.4) |
| GENEPSO                                | 99 (9.7) | 918 (90.3) | 23 (3.9) | 575 (96.2) |
| HEBON                                  | 61 (7.6) | 741 (92.4) | 21 (8.9) | 216 (91.1) |
| Otherb                                 | 208 (14.5) | 1231 (85.6) | 40 (6.1) | 614 (93.9) |
| Breast cancer                          |       |       |       |       |
| No                                     | 381 (68.7) | 2658 (62.4) | 127 (73.0) | 1685 (63.1) |
| Yes                                    | 174 (31.4) | 1605 (37.7) | 47 (27.0) | 985 (36.9) |

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**SUPPLEMENTAL TABLE 2**

Characteristics of 4818 *BRCA1* and 2844 *BRCA2* mutation carriers in the full-retrospective IBCCS (continued)

| Characteristic                              | *BRCA1* mutation carriers | *BRCA2* mutation carriers |
|---------------------------------------------|---------------------------|---------------------------|
|                                             | OvCa+ (n=4818)            | OvCa−                      | OvCa+ (n=2844)            | OvCa−                      |
| No ovarian cancer                           | 209 (49.6)                | 2143 (63.4)               | 86 (66.7)                 | 1571 (78.4)                |
| 1                                           | 148 (35.2)                | 884 (26.1)                | 31 (24.0)                 | 343 (17.1)                 |
| ≥2                                          | 64 (15.2)                 | 355 (10.5)                | 12 (9.3)                  | 89 (4.4)                   |
| Missing                                     | 133                       | 880                       | 44                       | 667                       |

Data are presented as number (percentage), unless otherwise indicated.

BRCA, breast cancer; CNIO, Spanish National Cancer Center; DKFZ, German Consortium for Translational Cancer Research; EMBRACE, Epidemiological Study of Familial Breast Cancer; GC-HBOC, German Consortium of Hereditary Breast and Ovarian Cancer; GENEPSO, Gene Etude Prospective Sein Ovaine; HCSC, Health Care Service Corporation; HEBON, Hereditary Breast and Ovarian Cancer Research Group Netherlands; HSP, Henoch-Scho¨nlein purpura; iBCCS, International *BRCA1/2* Carrier Cohort Study; IHCC, International Hereditary Cancer Center; INHERIT, Interdisciplinary HEalth Research International Team on BRastic CAncer susceptibility; MODSQUAD, Modifier Study of Quantitative Effects on Disease; MUV, Medical University of Vienna; NIO, National Institute of Oceanography; OUH, Oxford University Hospitals; OvCa, ovarian cancer; RRSO, risk-reducing salpingo-oophorectomy; SD, standard deviation.

* The IBCCS is a collaboration of EMBRACE, GENEPSO, HEBON, and other studies; † Other studies included the following: MUV, MODSQUAD, GC-HBOC, Lund-BRCA, OUH, HCSC, INHERIT, NIO, IHCC, CNIO, Stockholm-BRCA, Milan Italy, HSP, DKFZ, and Dusseldorf Germany, Belgium (order is based on number of carriers included in the analyses).

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## SUPPLEMENTAL TABLE 3
The association between aspects of oral contraceptive use and risk of ovarian cancer for 4818 \textit{BRCA1} and 2844 \textit{BRCA2} mutation carriers in the full-retrospective cohort

