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

Date:
2021-07-01

Citation:
Schrijver, L. H., Antoniou, A. C., Olsson, H., Mooij, T. M., Roos-Blom, M. J., Azarang, L., Adlard, J., Ahmed, M., Barrowdale, D., Davidson, R., Donaldson, A., Eeles, R., Evans, D. G., Frost, D., Henderson, A., Izatt, L., Ong, K. R., Bonadona, V., Coupier, I. ,... Layet, V. (2021). Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers: an international cohort study. American Journal of Obstetrics and Gynecology, 225 (1), pp.51-51.e17. https://doi.org/10.1016/j.ajog.2021.01.014.

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GYNECOLOGY

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 calendar year of start with risk of ovarian cancer.

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_{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

Introduction

Mutations in the *BRCA1* and *BRCA2* genes are associated with a high lifetime risk of ovarian cancer. The average cumulative risk of ovarian cancer up to the age of 70 years has been estimated to be 41% (95% confidence interval [CI], 33–50) for *BRCA1* mutation carriers and 15% (95% CI, 10–23) for *BRCA2* mutation carriers.[1] The use of oral contraceptives is a strong protective factor (approximately 50%, with a dose-response association observed with duration of use) for ovarian cancer in the general population and has been suggested as chemoprevention for *BRCA1* and *BRCA2* mutation carriers.[2–5] Although the effects of using oral contraceptives in the general population are well established, the estimated risk

Cite this article as: Schrijver LH, Antoniou AC, Olsson H, et al. Oral contraceptive use and ovarian cancer risk for *BRCA1/2* mutation carriers: an international cohort study. Am J Obstet Gynecol 2021;XX:x.ex–x.ex.

0002-9378

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https://doi.org/10.1016/j.ajog.2021.01.014

AJOG at a Glance

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.

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.

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.

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

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 ("oral contraceptive univariate") and a multivariate analysis, including all of these aspects of oral contraceptive use ("oral contraceptive multivariate"). In addition, the analysis of duration of oral contraceptive use was stratified by recency of use. All characteristics of oral contraceptive use were considered time-dependent covariates, computed 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.[10] 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 based on fitting category-specific means. Analyses were performed using Stata (version 13; StataCorp, 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_{trend}<.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_{trend}=.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 [*BRCA1* HR, 0.40 (95% CI, 0.22−0.71); *BRCA2* HR, 0.36 (95% CI, 0.14−0.92)]; 10−19 years ago [*BRCA1* HR, 0.54 (95% CI, 0.36−0.82); *BRCA2* HR, 0.58 (95% CI, 0.24−1.42)]; ≥20 years ago [*BRCA1* HR, 0.61 (95% CI, 0.43−0.87); *BRCA2* HR, 0.78 (95% CI, 0.40−1.52)]; trend [*BRCA1*, *P*=.025; *BRCA2*, *P*=.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 [HR, 0.43; 95% CI, 0.28−0.65]; 20−23 years [HR, 0.51;

TABLE 1
Characteristics of 3989 *BRCA1* and 2445 *BRCA2* mutation carriers in the left-truncated IBCCS cohort

	BRCA1 mutation carriers				*BRCA2* mutation carriers			
	OvCa+		OvCa−		OvCa+		OvCa−	
Characteristics	N=3989				N=2445			
n (%)	346	(8.7)	3643	(91.3)	106	(4.3)	2339	(95.7)
Mean age at start of follow-up (SD), y	48.4	(8.9)	36.4	(11.5)	54.0	(9.1)	39.0	(11.8)
Mean age at end of follow-up (SD), y	51.7	(8.9)	40.5	(11.4)	56.9	(9.1)	43.4	(11.7)
Age at end of follow-up, y								
<37	14	(4.1)	1413	(38.8)	4	(3.8)	696	(29.8)
37–46	89	(25.7)	1202	(33.0)	8	(8.6)	771	(33.0)
>47	243	(70.2)	1028	(28.2)	94	(88.7)	872	(37.3)
Mean person-years (y/person) (SD)	3.2	(1.2)	4.2	(1.2)	2.9	(1.2)	4.4	(1.1)
Censored for the following:								
Ovarian cancer	346	(100.0)	0	(0.0)	106	(100.0)	0	(0.0)
DNA test or baseline questionnaire	0	(0.0)	3521	(96.6)	0	(0.0)	2273	(97.2)
Other cancer	0	(0.0)	41	(1.1)	0	(0.0)	29	(1.2)
Bilateral RRSO	0	(0.0)	81	(2.2)	0	(0.0)	37	(1.6)
Year at end of follow-up								
1990–2000	137	(39.6)	1122	(30.8)	33	(31.1)	370	(15.8)
2001–2005	133	(38.4)	1354	(37.2)	42	(39.6)	976	(41.7)
2006–2012	76	(22.0)	1167	(32.0)	31	(29.3)	993	(42.5)
Birth year								
1920–1944	87	(25.1)	292	(8.0)	55	(51.9)	236	(10.1)
1945–1951	109	(31.5)	401	(11.0)	20	(18.9)	308	(13.2)
1952–1980	150	(43.4)	2950	(81.0)	31	(29.3)	1795	(76.7)
Study[a]								
EMBRACE	129	(9.8)	1183	(90.2)	64	(5.5)	1095	(94.5)
GENEPSO	64	(6.9)	865	(93.1)	15	(2.7)	546	(97.3)
Other[b]	153	(8.8)	1595	(91.3)	27	(3.7)	698	(96.3)

