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## ARTICLE

# Oral Contraceptive Use and Breast Cancer Risk: Retrospective and Prospective Analyses From a BRCA1 and BRCA2 Mutation Carrier Cohort Study

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## Abstract

**Background:** For BRCA1 and BRCA2 mutation carriers, the association between oral contraceptive preparation (OCP) use and breast cancer (BC) risk is still unclear.

**Methods:** Breast cancer risk associations were estimated from OCP data on 6030 BRCA1 and 3809 BRCA2 mutation carriers using age-dependent Cox regression, stratified by study and birth cohort. Prospective, left-truncated retrospective and full-cohort retrospective analyses were performed.

**Results:** For BRCA1 mutation carriers, OCP use was not associated with BC risk in prospective analyses (hazard ratio [HR] = 1.08, 95% confidence interval [CI] = 0.75 to 1.56), but in the left-truncated and full-cohort retrospective analyses, risks were increased by 26% (95% CI = 6% to 51%) and 39% (95% CI = 23% to 58%), respectively. For BRCA2 mutation carriers, OCP use was associated with BC risk in prospective analyses (HR = 1.75, 95% CI = 1.03 to 2.97), but retrospective analyses were inconsistent (left-truncated:

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HR = 1.06, 95% CI = 0.85 to 1.33; full cohort: HR = 1.52, 95% CI = 1.28 to 1.81). There was evidence of increasing risk with duration of use, especially before the first full-term pregnancy (BRCA1: both retrospective analyses,  $P < .001$  and  $P = .001$ , respectively; BRCA2: full retrospective analysis,  $P = .002$ ).

**Conclusions:** Prospective analyses did not show that past use of OCP is associated with an increased BC risk for BRCA1 mutation carriers in young middle-aged women (40–50 years). For BRCA2 mutation carriers, a causal association is also not likely at those ages. Findings between retrospective and prospective analyses were inconsistent and could be due to survival bias or a true association for younger women who were underrepresented in the prospective cohort. Given the uncertain safety of long-term OCP use for BRCA1/2 mutation carriers, indications other than contraception should be avoided and non-hormonal contraceptive methods should be discussed.

Women with germline mutations in BRCA1 and BRCA2 are at substantially increased risk of breast and ovarian cancers (1). The use of oral contraceptive preparations (OCPs) has been found to be associated with reduced ovarian cancer risk for both BRCA1 and BRCA2 mutation carriers (2–7). However, a key issue in the clinical management of these mutation carriers is whether or not use of OCPs is associated with breast cancer (BC) risk. Prior findings are inconsistent and based on only a few retrospective studies with the potential for recall, survival, and testing biases. To evaluate the risk of BC associated with use of OCPs for mutation carriers, we harmonized and combined the data from three large international cohort consortia. We analyzed the association between the use of OCPs and BC risk in the first prospective analysis. For comparison with the literature with a larger sample size, we also conducted left-truncated and full cohort retrospective analyses in the same cohort at younger ages.

## Methods

### Study Design and Study Participants

We harmonized and pooled information from three large cohorts: the International BRCA1/2 Carrier Cohort Study (IBCCS), the Kathleen Cunningham Foundation Consortium for Research Into Familial Breast Cancer (kConFab) Follow-Up Study, and the Breast Cancer Family Registry (BCFR). The IBCCS/kConFab/BCFR collaboration combined 21 cohort studies conducted in Western countries (1,8–11). Women were eligible if they had a pathogenic mutation in either BRCA1 or BRCA2 and were between age 18 and 80 years at study enrollment. Women were excluded if they had mutations in both genes or were born before 1920, because their reproductive years preceded the availability of OCPs. The total eligible group, enrolled in the prospective, retrospective, or both analyses, consisted of 6030 BRCA1 and 3809 BRCA2 mutation carriers.

### Data Collection

Baseline and consecutive follow-up questionnaires elicited detailed information on known or suspected risk factors for breast and ovarian cancer. Data collection on OCP use included ever use (no/yes), age at first or last use (years), and duration of use (years); age at first and last use for each period of use were available for 75% of the women. Data on preventive surgeries and cancer occurrence were collected from questionnaires, from medical record validation, and from linkages to cancer and/or pathology registries. Information on vital status was obtained from municipal or death registries or from contact persons in the family.

### Statistical Analysis

To estimate hazard ratios (HRs), time-dependent Cox proportional hazards regression models were used, with age as the time scale, and stratified by birth cohort and study. The proportional hazard assumption was not violated when comparing log-minus-log and hazard curves with each other. The effect of familial clustering on estimates of precision was accounted for using robust variance estimation. All tests of statistical significance were two-sided. Associations by birth cohort, attained age ( $\leq 35$  years,  $> 35$  years), and study were also assessed. Hazard ratios were estimated for both prospective and retrospective (left-truncated and full-cohort) models in the same study population to enable a comparison with the literature, and to investigate potential biases and age-specific differences. For prospective analyses, OCP data from baseline and follow-up questionnaires were combined and imputed for the interval between age at last questionnaire and age at linkage with cancer registries. For retrospective analyses, only data from the baseline questionnaire were used. Characteristics of OCP use that were identified a priori for investigation included ever use of OCPs (use for more than six months), recency of use (time since last use, in years), age at first use (years), calendar year at first use ( $< 1975$ ,  $\geq 1975$ , proxy for changes in OCP formulations; specific formulations unknown), total duration of use (years), and duration of use before first full-term pregnancy (FFTP); they were time-dependently included in the model, for each year of observation. Potential confounders were family history, defined as the number of first- or second-degree relatives diagnosed with BC (none, 1,  $\geq 2$ ), parity (no/yes, time-dependent), age at FFTP (time-dependent), breast feeding (never/ever and duration in years, time-dependent), and risk-reducing salpingo-oophorectomy (RRSO; no/yes and “no or  $< 3$  years since RRSO”/“yes,  $\geq 3$  years since RRSO”; time-dependent). None of these variables changed the hazard ratio for OCP exposure and BC risk by more than 10%, and therefore they were not included in the final analyses.

All statistical tests were two-sided, a  $P$  value of less than .05 was considered statistically significant. The analyses were performed using STATA-13.0 (Statcorp, College Station, TX).

### Prospective Cohort Analysis

Prospective follow-up started at baseline cohort recruitment or mutation testing, whichever came last, to standardize the potential influence of being aware of the mutation on use of OCPs during follow-up. If age at mutation testing was unknown (1%) or if women were tested in a research setting and it was unknown whether they opted for a clinical test (6%), follow-up started at baseline questionnaire completion. At start of follow-up, women had no history of cancer (exclusive nonmelanoma skin cancer) and had not undergone a

bilateral risk-reducing mastectomy (RRM). Person-years were censored at age of diagnosis of first primary BC (invasive or in situ), diagnosis of another cancer, RRM, death, last follow-up, or age 80 years, whichever came first. Last follow-up was defined as last questionnaire, contact, or linkage, whichever came last.

## Retrospective Cohort Analysis

Two retrospective analyses were conducted. In “full-cohort” retrospective analyses, follow-up commenced at birth. The “left-truncated” retrospective analysis started follow-up five years preceding the date of the baseline questionnaire to reduce the possibility of survival bias. At the start of follow-up, carriers were included in this left-truncated analysis only if they had not been diagnosed with cancer (exclusive nonmelanoma skin cancer) or undergone RRM. In both retrospective analyses, person-years were censored at age of diagnosis of the first primary BC (invasive or in situ), diagnosis of another cancer, RRM, mutation test, or baseline questionnaire, whichever came first. By taking age at mutation testing into account, all women were unaware of carrying the mutation during retrospective person-years. To account for the oversampling of affected individuals, a weighted cohort approach was used, as described by Antoniou et al. (12).

Details on study design, study participants, data collection, and statistical analyses can be found in the [Supplementary Methods](#) (available online).