| Variable                          | \textit{BRCA1} mutation carriers | \textit{BRCA2} mutation carriers | Weighted $^{bc}$ HR (95% CI)$^{d}$ | Weighted $^{bc}$ HR (95% CI)$^{d}$ |
|-----------------------------------|----------------------------------|----------------------------------|------------------------------------|------------------------------------|
|                                   | OvCa+, n (%)$^a$ | OvCa−, n (%)$^a$ | OvCa+, n (%)$^a$ | OvCa−, n (%)$^a$ |
| Oral contraceptive use            |                                |                                |                                    |                                    |
| Never (≤6 mo)                     | 235 (46.4)                    | 793 (19.7)                      | 1.00                               | 85 (52.8)                          |
| Ever                              | 272 (53.7)                    | 3235 (80.3)                     | 0.64 (0.50–0.81)                   | 76 (47.2)                          |
| Ever, starting age unknown        | 19 153                        | 7 104                           |                                     | 0.66 (0.43–1.00)                   |
| Missing                           | 29 82                         | 6 56                            |                                     |                                    |
| Calendar year at start            |                                |                                |                                    |                                    |
| Never (≤6 mo)                     | 235 (46.4)                    | 793 (19.7)                      | 1.00                               | 85 (52.8)                          |
| ≤1975                             | 182 (35.9)                    | 909 (22.6)                      | 0.57 (0.44–0.75)                   | 60 (37.3)                          |
| >1975                             | 90 (17.8)                     | 2326 (57.8)                     | 0.77 (0.54–1.09)                   | 16 (9.9)                           |
| Ever, starting year unknown       | 19 153                        | 7 104                           |                                     | 0.49 (0.25–0.97)                   |
| Missing                           | 29 82                         | 6 56                            |                                     |                                    |
| Total duration of use             |                                |                                |                                    |                                    |
| Never (≤6 mo)                     | 235 (48.3)                    | 793 (20.8)                      | 1.00                               | 85 (53.8)                          |
| <5 y                              | 92 (18.9)                     | 692 (18.2)                      | 0.84 (0.61–1.14)                   | 24 (15.2)                          |
| 5–9 y                             | 79 (16.2)                     | 1010 (26.5)                     | 0.74 (0.53–1.04)                   | 19 (12.0)                          |
| ≥10 y                             | 81 (16.6)                     | 1316 (34.5)                     | 0.44 (0.31–0.61)                   | 30 (19.0)                          |
| Ever, no period specific data     | 39 370                        | 10 237                          |                                     | 0.59 (0.35–0.99)                   |
| Missing                           | 29 82                         | 6 56                            |                                     |                                    |
| Trend$^e$                         |                                | $P=4.6\times10^{-4}$            |                                    | $P=0.369$                         |
| Time since last use               |                                |                                |                                    |                                    |
| Never (≤6 mo)                     | 235 (48.3)                    | 793 (20.8)                      | 1.00                               | 85 (53.8)                          |
| <10 y                             | 56 (11.5)                     | 1712 (44.9)                     | 0.53 (0.37–0.77)                   | 14 (8.9)                           |
| 10–19 y                           | 94 (19.3)                     | 773 (20.3)                      | 0.70 (0.51–0.95)                   | 22 (13.9)                          |
| ≥20 y                             | 102 (20.9)                    | 533 (14.0)                      | 0.73 (0.54–1.00)                   | 37 (23.4)                          |
| Ever, no period specific data     | 39 370                        | 10 237                          |                                     | 0.76 (0.45–1.26)                   |
| Missing                           | 29 82                         | 6 56                            |                                     |                                    |
| Trend$^e$                         |                                | $P=.113$                        |                                    | $P=0.162$                         |

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| Variable                  | BRCA1 mutation carriers | BRCA2 mutation carriers | Weighted, b,c HR (95% CI)d |
|--------------------------|-------------------------|-------------------------|-----------------------------|
|                          | OvCa+ , n (%)a          | OvCa− , n (%)a          |                              |
| Starting age             |                         |                         |                             |
| Never (<6 mo)            | 235 (46.4)              | 793 (19.7)              | 1.00                        |
| ≤19 y                    | 83 (16.4)               | 2014 (50.0)             | 0.54 (0.38—0.76)            |
| 20—23 y                  | 86 (17.0)               | 703 (17.5)              | 0.68 (0.49—0.95)            |
| >23 y                    | 103 (20.3)              | 518 (12.9)              | 0.69 (0.51—0.95)            |
| Ever, starting age unknown | 19                     | 153                     | 7                           |
| Missing                  | 29                      | 82                      | 6                           |
| TrendP                   |                         |                         | P=.292                      |

BRCA, breast cancer; CI, confidence interval; EMBRACE, Epidemiological Study of Familial Breast Cancer; GENEPSO, Gene Etude Prospective Sein Ovaire; HEBON, Hereditary Breast and Ovarian Cancer Research Group Netherlands; HR, hazard ratio; OvCa, ovarian cancer.

a Distribution of variables at end of follow-up. b Weighted: to account for the oversampling of affected individuals (breast and ovarian cancer). c Unweighted results: BRCA1 HR, 0.91; 95 CI%, 0.77—1.08; BRCA2 HR, 1.02; 95 CI%, 0.76—1.36. In both unweighted and weighted analyses, the same characteristics of oral contraceptive use were significantly associated. d Intrinsically stratified on study (EMBRACE, GENEPSO, HEBON, other) and birth cohort (1920–1941, 1942–1950, 1951–1992). Clustered on family membership. Trend tests were based on the P value of the category-specific mean as a continuous variable of ever oral contraceptive users.

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