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(continued)

TABLE 1
Characteristics of 3989 *BRCA1* and 2445 *BRCA2* mutation carriers in the left-truncated IBCCS cohort *(continued)*

Characteristics	*BRCA1* mutation carriers				*BRCA2* mutation carriers			
	OvCa+		OvCa−		OvCa+		OvCa−	
	N=3989				N=2445			
Breast cancer								
No	215	(62.4)	2255	(61.9)	71	(67.0)	1458	(62.3)
Yes	131	(37.9)	1388	(37.9)	35	(33.0)	881	(37.7)
Number of ovarian cancers among first- and second-degree relatives								
0	132	(51.8)	1877	(64.0)	53	(68.0)	1435	(78.7)
1	90	(35.3)	752	(25.6)	17	(21.8)	309	(17.0)
≥2	33	(12.9)	305	(10.4)	8	(10.3)	79	(4.3)
Missing	91		708		27		516	
Cancer type unknown	0		1		1		0	

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 Ovaire; *HCSC*, Health Care Service Corporation; *HEBON*, Hereditary Breast and Ovarian Cancer Research Group Netherlands; *HSP*, Henoch-Schönlein purpura; *IBCCS*, International *BRCA1/2* Carrier Cohort Study; *IHCC*, International Hereditary Cancer Center; *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; *OUH*, Oxford University Hospitals; *OvCa*, ovarian cancer; *RRSO*, risk-reducing salpingo-oophorectomy; *SD*, standard deviation.

[a] IBCCS is a collaboration of EMBRACE, GENEPSO, and "other" studies; [b] Other studies include the following: HEBON, MUV, MODSQUAD, GC-HBOC, Lund-BRCA, OUH, NIO, INHERIT, HCSC, 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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95% CI, 0.33−0.78]; >24 years [HR, 0.63; 95% CI, 0.41−0.97]; P_{trend}=.15). Calendar year of first use did not modify the HR for ever use for *BRCA1* and *BRCA2* mutation carriers.

Age at first use, duration of use, and time since last use of oral contraceptives are closely related. For instance, at censoring, the average duration of use of oral contraceptives was longer for recent users than for those who stopped a long time ago (*BRCA1*: 11±5.8 years for recent users vs 5±3.4 years for those who stopped >20 years ago). In addition, *BRCA1* mutation carriers used oral contraceptives for a longer duration when they had started at a younger age. For ages at first oral contraceptive used ≤19 years or ≥24 years, mean durations of use were 10 (±5.6) and 7 (±5.9) years, respectively. Therefore, we conducted multivariate analyses, including duration of use, time since last use, and age at first use of oral contraceptives in the same model. In this model, only duration of use of oral contraceptives remained independently associated with ovarian cancer risk (<5 years [reference, 5−9 years; HR, 0.67; 95% CI, 0.40−1.12]; ≥10 years [HR, 0.37; 95% CI, 0.19−0.73]; P_{trend}=.008) for *BRCA1* mutation carriers. The sample size was too limited to perform comparable multivariate analysis for *BRCA2* mutation carriers.