## Results

### BRCA1 Mutation Carriers

The prospective cohort comprised 2276 women, of whom 269 (11.8%) were diagnosed with incident BC during follow-up. The left-truncated retrospective and full-cohort retrospective analyses included 3828 women (1095, 28.6%, with BC) and 5705 women (2525, 44.3%, with BC), respectively (Table 1). The proportion of young women (<35 years) with BC was lowest in the prospective cohort (14.1% vs 27.9% and 29.7%, respectively). In total, 83% of all women in the prospective cohort and 73% and 75% of women in the retrospective cohorts had ever used OCPs by the end of follow-up (Table 2).

From the prospective cohort analysis, ever OCP use was not associated with BC risk (HR = 1.08, 95% confidence interval [CI] = 0.75 to 1.56). Hazard ratios did not vary according to total duration of use, age at first use, recency of use, or duration of use before FFTP (Table 2). In contrast, from the left-truncated and full-cohort retrospective analyses, we found an association between ever OCP use and BC risk (HR = 1.26, 95% CI = 1.06 to 1.51, and HR = 1.39, 95% CI = 1.23 to 1.58, respectively). Risk increased with longer lifetime duration of use (eg, left-truncated; use < 5 years: HR = 1.28; 5–9 years: HR = 1.27; ≥10 years: HR = 1.37;  $P_{\text{trend}} = .01$ ) and longer duration of use preceding FFTP (eg, left-truncated; <5 years: HR = 1.05; 5–9 years: HR = 1.15; ≥10 years: HR = 1.41;  $P_{\text{trend}} = .001$ ). From the full-cohort retrospective analysis, but not from the left-truncated analysis, there was an increased risk of BC with younger age at first OCP use ( $P_{\text{trend}} < .001$ ) and longer duration of use after FFTP ( $P_{\text{trend}} = .02$ ).

The hazard ratios for associations between ever OCP use and BC risk did not vary by birth cohort or study in either the left-truncated analysis or the full-cohort retrospective analysis. The numbers in birth cohort and study strata were too low to draw conclusions from the prospective analysis (data not shown).

Additional results were restricted to the left-truncated retrospective and prospective analyses as they are susceptible to fewer biases. When stratified by attained age (≤35, >35 years) (Table 3), the left-truncated retrospective analysis suggested that the positive trend with longer duration of use before FFTP was restricted to younger women (≤35 years; <5 years: HR = 1.19; 5–9 years: HR = 1.37; ≥10 years: HR = 1.88; >35 years; <5 years: HR = 1.10; 5–9 years: HR = 1.12; ≥10 years: HR = 1.18;  $P_{\text{difference}} = .08$ ). The sample size was too small to carry out a stratified analysis using the prospective data, with only two to 11 BC cases per category.

To try to explain the different findings from the prospective and left-truncated retrospective analyses, we performed exploratory analyses of time since last OCP use before FFTP. From the left-truncated retrospective analysis, BC risk decreased with a longer time since “last OCP use before FFTP” ( $P_{\text{trend}} = .02$ ) (Figure 1). Although the magnitude of the hazard ratios was smaller from the prospective analysis, the hazard ratios followed a similar pattern.

### BRCA2 Mutation Carriers

The prospective, left-truncated retrospective, and full retrospective cohorts comprised 1610 women (157, 9.8%, with incident BC diagnosed during follow-up), 2512 women (752, 29.9%, with BC), and 3521 women (1548, 44.0%, with BC), respectively (Table 4). As for BRCA1 mutation carriers, for BRCA2 mutation carriers, the proportion of young women (<35 years) with BC was lowest in the prospective cohort (8.2% vs 16.1% and 16.4%, respectively).

In total, 83%, 75%, and 72% of all women from the prospective, left-truncated, and full retrospective cohorts, respectively, had ever used OCPs by the end of follow-up (Table 5).

We found a positive association between ever OCP use and BC risk from both the prospective and full-cohort retrospective analyses (HR = 1.75, 95% CI = 1.03 to 2.97, and HR = 1.52, 95% CI = 1.28 to 1.81, respectively) but not from the left-truncated analysis (HR = 1.06, 95% CI = 0.85 to 1.33). From the full-cohort retrospective analysis, BC risk was higher for women with younger age at first use (≤17 years: HR = 1.53; 18–22 years: HR = 1.66; ≥23 years: HR = 1.40;  $P_{\text{trend}} = .02$ ) and longer duration of use (<5 years: HR = 1.46; 5–9 years: HR = 1.68; ≥10 years: HR = 1.70;  $P_{\text{trend}} < .001$ ), most clearly for use before FFTP (<5 years: HR = 1.30; 5–9 years: HR = 1.38; ≥10 years: HR = 1.64;  $P_{\text{trend}} = .002$ ). There was no evidence of variation in the hazard ratios by any of these characteristics from the prospective or left-truncated analyses.

The association between ever OCP use and BC risk did not vary by birth cohort or study from the retrospective analyses (data not shown; the numbers were too low in the prospective cohort to perform these analyses). The results from the stratified analyses by age were consistent with the unstratified retrospective analyses (left-truncated; all ages: HR = 1.06; ≤35 years: HR = 1.01; >35 years: HR = 1.03). For BRCA2 mutation carriers, we repeated the exploratory analysis by time since last OCP use before FFTP that we conducted for BRCA1 mutation carriers, but no evidence for an association was found (data not shown).

## Discussion

For BRCA1 mutation carriers, no association between ever OCP use and BC risk was found from the prospective analysis. From the left-truncated retrospective analysis, however, we found a positive association (HR = 1.26), which was stronger without

**Table 1.** Characteristics of BRCA1 mutation carrier cohort, by study design

| BRCA1                                                              | Prospective<br>(n = 2276) |             | Retrospective “left-truncated”<br>(n = 3828) |             | Retrospective “full-cohort”<br>(n = 5705) |             |
|--------------------------------------------------------------------|---------------------------|-------------|----------------------------------------------|-------------|-------------------------------------------|-------------|
|                                                                    | BC+                       | BC-         | BC+                                          | BC-         | BC+                                       | BC-         |
| No. (%)                                                            | 269 (11.8)                | 2007 (88.2) | 1095 (28.6)                                  | 2733 (71.4) | 2525 (44.3)                               | 3180 (55.7) |
| Mean age at start of FUP (SD), y                                   | 40.7 (10.3)               | 37.5 (11.8) | 38 (9.4)                                     | 34.1 (11.8) | Birth                                     | Birth       |
| Mean age at end of FUP (SD), y                                     | 44.9 (10.3)               | 43.1 (12.2) | 41 (9.3)                                     | 38.4 (11.6) | 40.1 (8.8)                                | 38.7 (11.6) |
| Age at end of FUP, No. (%)                                         |                           |             |                                              |             |                                           |             |
| <35 y                                                              | 38 (14.1)                 | 560 (27.9)  | 305 (27.9)                                   | 1111 (40.7) | 750 (29.7)                                | 1237 (38.9) |
| 35–64 y                                                            | 216 (80.3)                | 1327 (66.2) | 770 (70.3)                                   | 1555 (56.9) | 1746 (69.2)                               | 1869 (58.7) |
| 65+ y                                                              | 15 (5.6)                  | 120 (6.0)   | 20 (1.8)                                     | 67 (2.5)    | 29 (1.2)                                  | 74 (2.3)    |
| Mean years of FUP (SD), y                                          | 4.2 (3.3)                 | 5.6 (3.7)   | 3.0 (1.3)                                    | 4.3 (1.1)   | 40.1 (8.8)                                | 38.7 (11.6) |
| Censored for, No. (%)                                              |                           |             |                                              |             |                                           |             |
| Breast cancer                                                      | 269 (100.0)               | —           | 1095 (100.0)                                 | —           | 2525 (100.0)                              | —           |
| Ovarian cancer*                                                    | —                         | 49 (2.4)    | —                                            | 240 (8.8)   | —                                         | 413 (13.0)  |
| Other cancer*                                                      | —                         | 45 (2.2)    | —                                            | 34 (1.2)    | —                                         | 145 (4.6)   |
| Bilateral RRM*,†                                                   | —                         | 301 (15.0)  | —                                            | 201 (7.4)   | —                                         | 252 (7.9)   |
| Death*                                                             | —                         | 5 (0.3)     | —                                            | 0 (0.0)     | —                                         | 0 (0.0)     |
| Maximum FUP*                                                       | —                         | 1607 (80.1) | —                                            | 2258 (86.6) | —                                         | 2370 (74.5) |
| Year at end of FUP, No. (%)                                        |                           |             |                                              |             |                                           |             |
| 1959–1989                                                          | 0 (0.0)                   | 0 (0.0)     | 0 (0.0)                                      | 0 (0.0)     | 573 (22.7)                                | 114 (3.6)   |
| 1990–2000                                                          | 26 (9.7)                  | 32 (1.6)    | 558 (51.0)                                   | 902 (33.0)  | 1327 (52.6)                               | 1150 (36.2) |
| 2001–2012                                                          | 243 (90.3)                | 1975 (98.4) | 537 (49.0)                                   | 1831 (67.0) | 625 (24.8)                                | 1916 (60.3) |
| Birth year, No. (%)                                                |                           |             |                                              |             |                                           |             |
| 1920–1959                                                          | 111 (41.3)                | 552 (27.5)  | 508 (46.4)                                   | 886 (32.4)  | 1637 (64.8)                               | 1181 (37.1) |
| 1960–1970                                                          | 114 (42.4)                | 640 (31.9)  | 422 (38.5)                                   | 916 (33.5)  | 699 (27.7)                                | 1026 (32.3) |
| 1971–1992                                                          | 44 (16.4)                 | 815 (40.6)  | 165 (15.1)                                   | 931 (34.1)  | 189 (7.5)                                 | 973 (30.6)  |
| Study, No. (%)                                                     |                           |             |                                              |             |                                           |             |
| 1. EMBRACE‡                                                        | 41 (8.7)                  | 432 (91.3)  | 309 (30.4)                                   | 707 (69.6)  | 740 (47.4)                                | 820 (52.6)  |
| 2. GENEPSO‡                                                        | 46 (9.4)                  | 442 (90.6)  | 136 (17.3)                                   | 649 (82.7)  | 325 (32.0)                                | 691 (68.0)  |
| 3. HEBON‡                                                          | 40 (16.5)                 | 202 (83.5)  | 84 (21.1)                                    | 314 (78.9)  | 330 (41.2)                                | 472 (58.9)  |
| 4. kConFab                                                         | 55 (16.9)                 | 270 (83.1)  | —                                            | —           | —                                         | —           |
| 5. BCFR                                                            | 50 (15.3)                 | 277 (84.7)  | 257 (39.4)                                   | 396 (60.6)  | 456 (51.4)                                | 432 (48.7)  |
| 6. Other‡,§                                                        | 37 (8.8)                  | 384 (91.2)  | 309 (31.7)                                   | 667 (68.3)  | 674 (46.8)                                | 765 (53.2)  |
| RRSO, No. (%)                                                      |                           |             |                                              |             |                                           |             |
| No                                                                 | 153 (56.9)                | 1284 (64.0) | 1059 (96.7)                                  | 2601 (95.2) | 2465 (97.6)                               | 3041 (95.6) |
| Yes                                                                | 116 (43.1)                | 723 (36.0)  | 36 (3.3)                                     | 132 (4.8)   | 60 (2.4)                                  | 139 (4.4)   |
| No. of breast cancers among 1st- and 2nd-degree relatives, No. (%) |                           |             |                                              |             |                                           |             |
| No BC                                                              | 54 (20.1)                 | 546 (27.2)  | 259 (23.7)                                   | 678 (24.8)  | 593 (23.5)                                | 817 (25.7)  |
| 1                                                                  | 91 (33.8)                 | 628 (31.3)  | 317 (29.0)                                   | 763 (27.9)  | 679 (26.9)                                | 888 (27.9)  |
| ≥2                                                                 | 108 (40.2)                | 629 (31.3)  | 288 (26.3)                                   | 872 (31.9)  | 669 (26.5)                                | 961 (30.2)  |
| Missing                                                            | 13 (4.8)                  | 192 (9.6)   | 190 (17.4)                                   | 398 (14.6)  | 524 (20.8)                                | 489 (15.4)  |
| Cancer type unknown                                                | 3 (1.1)                   | 12 (0.6)    | 41 (3.7)                                     | 22 (0.8)    | 60 (2.4)                                  | 25 (0.8)    |
| Parity, No. (%)                                                    |                           |             |                                              |             |                                           |             |
| Nulliparous                                                        | 51 (19.0)                 | 602 (30.0)  | 250 (22.8)                                   | 914 (33.4)  | 513 (20.3)                                | 1020 (32.1) |
| Parous                                                             | 208 (77.3)                | 1405 (70.0) | 845 (77.2)                                   | 1819 (66.6) | 2012 (79.7)                               | 2160 (67.9) |
| Missing                                                            | 10 (3.7)                  | 0 (0.0)     | 0 (0.0)                                      | 0 (0.0)     | 0 (0.0)                                   | 0 (0.0)     |

\*After exclusion of women in the preceding categories. BC = breast cancer; FUP = follow-up; RRM = risk-reducing mastectomy.

†RRM occurring at the same age or within one year of BC diagnosis was ignored.

‡IBCCS is a collaboration of 1) EMBRACE, 2) GENEPSO, 3) HEBON, and 6) other.

§“Other” included the following studies: MUV, MODSQUAD, GC-HBOC, Lund-BRCA, OUH, NIO, IHCC, HCSC, Stockholm-BRCA, INHERIT, CNIO, Milan Italy, HSP, DKFZ, Dusseldorf Germany, Belgium (order is based on number of carriers included in the analyses).

left-truncation (full cohort: HR = 1.39). Longer duration of use, especially before FFTP, was associated with an increasing risk of BC from both retrospective analyses, but not from the prospective analysis. The increasing risk associated with a younger age at first use found from the full-cohort retrospective analysis was not observed in the left-truncated retrospective or prospective analyses. For BRCA2 mutation carriers, we found positive associations between ever OCP use and BC risk from both the

prospective and full-cohort retrospective analyses (HR = 1.75 and HR = 1.52, respectively). However, there was no increased risk after left-truncation (HR = 1.06). From full-cohort retrospective analyses, increasing risks with younger age at first use and longer durations of use, especially before FFTP, were found, but these trends again did not persist in left-truncated retrospective or prospective analyses. It is important to note, however, that for both BRCA1 and BRCA2 mutation carriers, the confidence

Table 2. Breast cancer HR estimates by OCP use characteristics for BRCA1 mutation carriers, by study design