Analyses on the duration of use of oral contraceptives stratified by time since last use (Table 3) showed that the inverse association between duration of use and ovarian cancer risk persisted for a long period (≥15 years). It seemed that the association for long-term users (≥10 years of use) was somewhat stronger in more recent years (<15 years since use) after oral contraceptive use (*BRCA1*: <15 years since last use [HR, 0.24; 95% CI, 0.14−0.43]; >15 years since last use [HR, 0.56; 95% CI, 0.18−0.59]); however, this interaction was not statistically significant. The finding for attained age was consistent with findings for time since last oral contraceptive use. A significant inverse association with duration of oral contraceptive use was observed only for *BRCA1* mutation carriers younger than age 50 (Supplemental

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

	BRCA1 mutation carriers					*BRCA2* mutation carriers				
Variable	OvCa+, n (%)[c]		OvCa−, n (%)[c]		Weighted,[a,b] HR (95% CI)[d]	OvCa+, n (%)[c]		OvCa−, n (%)[c]		Weighted,[a,b] HR (95% CI)[e]
Oral contraceptive use										
Never (<6 mo)	133	(41.4)	659	(19.1)	1.00	46	(46.5)	426	(19.3)	1.00
Ever	188	(58.6)	2788	(88.9)	0.51 (0.36−0.71)	53	(53.5)	1782	(80.7)	0.65 (0.35−1.19)
Ever, starting age unknown	11		125			4		87		
Missing	14		71			3		44		
Calendar year at start										
Never (<6 mo)	133	(41.4)	659	(19.1)	1.00	46	(46.5)	426	(19.3)	1.00
≤1975	114	(35.5)	684	(19.8)	0.45 (0.33−0.62)	39	(39.4)	492	(22.3)	0.73 (0.38−1.39)
>1975	74	(23.1)	2104	(61.0)	0.56 (0.35−0.88)	14	(14.1)	1290	(58.4)	0.49 (0.23−1.05)
Ever, starting year unknown	11		125			4		87		
Missing	14		71			3		44		
Total duration of use										
Never (<6 mo)	133	(43.0)	659	(20.2)	1.00	46	(47.4)	426	(20.4)	1.00
<5 y	67	(21.7)	616	(18.9)	0.79 (0.53−1.19)	17	(17.5)	401	(19.2)	0.87 (0.42−1.80)
5−9 y	53	(17.2)	867	(26.6)	0.54 (0.35−0.85)	13	(13.4)	557	(26.6)	0.51 (0.23−1.12)
≥10 y	56	(18.2)	1121	(34.4)	0.32 (0.21−0.50)	21	(21.7)	707	(33.8)	0.60 (0.28−1.27)
Ever, no period specific data	23		309			6		204		
Missing	14		71			3		44		
Trend[f]					*P*=2.0E-04					*P*=.449
Time since last use										
Never (<6 mo)	133	(43.0)	659	(20.2)	1.00	46	(47.4)	426	(20.4)	1.00
<10 y	29	(9.4)	1478	(45.3)	0.40 (0.22−0.71)	7	(7.2)	825	(39.5)	0.36 (0.14−0.92)
10−19 y	60	(19.4)	648	(19.9)	0.54 (0.36−0.82)	12	(12.4)	415	(19.9)	0.58 (0.24−1.42)
≥20 y	87	(28.2)	478	(14.7)	0.61 (0.43−0.87)	32	(33.0)	425	(20.3)	0.78 (0.40−1.52)
Ever, no period specific data	23		309			6		204		
Missing	14		71			3		44		
Trend[f]					*P*=.025					*P*=.258

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(continued)

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 (%)[c]		OvCa−, n (%)[c]		Weighted,[a,b] HR (95% CI)[d]	OvCa+, n (%)[c]		OvCa−, n (%)[c]		Weighted,[a,b] HR (95% CI)[e]
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[f]					*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: *BRCA1* HR, 0.72; 95 CI%, 0.58−0.90; *BRCA2* HR, 0.80; 95 CI%, 0.55−1.17. In both unweighted and weighted analyses, the same characteristics of oral contraceptive use were significantly associated; [c] Distribution of variables at end of follow-up; [d] Intrinsically stratified on study (EMBRACE, GENEPSO, other) and birth cohort (1920−1946, 1947−1954, 1955−1980). Clustered on family membership; [e] Intrinsically stratified on study (EMBRACE, other incl GENEPSO) and birth cohort (1920−1943, 1944−1980). Clustered on family membership; [f] 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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Table 1). However, the difference in the effect sizes was not significant.

Analyses stratified for birth cohort (univariate, unweighted) suggested that the significant inverse association between duration of use and ovarian cancer risk was limited to more recent birth cohorts (1920−1946 [*P*=.144]; 1947−1954 [*P*=.373]; 1955−1980 [*P*=.009]; data not shown). Sample size was limited to examine if this could be explained by recency of use.