|                               | Prospective |  |             |                     | Retrospective "left-truncated" |  |             |  | Retrospective "full-cohort" |  |             |                        |
|-------------------------------|-------------|--|-------------|---------------------|--------------------------------|--|-------------|--|-----------------------------|--|-------------|------------------------|
|                               | BC+         |  | BC-         |                     | BC+                            |  | BC-         |  | BC+                         |  | BC-         |                        |
|                               | No. (%)†    |  | No. (%)†    | HR (95% CI)‡        | No. (%)†                       |  | No. (%)†    |  | No. (%)†                    |  | No. (%)†    | Weighted* HR (95% CI)§ |
| OCP use                       |             |  |             |                     |                                |  |             |  |                             |  |             |                        |
| Never (<6 mo)                 | 39 (14.5)   |  | 290 (14.5)  | 1.00                | 205 (18.7)                     |  | 552 (20.2)  |  | 603 (23.9)                  |  | 672 (21.1)  | 1.00                   |
| Ever                          | 227 (84.4)  |  | 1665 (83.0) | 1.08 (0.75 to 1.56) | 848 (77.4)                     |  | 2039 (74.6) |  | 1804 (71.5)                 |  | 2335 (73.4) | 1.39 (1.23 to 1.58)¶   |
| Ever, starting age unknown    | 9 (3.4)     |  | 69 (3.4)    |                     | 20 (1.8)                       |  | 95 (3.5)    |  | 68 (2.7)                    |  | 110 (3.5)   |                        |
| Missing                       | 3 (1.1)     |  | 52 (2.6)    |                     | 22 (2.0)                       |  | 47 (1.7)    |  | 50 (2.0)                    |  | 63 (2.0)    |                        |
| Calendar year at start        |             |  |             |                     |                                |  |             |  |                             |  |             |                        |
| Never (<6 mo)                 | 39 (14.5)   |  | 290 (14.5)  | 1.00                | 205 (18.7)                     |  | 552 (20.2)  |  | 603 (23.9)                  |  | 672 (21.1)  | 1.00                   |
| ≤1975                         | 61 (22.7)   |  | 256 (12.8)  | 1.25 (0.79 to 1.96) | 246 (22.5)                     |  | 377 (13.8)  |  | 845 (33.5)                  |  | 512 (16.1)  | 1.49 (1.29 to 1.71)    |
| >1975                         | 157 (58.4)  |  | 1340 (66.8) | 0.99 (0.66 to 1.48) | 602 (55.0)                     |  | 1662 (60.8) |  | 959 (38.0)                  |  | 1823 (57.3) | 1.27 (1.09 to 1.48)    |
| Ever, starting year unknown   | 9 (3.4)     |  | 69 (3.4)    |                     | 20 (1.8)                       |  | 95 (3.5)    |  | 68 (2.7)                    |  | 110 (3.5)   |                        |
| Missing                       | 3 (1.1)     |  | 52 (2.6)    |                     | 22 (2.0)                       |  | 47 (1.7)    |  | 50 (2.0)                    |  | 63 (2.0)    |                        |
| Time since last use, y        |             |  |             |                     |                                |  |             |  |                             |  |             |                        |
| Never (<6 mo)                 | 39 (14.5)   |  | 290 (14.5)  | 1.00                | 205 (18.7)                     |  | 552 (20.2)  |  | 603 (23.9)                  |  | 672 (21.1)  | 1.00                   |
| ≤3                            | 45 (16.7)   |  | 392 (19.5)  | 0.96 (0.60 to 1.55) | 218 (19.9)                     |  | 772 (28.3)  |  | 528 (20.9)                  |  | 885 (27.8)  | 1.53 (1.30 to 1.80)    |
| >3-9                          | 48 (17.8)   |  | 328 (16.3)  | 1.14 (0.72 to 1.80) | 104 (9.5)                      |  | 277 (10.1)  |  | 300 (11.9)                  |  | 317 (10.0)  | 1.42 (1.19 to 1.70)    |
| ≥10                           | 95 (35.3)   |  | 622 (31.0)  | 1.11 (0.75 to 1.65) | 283 (25.8)                     |  | 583 (21.3)  |  | 552 (21.9)                  |  | 681 (21.4)  | 1.44 (1.22 to 1.69)    |
| Ever, no period-specific data | 39 (14.5)   |  | 323 (16.1)  |                     | 263 (24.0)                     |  | 502 (18.4)  |  | 492 (19.5)                  |  | 562 (17.7)  |                        |
| Missing                       | 3 (1.1)     |  | 52 (2.6)    |                     | 22 (2.0)                       |  | 47 (1.7)    |  | 50 (2.0)                    |  | 63 (2.0)    | .71                    |
| P <sub>trend</sub> per year   |             |  |             | .3                  |                                |  |             |  |                             |  |             |                        |
| Starting age, y               |             |  |             |                     |                                |  |             |  |                             |  |             |                        |
| Never (<6 mo)                 | 39 (14.5)   |  | 290 (14.5)  | 1.00                | 205 (18.7)                     |  | 552 (20.2)  |  | 603 (23.9)                  |  | 672 (21.1)  | 1.00                   |
| ≤17                           | 71 (26.4)   |  | 592 (29.5)  | 1.16 (0.76 to 1.79) | 275 (25.1)                     |  | 745 (27.3)  |  | 498 (19.7)                  |  | 846 (26.6)  | 1.85 (1.55 to 2.20)    |
| 18-22                         | 109 (40.5)  |  | 733 (36.5)  | 1.11 (0.75 to 1.65) | 392 (35.8)                     |  | 924 (33.8)  |  | 850 (33.7)                  |  | 1043 (32.8) | 1.44 (1.24 to 1.67)    |
| >22                           | 38 (14.1)   |  | 271 (13.5)  | 0.96 (0.60 to 1.53) | 181 (16.5)                     |  | 370 (13.5)  |  | 456 (18.1)                  |  | 446 (14.0)  | 1.17 (1.00 to 1.37)    |
| Ever, starting age unknown    | 9 (3.4)     |  | 69 (3.4)    |                     | 20 (1.8)                       |  | 95 (3.5)    |  | 68 (2.7)                    |  | 110 (3.5)   |                        |
| Missing                       | 3 (1.1)     |  | 52 (2.6)    |                     | 22 (2.0)                       |  | 47 (1.7)    |  | 50 (2.0)                    |  | 63 (2.0)    | 6.00E to 05            |
| P <sub>trend</sub> per year   |             |  |             | .57                 |                                |  |             |  |                             |  |             |                        |
| Total duration of use, y      |             |  |             |                     |                                |  |             |  |                             |  |             |                        |
| Never (<6 mo)                 | 39 (14.5)   |  | 290 (14.5)  | 1.00                | 205 (18.7)                     |  | 552 (20.2)  |  | 603 (23.9)                  |  | 672 (21.1)  | 1.00                   |
| <5                            | 67 (24.9)   |  | 484 (24.1)  | 1.13 (0.75 to 1.71) | 135 (12.3)                     |  | 209 (15.0)  |  | 321 (12.7)                  |  | 466 (14.7)  | 1.25 (1.04 to 1.50)    |
| 5-9                           | 55 (20.5)   |  | 537 (26.8)  | 0.93 (0.60 to 1.43) | 186 (17.0)                     |  | 573 (21.0)  |  | 437 (17.3)                  |  | 663 (20.9)  | 1.45 (1.23 to 1.72)    |
| ≥10                           | 92 (34.2)   |  | 545 (27.2)  | 1.16 (0.77 to 1.73) | 284 (25.9)                     |  | 650 (23.8)  |  | 622 (24.6)                  |  | 754 (23.7)  | 1.67 (1.42 to 1.96)    |
| Ever, no period-specific data | 13 (4.8)    |  | 99 (4.9)    |                     | 263 (24.0)                     |  | 502 (18.4)  |  | 492 (19.5)                  |  | 562 (17.7)  |                        |
| Missing                       | 3 (1.1)     |  | 52 (2.6)    |                     | 22 (2.0)                       |  | 47 (1.7)    |  | 50 (2.0)                    |  | 63 (2.0)    | 4.9E to 10             |
| P <sub>trend</sub> per year   |             |  |             | .66                 |                                |  |             |  |                             |  |             |                        |
| Duration by FFTP              |             |  |             |                     |                                |  |             |  |                             |  |             |                        |
| Before FFTP, y                |             |  |             |                     |                                |  |             |  |                             |  |             |                        |
| Never (<6 mo)                 | 70 (26.0)   |  | 487 (24.3)  | 1.00                | 317 (29.0)                     |  | 775 (28.4)  |  | 937 (37.1)                  |  | 946 (29.8)  | 1.00                   |
| <5                            | 37 (13.8)   |  | 349 (17.4)  | 1.10 (0.71 to 1.72) | 144 (13.2)                     |  | 157 (16.7)  |  | 321 (12.7)                  |  | 514 (16.2)  | 1.19 (0.99 to 1.42)    |
| 5-9                           | 44 (16.4)   |  | 474 (23.6)  | 0.93 (0.60 to 1.45) | 194 (17.7)                     |  | 598 (21.9)  |  | 401 (15.9)                  |  | 690 (21.7)  | 1.39 (1.16 to 1.66)    |
| ≥10                           | 38 (14.1)   |  | 278 (13.9)  | 1.17 (0.73 to 1.88) | 155 (14.2)                     |  | 354 (13.0)  |  | 324 (12.8)                  |  | 405 (12.7)  | 2.02 (1.64 to 2.50)    |
| P <sub>trend</sub> per year   |             |  |             | .93                 |                                |  |             |  |                             |  |             | 4.5E to 11             |
|                               |             |  |             |                     |                                |  |             |  |                             |  |             | (continued)            |