Study-specific analyses (univariate, unweighted, data not shown) have shown that for *BRCA1* mutation carriers, the association between ever use and ovarian cancer risk was comparable for all studies (HR estimates varied between 0.43 and 0.82). For *BRCA2* mutation carriers, sample size was too limited to stratify for study.

In the analyses of oral contraceptive use and ovarian cancer risk, we included women with a personal history of breast cancer, treating breast cancer as a time-dependent covariate. To further explore the impact of a potential association between oral contraceptive use and risk of breast cancer in these analyses, we censored for breast cancer diagnosis in a sensitivity analysis and thus excluded women with a personal breast cancer history. We found a virtually identical inverse association between oral contraceptive use and risk of ovarian cancer (ever vs never: *BRCA1* HR, 0.47 [95% CI, 0.32−0.70]; *BRCA2* HR, 0.57 [95% CI, 0.27−1.19]).

Results of the multiple imputation sensitivity analyses using the Cox model with either fixed- or random-effects agreed with our main results for duration of oral contraceptive use. For *BRCA1* mutation carriers, a longer duration of oral contraceptive use was associated with a reduction in ovarian cancer risk (main results [HR, 0.92; *P*<.001]; multiple imputation fixed model [HR, 0.94; *P*<.001]; multiple imputation random model [HR, 0.94; *P*<.001]). For *BRCA2* mutation carriers, no significant trend was found for duration of oral contraceptive use (main results [HR, 0.97; *P*=.45]; multiple imputation fixed model [HR, 0.98; *P*=.33]; multiple imputation random model [HR, 0.98; *P*=.49]).

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 (%)[a]		OvCa−, n (%)[a]		Oral contraceptive univariate,[b,c] HR (95% CI)	Oral contraceptive multivariate,[b,c,d] 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						
<5	67	(21.7)	616	(18.9)	1.00	1.00
5–9	53	(17.2)	867	(26.6)	0.69 (0.43–1.09)	0.67 (0.40–1.12)
≥10	56	(18.2)	1121	(34.4)	0.40 (0.25–0.65)	0.37 (0.19–0.73)
Trend[e]					*P*=2.0E-04	*P*=.008
Time since last use, y						
<10	29	(9.4)	1478	(45.3)	1.00	1.00
10–19	60	(19.4)	648	(19.9)	1.35 (0.77–2.37)	0.96 (0.50–1.83)
≥20	87	(28.2)	478	(14.7)	1.50 (0.85–2.66)	0.79 (0.35–1.78)
Trend[e]					*P*=.015	*P*=.238
Starting age, y						
≤19	58	(18.8)	1632	(50.0)	1.00	1.00
20–23	51	(16.5)	580	(17.8)	1.07 (0.68–1.70)	0.98 (0.61–1.58)
>23	67	(21.7)	392	(12.0)	1.51 (0.91–2.50)	1.15 (0.65–2.04)
Trend[e]					*P*=.154	*P*=.665
Ever, starting age unknown	23		309			
Missing	14		71			
Stratified for recency of use					HR (95% CI)[c]	
Total duration of use						
Never (<6 mo)	133	(43.0)	659	(20.2)	1.00	
<15 y since last use						
<5 y	10	(3.2)	288	(8.8)	1.21 (0.55–2.68)	
5–9 y	16	(5.2)	580	(17.8)	0.61 (0.30–1.24)	
≥10 y	25	(8.1)	956	(29.3)	0.24 (0.14–0.43)	
Trend[c]					*P*=2.2e-04	
>15 y since last use						
<5 y	57	(18.5)	328	(10.1)	0.72 (0.48–1.07)	
5–9 y	37	(12.0)	287	(8.8)	0.47 (0.29–0.76)	
≥10 y	31	(10.0)	165	(5.1)	0.56 (0.18–0.59)	
Trend[c]					*P*=.374	
Ever, no period specific data	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.

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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 risk of 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,[4,6,9,11] and only 1 conducted left-truncated analyses. The study of McLaughlin et al[6] included a subset of the participants in Kotsopoulos et al[4] and the study of Antoniou et al[9] included a subset of the carriers included in this study. For both *BRCA1* and *BRCA2* mutation carriers, 2 independent studies[4,11] 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[4] 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,[9] a subset of our study. The study of Antoniou et al[9] 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 or 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.[12] 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.[13] 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)*.[1] 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;[14,15] however, the uptake of a risk-reducing mastectomy is low (35%−44%)[16] 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,[8,9] in which women 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.[12,17–21] 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.[19] However, studies of *BRCA1* and *BRCA2* mutation carriers are lacking.[22–24] 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.