Table 2. (continued)

|                               | Prospective     |                 |                     | Retrospective "left-truncated" |                 |                           | Retrospective "full-cohort" |                 |                           |
|-------------------------------|-----------------|-----------------|---------------------|--------------------------------|-----------------|---------------------------|-----------------------------|-----------------|---------------------------|
|                               | BC+<br>No. (%)† | BC-<br>No. (%)† | HR (95% CI)‡        | BC+<br>No. (%)†                | BC-<br>No. (%)† | Weighted*<br>HR (95% CI)§ | BC+<br>No. (%)†             | BC-<br>No. (%)† | Weighted*<br>HR (95% CI)§ |
| After FFTP, y                 |                 |                 |                     |                                |                 |                           |                             |                 |                           |
| Never (<6 mo)                 | 117 (43.5)      | 1087 (54.2)     | 1.00                | 514 (46.9)                     | 1505 (55.1)     | 1.00                      | 1253 (49.6)                 | 1752 (55.1)     | 1.00                      |
| <5                            | 36 (13.4)       | 255 (12.7)      | 1.14 (0.75 to 1.73) | 136 (12.4)                     | 107 (11.2)      | 1.15 (0.92 to 1.44)       | 322 (12.8)                  | 365 (11.5)      | 1.08 (0.91 to 1.28)       |
| 5-9                           | 17 (6.3)        | 134 (6.7)       | 0.89 (0.51 to 1.54) | 84 (7.7)                       | 190 (7.0)       | 1.04 (0.80 to 1.35)       | 214 (8.5)                   | 221 (7.0)       | 1.12 (0.93 to 1.36)       |
| ≥10                           | 19 (7.1)        | 112 (5.6)       | 1.04 (0.60 to 1.79) | 76 (6.9)                       | 182 (6.7)       | 1.01 (0.76 to 1.35)       | 194 (7.7)                   | 217 (6.8)       | 1.18 (0.95 to 1.45)       |
| P <sub>trend</sub> per year   |                 |                 | .99                 |                                |                 | .76                       |                             |                 | .02                       |
| Ever, no period-specific data | 77 (28.6)       | 367 (18.3)      |                     | 263 (24.0)                     | 502 (18.4)      |                           | 492 (19.5)                  | 562 (17.7)      |                           |
| OCP or FFTP data missing      | 3 (1.1)         | 52 (2.6)        |                     | 22 (2.0)                       | 47 (1.7)        |                           | 50 (2.0)                    | 63 (2.0)        |                           |

\*Weighted to account for the oversampling of affected individuals. BC = breast cancer; CI = confidence interval; FFTP = first full-term pregnancy; HR = hazard ratio; OCP = oral contraceptive preparation.

†Distribution of variables at end of follow-up.

‡Intrinsically stratified on study (EMBRACE, GENEPSo, HEBON, kConFab, BCFR, other) and birth cohort (1920-1960 < 1961-1992). Clustered on family membership.

§Intrinsically stratified on study (EMBRACE, GENEPSo, HEBON, BCFR, other) and birth cohort (1920-1952, 1953-1964, 1965-1992). Clustered on family membership.

||Duration before FFTP and after FFTP included in one multivariable model. Nulliparous women only contributed to various duration categories before FFTP and were placed in the category "never user" after FFTP. Adjusted for age at FFTP (nulliparous, ≤20, 21-25, >25 years).

¶Unweighted results: Left-truncated HR = 1.24, 95% CI = 1.05 to 1.45; Full cohort HR = 1.38, 95% CI = 1.25 to 1.52.

intervals of the estimates from the retrospective and prospective analyses overlapped.

All studies on OCP use and risk of BC for BRCA1/2 mutation carriers to date have performed full-cohort retrospective analyses (6,13-17). Among "independent" studies, using data not included in the present study, most found a statistical significantly increased association with BC risk for BRCA1 mutation carriers, comparable with our full-cohort retrospective analysis (13,17,18). In addition, Kotsopoulos et al. and Ursin et al. also found that the increased risk was limited to early-onset BC (<40 years) (17,18). For BRCA2 mutation carriers, results from two previous independent full-cohort analyses were very inconsistent (odds ratio = 0.94 vs HR = 2.07). However, in our study, the magnitude of the associations estimated from the full-cohort analysis became weaker (BRCA1) or even disappeared (BRCA2) when survivors of more than five years were excluded (left-truncated retrospective analyses). This might suggest the presence of survival bias, driven by a lower stage at diagnosis for OCP users compared with nonusers, as found for the general population (19). However, a true age-related effect that disappears when the cohort gets older might be another explanation. Apart from survival bias, there was evidence for testing bias, resulting from the non-random uptake of genetic testing. We adjusted for the oversampling of carriers with BC by using the weighted cohort approach (12). Furthermore, the presence of recall and response biases cannot be excluded in the retrospective analyses.

We consider the findings from prospective analyses to be our main results, as they are free of testing bias and hardly influenced by recall and survival bias. They showed no association between the various characteristics of OCP use and BC risk for BRCA1 mutation carriers, whereas compared with never users, ever OCP users had a higher risk of BC for BRCA2 mutation carriers. However, trends with duration, starting age, or recency of OCP use were absent. Such trends might have been expected if the association had been causal, but power was limited to detect such trends. Results of our adequately powered next-best left-truncated analyses support the absence of an association between OCP use and risk of BC for BRCA2 mutation carriers.

Although prospective results showed no associations for BRCA1 mutation carriers, weak associations between OCP use and BC risk arose in left-truncated analyses. This seemed to be driven by duration of use before FFTP. Exploratory analyses showed that duration of OCP use before FFTP was associated with BC risk diagnosed before age 35 years, consistent with findings of Pike et al. in the general population (20). The prospective cohort included a much smaller proportion of such young BC cases (≤35 years 14.1% vs 27.9%, respectively) (Table 1). Additionally, the positive association of OCP use before FFTP with risk of early-onset BC seemed to diminish with time since last use before FFTP. Thus, the prospective cohort may have been too old to detect the temporal effect of OCP use before FFTP on risk of early-onset BC.

We did not consider a combined BRCA1/2 mutation carrier analysis to increase prospective power, because of our own gene-specific findings and those of studies that reported different associations for BRCA1 and BRCA2 mutation carriers (21-23). Such differences may be caused by differences in BC subtype, being more often ER-negative in BRCA1-associated BC and ER-positive in BRCA2-associated BC in young middle-aged women (24).