Acknowledgments

Study-specific acknowledgments

The Spanish National Cancer Center would like to thank Alicia Barroso, Rosario Alonso, and Guillermo Pita for their assistance.

We would like to acknowledge the members of the following Gene Etude Prospective Sein Ovaire centers—the Coordinating Center, Institut Paoli-Calmettes, Marseille, France, Catherine Noguès, Lilian Laborde, Pauline Pontois, Emanuelle Breysse, and Margot Berline, and the Collaborating Centers, Institut Curie, Paris, Dominique Stoppa-Lyonnet, Marion Gauthier-Villars, Bruno Buecher, and Chrystelle Colas; Institut Gustave Roussy, Villejuif, Olivier Caron; Hôpital René Huguenin and Institut Curie, Saint Cloud, Catherine Noguès, Emmanuelle Mouret-Fourme, Claire Saule, and Chrystelle Colas; Centre Paul Strauss, Strasbourg, Jean-Pierre Fricker; Centre Léon Bérard, Lyon, Christine Lasset, Valérie Bonadona, and Sophie Dussard; Centre François Baclesse, Caen, Pascaline Berthet; Hôpital d'Enfants, Centre Hospitalier Universitaire (CHU) Dijon — Centre Georges François Leclerc, Dijon, Laurence Faivre; Centre Alexis Vautrin, Vandoeuvre-les-Nancy, Elisabeth Luporsi; Centre Antoine Lacassagne, Nice, Véronique Mari; Institut Claudius Regaud, Toulouse, Laurence Gladieff; Réseau Oncogénétique Poitou Charente, Niort, Paul Gesta and Stéphanie Chieze-Valéro; Institut Paoli-Calmettes, Marseille, Catherine Noguès, Jessica Moretta Hagay Sobol, François Eisinger, and Cornel Popovici; Institut Bergonié, Bordeaux, Michel Longy; Centre Eugène Marquis, Rennes, Louise Grivelli; GH Pitié Salpétrière, Paris, Chrystelle Colas, Florent Soubrier, and Patrick Benusiglio; CHU Arnaud de Villeneuve, Montpellier, Isabelle Coupier, Pascal Pujol, and Carole Corsini; Centres Paul Papin and ICO, Angers, Marie-Emmanuelle Morin-Meschin; CliniqueCatherine de Sienne, Nantes, Alain Lortholary; Centre Oscar Lambret, Lille, Claude Adenis and Audrey Maillez; Institut Jean Godinot, Reims, Tan Dat Nguyen; Centre René Gauducheau, Nantes, Capucine Delnatte and Caroline Abadie; Centre Henri Becquerel, Rouen, Julie Tinat and Isabelle Tennevet; Hôpital Civil, Strasbourg, Christine Maugard; Centre Jean Perrin, Clermont-Ferrand, Yves-Jean Bignon and Mathilde Gay Bellile; Polyclinique Courlancy, Reims, Clotilde Penet; Clinique Sainte Catherine, Avignon, Hélène Dreyfus; Hôpital Saint-Louis, Paris, Odile Cohen-Haguenauer; CHRU Dupuytren, Limoges, Brigitte Gilbert and Laurence Venat-Bouvet; CHU de Grenoble, Dominique Leroux, Clémentine Legrand, and Hélène Dreyfus; Hôpital de la Timone, Marseille, Hélène Zattara-Cannoni; Hôpital Jacques Monod, le Havre, Valérie Layet and Elodie Lacaze; CHU Chambéry, Chambéry, Sandra Fert-Ferrer; Hôpital Clarac, Fort de France, Odile Bera; CHU la Milétrie, Poitiers, Brigitte Gilbert-Dussardier, David Tougeron, and Stéphanie Chieze-Valéro; Hôpital Saint-Louis, la Rochelle, Hakima Lallaoui; and CH Pellegrin, Bordeaux, Julie Tinat.

The Health Care Service Corporation would like to acknowledge Alicia Tosar and Paula Diaque for their technical assistance.