This is the first prospective study to investigate the association between OCP use and BC risk for BRCA1 and BRCA2 mutation carriers. Two previous reports were based on left-truncated retrospective analyses; however, these form a subset of current retrospective analysis. Brohet et al. (IBCCS) found a hazard ratio of 1.48 (95% CI = 0.92 to 2.36) for ever OCP use in 967 BRCA1/2

**Table 3.** Breast cancer HR estimates for BRCA1 mutation carriers stratified by attained age, the left-truncated retrospective cohort

|                               | Retrospective "left-truncated" |                             |                      |                             |                             |                      |
|-------------------------------|--------------------------------|-----------------------------|----------------------|-----------------------------|-----------------------------|----------------------|
|                               | BC+<br>No. (%) <sup>*</sup>    | BC-<br>No. (%) <sup>*</sup> | HR (95% CI) †        | BC+<br>No. (%) <sup>*</sup> | BC-<br>No. (%) <sup>*</sup> | HR (95% CI) †        |
|                               | ≤35 y (n = 1955)               |                             |                      | >35 y (n = 2255)            |                             |                      |
| OCP use                       |                                |                             |                      |                             |                             |                      |
| Never (<6 mo)                 | 40 (11.1)                      | 249 (15.6)                  | 1.00                 | 165 (22.4)                  | 363 (23.9)                  | 1.00                 |
| Ever                          | 302 (84.1)                     | 1283 (80.4)                 | 1.41 (1.01 to 1.97)  | 546 (74.2)                  | 1062 (69.9)                 | 1.19 (0.99 to 1.44)  |
| Ever, starting age Unknown    | 6 (1.7)                        | 45 (2.8)                    |                      | 14 (1.9)                    | 63 (4.2)                    |                      |
| Missing                       | 11 (3.1)                       | 19 (1.2)                    |                      | 11 (1.5)                    | 31 (2.0)                    |                      |
| Duration by FFTP‡             |                                |                             |                      |                             |                             |                      |
| Before FFTP, y                |                                |                             |                      |                             |                             |                      |
| Never (<6 mo)                 | 57 (15.9)                      | 312 (19.6)                  | 1.00                 | 260 (35.3)                  | 553 (36.4)                  | 1.00                 |
| <5                            | 39 (10.9)                      | 284 (17.8)                  | 1.19 (0.77 to 1.84)§ | 105 (14.3)                  | 240 (15.8)                  | 1.10 (0.86 to 1.40)§ |
| 5–9.99                        | 78 (21.7)                      | 426 (26.7)                  | 1.37 (0.93 to 2.02)  | 116 (15.8)                  | 249 (16.4)                  | 1.12 (0.87 to 1.45)  |
| ≥10                           | 81 (22.6)                      | 255 (16.0)                  | 1.88 (1.27 to 2.79)¶ | 74 (10.1)                   | 157 (10.3)                  | 1.18 (0.87 to 1.60)¶ |
| P <sub>trend</sub> per year   |                                |                             | .001#                |                             |                             | .08 #                |
| After FFTP, y                 |                                |                             |                      |                             |                             |                      |
| Never (<6 mo)                 | 178 (49.6)                     | 962 (60.3)                  | 1.00                 | 336 (45.7)                  | 715 (47.1)                  | 1.00                 |
| <5                            | 41 (11.4)                      | 176 (11.0)                  | 1.03 (0.70 to 1.50)  | 95 (12.9)                   | 189 (12.4)                  | 1.10 (0.86 to 1.40)  |
| 5–9.99                        | 24 (6.7)                       | 101 (6.3)                   | 1.09 (0.68 to 1.76)  | 60 (8.2)                    | 129 (8.5)                   | 1.01 (0.76 to 1.36)  |
| ≥10                           | 12 (3.3)                       | 38 (2.4)                    | 1.93 (0.99 to 3.75)  | 64 (8.7)                    | 166 (10.9)                  | 0.89 (0.67 to 1.18)  |
| P <sub>trend</sub> per year   |                                |                             | .4                   |                             |                             | .86                  |
| Ever, no period-specific data | 93 (25.9)                      | 300 (18.8)                  |                      | 170 (23.1)                  | 289 (19.0)                  |                      |
| OCP or FFTP data missing      | 11 (3.1)                       | 19 (1.2)                    |                      | 11 (1.5)                    | 31 (2.0)                    |                      |

BC = breast cancer; CI = confidence interval; FFTP = first full-term pregnancy; HR = hazard ratio; OCP = oral contraceptive preparations.

<sup>\*</sup>Distribution of variables at end of follow-up.

†Intrinsically stratified on study (EMBRACE, GENEPSO, HEBON, BCFR, other) and birth cohort (1920–1952, 1953–1964, 1965–1992). Clustered on family membership.

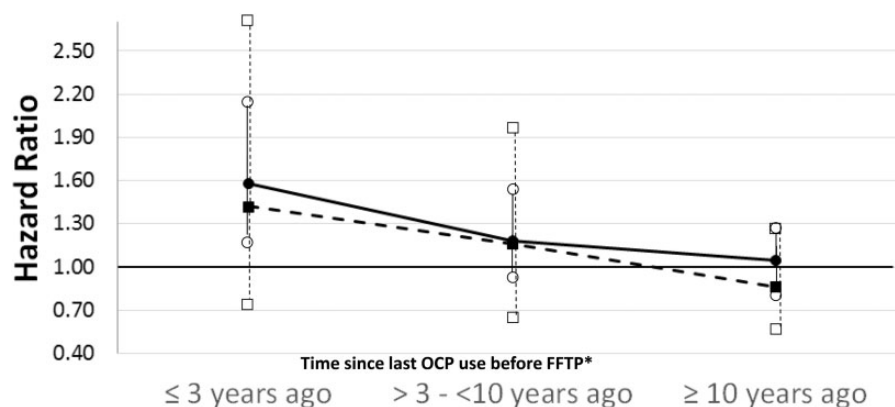
‡Duration before FFTP and after FFTP were included in one multivariable model. Nulliparous women only contributed to various duration categories before FFTP and were placed in the category "never user" after FFTP. Adjusted for age at FFTP (nulliparous, ≤20, 21–25, >25 years)

§Test for difference: *P* = .406.

||Test for difference: *P* = .757.

¶Test for difference: *P* = .055.

#Test for difference: *P* = .077.



**Figure 1.** Association between time since last oral contraceptive preparation use before first full-term pregnancy and breast cancer risk among BRCA1 mutation carriers. **Black dot** indicates retrospective "left-truncated" analysis. **Black square** indicates prospective analysis. **Nonfilled symbols** are 95% confidence intervals. <sup>\*</sup>Adjusted for oral contraceptive preparation use after first full-term pregnancy. FFTP = first full-term pregnancy; OCP = oral contraceptive preparation.

mutation carriers combined (14). Haile et al. (BCFR and kConFab), restricting analyses to women younger than age 50 years, found a hazard ratio of 0.77 (95% CI = 0.53 to 1.12) for ever OCP use in 497 BRCA1 mutation carriers and a hazard ratio of 1.62 (95% CI = 0.90 to 1.92) for 307 BRCA2 mutation carriers (16). Results by Haile et al. were inconsistent with our findings in mutation carriers younger

than age 50 years (BRCA1: HR = 1.32, 95% CI = 1.10 to 1.58; BRCA2: HR = 1.08, 95% CI = 0.86 to 1.36), and additionally, there was no evidence for heterogeneity between the harmonized studies in our cohort (BRCA1: *P* = .683; BRCA2: *P* = .882).

The association of OCP use with BC risk is not the only consideration in the clinical OCP management of BRCA1 and BRCA2

**Table 4.** Characteristics of BRCA2 mutation carrier cohort, by study design

| BRCA2                                                              | Prospective<br>(n = 1610) |             | Retrospective “left-truncated”<br>(n = 2512) |             | Retrospective “full-cohort”<br>(n = 3521) |             |
|--------------------------------------------------------------------|---------------------------|-------------|----------------------------------------------|-------------|-------------------------------------------|-------------|
|                                                                    | BC+                       | BC-         | BC+                                          | BC-         | BC+                                       | BC-         |
| No. (%)                                                            | 157 (9.8)                 | 1453 (90.3) | 752 (29.9)                                   | 1760 (70.6) | 1548 (44.0)                               | 1973 (56.0) |
| Mean age at start of FUP (SD), y                                   | 45.1 (10.1)               | 40 (12.6)   | 40.9 (9.6)                                   | 36.4 (12.5) | Birth                                     | Birth       |
| Mean age at end of FUP (SD), y                                     | 49 (10.3)                 | 45.1 (13.0) | 44 (9.5)                                     | 40.8 (12.3) | 43.4 (9.1)                                | 41 (12.4)   |
| Age at end of FUP, No. (%)                                         |                           |             |                                              |             |                                           |             |
| <35 y                                                              | 13 (8.2)                  | 337 (23.2)  | 121 (16.1)                                   | 593 (33.7)  | 254 (16.4)                                | 652 (33.1)  |
| 35–64 y                                                            | 132 (84.1)                | 993 (68.4)  | 611 (81.3)                                   | 1092 (62.0) | 1261 (81.4)                               | 1232 (62.5) |
| 65+ y                                                              | 12 (7.6)                  | 123 (8.5)   | 20 (2.7)                                     | 75 (4.3)    | 33 (2.1)                                  | 89 (4.5)    |
| Mean years of FUP (SD)                                             | 3.8 (3.1)                 | 5 (3.4)     | 3 (1.2)                                      | 4.5 (1.0)   | 43.4 (9.1)                                | 41 (12.4)   |
| Censored for, No. (%)                                              |                           |             |                                              |             |                                           |             |
| Breast cancer                                                      | 157 (100.0)               | —           | 752 (100.0)                                  | —           | 1548 (100.0)                              | —           |
| Ovarian cancer*                                                    | —                         | 9 (0.6)     | —                                            | 85 (4.8)    | —                                         | 142 (7.2)   |
| Other cancer*                                                      | —                         | 29 (2.0)    | —                                            | 36 (2.1)    | —                                         | 140 (7.1)   |
| Bilateral RRM*,†                                                   | —                         | 182 (12.5)  | —                                            | 117 (6.7)   | —                                         | 132 (6.7)   |
| Death†                                                             | —                         | 8 (0.6)     | —                                            | 2 (0.1)     | —                                         | 2 (0.1)     |
| Maximum FUP*                                                       | —                         | 1225 (84.3) | —                                            | 1520 (86.4) | —                                         | 1557 (78.9) |
| Year at end of FUP, No. (%)                                        |                           |             |                                              |             |                                           |             |
| 1959–1989                                                          | 0 (0.0)                   | 0 (0.0)     | 0 (0.0)                                      | 0 (0.0)     | 267 (17.3)                                | 70 (3.6)    |
| 1990–2000                                                          | 15 (9.6)                  | 12 (0.8)    | 335 (44.6)                                   | 320 (18.2)  | 767 (49.6)                                | 433 (22.0)  |
| 2001–2012                                                          | 142 (90.5)                | 1441 (99.2) | 417 (55.5)                                   | 1440 (81.8) | 514 (33.2)                                | 1470 (74.5) |
| Birth year, No. (%)                                                |                           |             |                                              |             |                                           |             |
| 1920–1959                                                          | 86 (54.8)                 | 459 (31.6)  | 406 (54.0)                                   | 612 (34.8)  | 1067 (68.9)                               | 776 (39.3)  |
| 1960–1970                                                          | 60 (38.2)                 | 481 (33.1)  | 281 (37.4)                                   | 598 (34.0)  | 401 (25.9)                                | 630 (31.9)  |
| 1971–1992                                                          | 11 (7.0)                  | 513 (35.3)  | 65 (8.6)                                     | 550 (31.3)  | 80 (5.2)                                  | 567 (28.7)  |
| Study, No. (%)                                                     |                           |             |                                              |             |                                           |             |
| 1. EMBRACE‡                                                        | 42 (8.7)                  | 441 (91.3)  | 269 (28.9)                                   | 662 (71.1)  | 611 (45.1)                                | 744 (54.9)  |
| 2. GENEPSO‡                                                        | 18 (5.5)                  | 307 (94.5)  | 71 (14.6)                                    | 416 (85.4)  | 161 (26.9)                                | 437 (73.1)  |
| 3. HEBON‡                                                          | 4 (5.3)                   | 71 (94.7)   | 26 (20.3)                                    | 102 (79.7)  | 90 (38.0)                                 | 147 (62)    |
| 4. kConFab                                                         | 38 (13.2)                 | 250 (86.8)  | —                                            | —           | —                                         | —           |
| 5. BCFR                                                            | 33 (12.9)                 | 222 (87.1)  | 226 (43.5)                                   | 294 (56.5)  | 356 (52.6)                                | 321 (47.4)  |
| 6. Other‡,§                                                        | 22 (12.0)                 | 162 (88.0)  | 160 (35.9)                                   | 286 (64.1)  | 330 (50.5)                                | 324 (49.5)  |
| RRSO, No. (%)                                                      |                           |             |                                              |             |                                           |             |
| No                                                                 | 106 (67.5)                | 1007 (69.3) | 725 (96.4)                                   | 1689 (96.0) | 1494 (96.5)                               | 1897 (96.2) |
| Yes                                                                | 51 (32.5)                 | 446 (30.7)  | 27 (3.6)                                     | 71 (4.0)    | 54 (3.5)                                  | 76 (3.9)    |
| No. of breast cancers among 1st- and 2nd-degree relatives, No. (%) |                           |             |                                              |             |                                           |             |
| No BC                                                              | 17 (10.8)                 | 285 (19.6)  | 131 (17.4)                                   | 292 (16.6)  | 276 (17.8)                                | 347 (17.6)  |
| 1                                                                  | 49 (31.2)                 | 446 (30.7)  | 231 (30.7)                                   | 452 (25.7)  | 422 (27.3)                                | 489 (25.2)  |
| ≥2                                                                 | 78 (49.7)                 | 556 (38.3)  | 209 (27.8)                                   | 715 (40.6)  | 446 (28.8)                                | 756 (38.3)  |
| Missing                                                            | 13 (8.3)                  | 153 (10.5)  | 143 (19.0)                                   | 292 (16.6)  | 350 (22.6)                                | 361 (18.3)  |
| Cancer type unknown                                                | 0 (0.0)                   | 13 (0.9)    | 38 (5.1)                                     | 9 (0.5)     | 54 (3.5)                                  | 11 (0.6)    |
| Parity, No. (%)                                                    |                           |             |                                              |             |                                           |             |
| Nulliparous                                                        | 22 (14.0)                 | 406 (27.9)  | 142 (18.9)                                   | 525 (29.8)  | 274 (17.7)                                | 572 (29.0)  |
| Parous                                                             | 127 (80.9)                | 1047 (72.1) | 610 (81.1)                                   | 1235 (70.2) | 1274 (82.3)                               | 1401 (71.0) |
| Missing                                                            | 8 (5.1)                   | 0 (0.0)     | 0 (0.0)                                      | 0 (0.0)     | 0 (0.0)                                   | 0 (0.0)     |

BC = breast cancer; FUP = follow-up; RRM = risk-reducing mastectomy.

\*After exclusion of women in the preceding categories.

†RRM occurring at the same age or within one year of BC diagnosis was ignored.

‡IBCCS is a collaboration of 1) EMBRACE, 2) GENEPSO, 3) HEBON, and 6) Other.

§“Other” included the following studies: GC-HBOC, MUV, MODSQUAD, INHERIT, HCSC, OUH, Lund-BRCA, CNIO, NIO, Stockholm-BRCA, Milan Italy, HSP (order is based on number of carriers included in the analyses).

mutation carriers, because these mutations are also associated with high risk of ovarian cancer (1). The meta-analysis by Moorman et al. reported a consistent inverse association for OCP use and risk of ovarian cancer, proportional with duration of use (25), although potential bias was not investigated. The relative risk reduction appears to be comparable to that in the general population, so that the absolute ovarian cancer risk reduction is large. However, in many Western countries, the majority of BRCA1 and BRCA2 mutation carriers (70%–75%) now opt

for RRSO between age 35 and 50 years, when childbearing is completed (26,27), whereas the uptake of RRM is lower (35%–44%) (28) and varies widely between countries. These aspects should be taken into consideration when balancing the risks and benefits of OCP use for BRCA1 and BRCA2 mutation carriers.