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Netherlands Cancer Institute (coordinating center), Amsterdam, the Netherlands, M.A. Rookus, F.B.L. Hogervorst, F.E. van

Leeuwen, M.A. Adank, M.K. Schmidt, and D.J. Jenner; Erasmus Medical Center, Rotterdam, the Netherlands, J.M. Collée, A.M.W. van den Ouweland, M.J. Hooning, and I.A. Boere; Leiden University Medical Center, the Netherlands, C.J. van Asperen, P. Devilee, R.B. van der Luijt, and T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, the Netherlands, M.R. Wevers and A.R. Mensenkamp; University Medical Center Utrecht, the Netherlands, M.G.E.M. Ausems and M.J. Koudijs; Amsterdam UMC, University of Amsterdam, the Netherlands, I. van de Beek; Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands, K. van Engelen and J.J.P. Gille; Maastricht University Medical Center, the Netherlands, E.B. Gómez García, M.J. Blok, and M. de Boer; University of Groningen, the Netherlands, L.P.V. Berger, A.H. van der Hout, M.J.E. Mourits, and G.H. de Bock; The Netherlands Comprehensive Cancer Organisation (IKNL):, S. Siesling and J. Verloop; the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), E.C. van den Broek. HEBON would like to thank the study participants and the registration teams of IKNL and PALGA for part of the data collection.

INHERIT would like to thank Dr Martine Dumont for sample management and skillful assistance.

The Masaryk Memorial Cancer Institute, Brno, Czech Republic, would like to thank Dita Hanouskova, Jitka Berkovcova, Sarka and Rathouzska for their technical assistance.

We wish to thank the Hungarian Breast and Ovarian Cancer Study group members (Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary: Maria Balogh, Janos Papp, Matrai Zoltan, and Judit Franko) and the clinicians and patients for their contributions to this study.

We would like to thank the following Swedish scientists participating as Swedish Breast Cancer Study collaborators from Lund University and University Hospital, Håkan Olsson and Carolina Ellberg, and from Stockholm and Karolinska University Hospital, Brita Arver.

Finally, we would like to thank Kelly-Anne Phillips, an Australian National Breast Cancer Foundation Fellow. ■

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Received April 6, 2020; revised Oct. 30, 2020; accepted Jan. 19, 2021.

The authors report no conflict of interest.

This work was supported by Cancer Research UK grants C12292/A20861 and C12292/A11174.

This work was partially supported by the Spanish Ministry of Economy and Competitiveness (SAF2014-57680-R) and the Spanish Centre for Biomedical Network Research on Rare Diseases. This work was partially supported by Chancellors Distinguished Chair in Biomedical Sciences Professorship. FPGMX grant number FISPI05/2275 and by the Mutua Madrileña Foundation (FMMA).

Part of this work was supported by the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program (grant number CRN-87521) and the Ministry of Economic Development, Innovation and Export Trade (grant number PSR-SIIRI-701). The PERSPECTIVE project was supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research (GPH-129344), the Ministère de l'Économie, de la Science et de l'Innovation du Québec through Genome Québec, and the Quebec Breast Cancer Foundation.

This study was supported by the German Cancer Research Center.

EMBRACE is supported by Cancer Research UK grants C1287/A10118 and C1287/A11990. D.G.E. is supported by a National Institute for Health Research (NIHR) grant through the Biomedical Research Centre, Manchester (IS-BRC-1215-20007). The investigators at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust are supported by an NIHR grant through the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. R.E. and E.B. are supported by a Cancer Research UK grant C5047/A8385. R.E. is also supported by the NIHR through the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. A.C.A. is funded by Cancer Research UK grants C12292/A20861, C12292/A11174.

The German Consortium of Hereditary Breast and Ovarian Cancer is supported by the German Cancer Aid (grant number 110837; R.K.S.). This work was supported by LIFE — Leipzig Research Center for Civilization Diseases, Universität Leipzig. LIFE is funded by means of the European Union, by the European Regional Development Fund, and by means of the Free State of Saxony within the framework of the excellence initiative.

The national French cohort, GENEPSO, had been supported by a grant from the Fondation de France and by grants from the Ligue Nationale Contre le Cancer and is being supported by a grant from Institute National du Cancer as part of the European program ERA-NET on Translational Cancer Research (TRANSCAN-JTC2012, n2014-008).

The Health Care Service Corporation was supported by a grant RD12/0036/0006 and 15/00059 from Instituto de Salud Carlos III (Spain), partially supported by European Regional Development FEDER funds.

The HEBON study is supported by the Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, and NKI2007-3756; the Netherlands Organisation of Scientific Research grant NWO 91109024; the Pink Ribbon grants 110005 and 2014-187.WO76; the Biobanking and BioMolecular Resources Research Infrastructure grant NWO 184.021.007/CP46; and the TRANSCAN grant JTC 2012 Cancer 12-054.

The International Hereditary Cancer Centre was supported by grant number PBZ_KBN_122/P05/2004 and by the National Center for Research and Development (NCBR) within the framework of the international ERA-NET TRANSAN JTC 2012 application number Cancer 12-054 (contract number ERA-NET-TRANSCAN/07/2014).

MODSQUAD — Czech Republic, Brno, was supported by MH CZ — DRO (MMCI, 00209805).

The Hungarian Breast and Ovarian Cancer Study was supported by Hungarian research grants KTIA-OTKA CK-80745 and NKFI OTKA K-112228 and by the Norwegian EEA Financial Mechanism HU0115/NA/2008-3/ÖP-9.

Lund-BRCA collaborators are supported by the Swedish Cancer Society, Lund Hospital Funds, and European Research Council advanced grant ERC-2011-294576. Stockholm-BRCA collaborators are supported by the Swedish Cancer Society.

This study was presented as a poster at the 7th International Symposium of the Hereditary Breast and Ovarian Cancer Foundation and the McGill Program in Cancer Genetics, Montreal, Québec, Canada, May 8—11, 2018.

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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

	Attained age of <50 y (n=3268)			Attained age of >50 y (n=958)		
Variable	OvCa+, n (%)[a]	OvCa−, n (%)[a]	HR (95% CI)[b,c]	OvCa+, n (%)[c]	OvCa−, n (%)[c]	HR (95% CI)[b,c]
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	77 (51.3)	2402 (77.0)		0 (0.0)	0 (0.0)	
45–64	73 (48.7)	716 (23.0)		165 (84.2)	663 (87.0)	
>65	0 (0.0)	0 (0.0)		31 (15.8)	99 (13.0)	
Oral contraceptive use						
Never (<6 mo)	50 (34.7)	467 (15.7)	1.00	83 (46.9)	251 (35.9)	1.00
Ever	94 (65.3)	2507 (84.3)		94 (53.1)	448 (64.1)	0.63 (0.43–0.92)
Ever, starting age unknown	0	91		11	41	
Missing	6	53		8	22	
Total duration of use						
Never (<6 mo)	50 (35.7)	467 (16.7)	1.00	83 (49.1)	251 (37.0)	1.00
<5 y	36 (25.7)	524 (18.7)	0.86 (0.52–1.44)	31 (18.3)	135 (19.9)	0.62 (0.38–1.02)
5–9 y	28 (20.0)	800 (28.5)	0.48 (0.27–0.85)	25 (14.8)	119 (17.6)	0.77 (0.45–1.33)
≥10 y	26 (18.6)	1013 (36.1)	0.27 (0.15–0.49)	30 (17.8)	173 (25.5)	0.52 (0.31–0.86)
Ever, no period specific data	4	261		19	62	
Missing	6	53		8	22	
Trend[d]			*P*=2.8E-04			*P*=.471

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.

[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] 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

	BRCA1 mutation carriers		*BRCA2* mutation carriers	
	OvCa+	OvCa−	OvCa+	OvCa−
Characteristic	n=4818		n=2844	
n (%)	555 (11.5)	4263 (88.5)	174 (6.1)	2670 (93.9)
Mean age at end of follow-up (SD)	50.2 (8.8)	40.6 (11.1)	55.1 (9.4)	43.3 (11.6)
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)	55.1 (9.4)	43.3 (11.6)
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 (30.2)	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)
Study[a]				
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)
Other[b]	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)*

	BRCA1 mutation carriers		*BRCA2* mutation carriers	
	OvCa+	OvCa−	OvCa+	OvCa−
Characteristic	n=4818		n=2844	
Number of ovarian cancers among first- and second-degree relatives				
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
Cancer type unknown	1	1	1	0

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 Ovaire; *HCSC*, Health Care Service Corporation; *HEBON*, Hereditary Breast and Ovarian Cancer Research Group Netherlands; *HSP*, Henoch-Schönlein purpura; *IBCCS*, International *BRCA1/2* Carrier Cohort Study; *IHCC*, International Hereditary Cancer Center; *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; *OUH*, Oxford University Hospitals; *OvCa*, ovarian cancer; *RRSO*, risk-reducing salpingo-oophorectomy; *SD*, standard deviation.

[a] The IBCCS is a collaboration of EMBRACE, GENEPSO, HEBON, and other studies; [b] 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 *BRCA1* and 2844 *BRCA2* mutation carriers in the full-retrospective cohort

	BRCA1 mutation carriers			*BRCA2* mutation carriers		
Variable	OvCa+, n (%)[a]	OvCa−, n (%)[a]	Weighted,[b,c] HR (95% CI)[d]	OvCa+, n (%)[a]	OvCa−, n (%)[a]	Weighted,[b,c] HR (95% CI)[d]
Oral contraceptive use						
Never (<6 mo)	235 (46.4)	793 (19.7)	1.00	85 (52.8)	513 (20.4)	1.00
Ever	272 (53.7)	3235 (80.3)	0.64 (0.50–0.81)	76 (47.2)	1997 (79.6)	0.66 (0.43–1.00)
Ever, starting age unknown	19	153		7	104	
Missing	29	82		6	56	
Calendar year at start						
Never (<6 mo)	235 (46.4)	793 (19.7)	1.00	85 (52.8)	513 (20.4)	1.00
≤1975	182 (35.9)	909 (22.6)	0.57 (0.44–0.75)	60 (37.3)	621 (24.7)	0.69 (0.45–1.07)
>1975	90 (17.8)	2326 (57.8)	0.77 (0.54–1.09)	16 (9.9)	1376 (54.8)	0.49 (0.25–0.97)
Ever, starting year unknown	19	153		7	104	
Missing	29	82		6	56	
Total duration of use						
Never (<6 mo)	235 (48.3)	793 (20.8)	1.00	85 (53.8)	513 (21.6)	1.00
<5 y	92 (18.9)	692 (18.2)	0.84 (0.61–1.14)	24 (15.2)	470 (19.8)	0.81 (0.46–1.43)
5–9 y	79 (16.2)	1010 (26.5)	0.74 (0.53–1.04)	19 (12.0)	615 (25.9)	0.62 (0.34–1.14)
≥10 y	81 (16.6)	1316 (34.5)	0.44 (0.31–0.61)	30 (19.0)	779 (32.8)	0.59 (0.35–0.99)
Ever, no period specific data	39	370		10	237	
Missing	29	82		6	56	
Trend[e]			*P*=4.6E-04			*P*=0.369
Time since last use						
Never (<6 mo)	235 (48.3)	793 (20.8)	1.00	85 (53.8)	513 (21.6)	1.00
<10 y	56 (11.5)	1712 (44.9)	0.53 (0.37–0.77)	14 (8.9)	921 (38.8)	0.44 (0.22–0.86)
10–19 y	94 (19.3)	773 (20.3)	0.70 (0.51–0.95)	22 (13.9)	483 (20.3)	0.70 (0.39–1.26)
≥20 y	102 (20.9)	533 (14.0)	0.73 (0.54–1.00)	37 (23.4)	460 (19.4)	0.76 (0.45–1.26)
Ever, no period specific data	39	370		10	237	
Missing	29	82		6	56	
Trend[e]			*P*=.113			*P*=.162

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(continued)

SUPPLEMENTAL TABLE 3

The association between aspects of oral contraceptive use and risk of ovarian cancer for 4818 *BRCA1* and 2844 *BRCA2* mutation carriers in the full-retrospective cohort *(continued)*

Variable	*BRCA1* mutation carriers			*BRCA2* mutation carriers		
	OvCa+, n (%)[a]	OvCa−, n (%)[a]	Weighted,[b,c] HR (95% CI)[d]	OvCa+, n (%)[a]	OvCa−, n (%)[a]	Weighted,[b,c] HR (95% CI)[d]
Starting age						
Never (<6 mo)	235 (46.4)	793 (19.7)	1.00	85 (52.8)	513 (20.4)	1.00
≤19 y	83 (16.4)	2014 (50.0)	0.54 (0.38−0.76)	25 (15.5)	1125 (44.8)	0.92 (0.47−1.80)
20−23 y	86 (17.0)	703 (17.5)	0.68 (0.49−0.95)	17 (10.6)	518 (20.6)	0.55 (0.28−1.07)
>23 y	103 (20.3)	518 (12.9)	0.69 (0.51−0.95)	34 (21.1)	354 (14.1)	0.65 (0.40−1.05)
Ever, starting age unknown	19	153		7	104	
Missing	29	82		6	56	
Trend[e]			*P*=.292			*P*=.396

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; [e] 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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