In conclusion, prospective analyses did not show that past use of OCP causes an increased BC risk for BRCA1 mutation carriers in young middle-aged women (40–50 years). For BRCA2

Table 5. Breast cancer HR estimates by OCP use characteristics for BRCA2 mutation carriers, by study design

|                               | Prospective |             |          |                     | Retrospective "left-truncated" |             |          |                           | Retrospective "full-cohort" |             |          |                           |
|-------------------------------|-------------|-------------|----------|---------------------|--------------------------------|-------------|----------|---------------------------|-----------------------------|-------------|----------|---------------------------|
|                               | BC+         | BC-         | No. (%)† | HR (95% CI)‡        | BC+                            | BC-         | No. (%)† | Weighted*<br>HR (95% CI)§ | BC+                         | BC-         | No. (%)† | Weighted*<br>HR (95% CI)§ |
|                               |             |             |          |                     |                                |             |          |                           |                             |             |          |                           |
| OCP use                       |             |             |          |                     |                                |             |          |                           |                             |             |          |                           |
| Never (<6 mo)                 | 17 (10.8)   | 214 (14.7)  |          | 1.00                | 161 (21.4)                     | 337 (19.2)  |          | 1.00                      | 376 (24.3)                  | 408 (20.7)  |          | 1.00                      |
| Ever                          | 137 (87.3)  | 1206 (83.0) |          | 1.75 (1.03 to 2.97) | 563 (74.9)                     | 1333 (75.7) |          | 1.06 (0.85 to 1.33)¶      | 1096 (70.8)                 | 1456 (73.8) |          | 1.52 (1.28 to 1.81)¶      |
| Ever, starting age unknown    | 3 (1.9)     | 42 (2.9)    |          |                     | 16 (2.1)                       | 63 (3.6)    |          |                           | 46 (3.0)                    | 73 (3.7)    |          |                           |
| Missing                       | 3 (1.9)     | 33 (2.3)    |          |                     | 12 (1.6)                       | 27 (1.5)    |          |                           | 30 (1.9)                    | 36 (1.8)    |          |                           |
| Calendar year at start        |             |             |          |                     |                                |             |          |                           |                             |             |          |                           |
| Never (<6 mo)                 | 17 (10.8)   | 214 (14.7)  |          | 1.00                | 161 (21.4)                     | 337 (19.2)  |          | 1.00                      | 376 (24.3)                  | 408 (20.7)  |          | 1.00                      |
| ≤1975                         | 51 (32.5)   | 226 (15.6)  |          | 1.77 (0.98 to 3.21) | 197 (26.2)                     | 279 (15.9)  |          | 1.06 (0.80 to 1.41)       | 554 (35.8)                  | 352 (17.8)  |          | 1.47 (1.22 to 1.78)       |
| >1975                         | 83 (52.9)   | 938 (64.6)  |          | 1.77 (0.96 to 3.25) | 366 (48.7)                     | 1054 (59.9) |          | 1.06 (0.83 to 1.37)       | 542 (35.0)                  | 1104 (56.0) |          | 1.63 (1.30 to 2.05)       |
| Ever, starting year unknown   | 3 (1.9)     | 42 (2.9)    |          |                     | 16 (2.1)                       | 63 (3.6)    |          |                           | 46 (3.0)                    | 73 (3.7)    |          |                           |
| Missing                       | 3 (1.9)     | 33 (2.3)    |          |                     | 12 (1.6)                       | 27 (1.5)    |          |                           | 30 (1.9)                    | 36 (1.8)    |          |                           |
| Time since last use, y        |             |             |          |                     |                                |             |          |                           |                             |             |          |                           |
| Never (<6 mo)                 | 17 (10.8)   | 214 (14.7)  |          | 1.00                | 161 (21.4)                     | 337 (19.2)  |          | 1.00                      | 376 (24.3)                  | 408 (20.7)  |          | 1.00                      |
| ≤3                            | 22 (14.0)   | 290 (20.0)  |          | 1.56 (0.77 to 3.17) | 96 (12.8)                      | 431 (24.5)  |          | 1.12 (0.80 to 1.57)       | 211 (13.6)                  | 471 (23.9)  |          | 1.54 (1.21 to 1.97)       |
| >3–<10                        | 17 (10.8)   | 201 (13.8)  |          | 1.60 (0.78 to 3.30) | 68 (9.0)                       | 179 (10.2)  |          | 1.27 (0.88 to 1.83)       | 173 (11.2)                  | 201 (10.2)  |          | 1.85 (1.46 to 2.36)       |
| ≥10                           | 70 (44.6)   | 507 (34.9)  |          | 1.77 (1.02 to 3.06) | 209 (27.8)                     | 432 (24.6)  |          | 1.09 (0.82 to 1.45)       | 415 (26.8)                  | 467 (23.7)  |          | 1.57 (1.27 to 1.94)       |
| Ever, no period-specific data | 28 (17.8)   | 208 (14.3)  |          |                     | 206 (27.4)                     | 354 (20.1)  |          |                           | 343 (22.2)                  | 390 (19.8)  |          |                           |
| Missing                       | 3 (1.9)     | 33 (2.3)    |          |                     | 12 (1.6)                       | 27 (1.5)    |          |                           | 30 (1.9)                    | 36 (1.8)    |          |                           |
| P <sub>trend</sub> per year   |             |             |          | .75                 |                                |             |          | .87                       |                             |             |          | .69                       |
| Starting age, y               |             |             |          |                     |                                |             |          |                           |                             |             |          |                           |
| Never (<6 mo)                 | 17 (10.8)   | 214 (14.7)  |          | 1.00                | 161 (21.4)                     | 337 (19.2)  |          | 1.00                      | 376 (24.3)                  | 408 (20.7)  |          | 1.00                      |
| ≤17                           | 31 (19.8)   | 373 (25.7)  |          | 1.58 (0.82 to 3.04) | 127 (16.9)                     | 425 (24.2)  |          | 0.90 (0.67 to 1.21)       | 211 (13.6)                  | 458 (23.2)  |          | 1.53 (1.17 to 1.99)       |
| 18–22                         | 69 (44.0)   | 574 (39.5)  |          | 1.88 (1.06 to 3.33) | 287 (38.2)                     | 648 (36.8)  |          | 1.11 (0.86 to 1.42)       | 554 (35.8)                  | 702 (35.6)  |          | 1.66 (1.14 to 1.73)       |
| >22                           | 34 (21.7)   | 217 (14.9)  |          | 1.72 (0.94 to 3.14) | 149 (19.8)                     | 260 (14.8)  |          | 1.10 (0.83 to 1.46)       | 331 (21.4)                  | 296 (15.0)  |          | 1.40 (1.14 to 1.73)       |
| Ever, starting age unknown    | 3 (1.9)     | 42 (2.9)    |          |                     | 16 (2.1)                       | 63 (3.6)    |          |                           | 46 (3.0)                    | 73 (3.7)    |          |                           |
| Missing                       | 3 (1.9)     | 33 (2.3)    |          |                     | 12 (1.6)                       | 27 (1.5)    |          |                           | 30 (1.9)                    | 36 (1.8)    |          |                           |
| P <sub>trend</sub> per year   |             |             |          | .83                 |                                |             |          | .20                       |                             |             |          | .02                       |
| Total duration of use         |             |             |          |                     |                                |             |          |                           |                             |             |          |                           |
| Never (<6 mo)                 | 17 (10.8)   | 214 (14.7)  |          | 1.00                | 161 (21.4)                     | 337 (19.2)  |          | 1.00                      | 376 (24.3)                  | 408 (20.7)  |          | 1.00                      |
| <5                            | 50 (31.9)   | 393 (27.1)  |          | 1.83 (1.04 to 3.25) | 101 (13.4)                     | 247 (14.0)  |          | 1.12 (0.80 to 1.57)       | 219 (14.2)                  | 276 (14.0)  |          | 1.46 (1.15 to 1.86)       |
| 5–9.99                        | 30 (19.1)   | 363 (25.0)  |          | 1.40 (0.75 to 2.61) | 129 (17.2)                     | 359 (20.4)  |          | 1.26 (0.93 to 1.71)       | 253 (16.3)                  | 388 (19.7)  |          | 1.68 (1.32 to 2.12)       |
| ≥10                           | 49 (31.2)   | 393 (27.1)  |          | 1.75 (0.98 to 3.16) | 143 (19.0)                     | 436 (24.8)  |          | 1.01 (0.74 to 1.37)       | 327 (21.1)                  | 475 (24.1)  |          | 1.70 (1.35 to 2.13)       |
| Ever, no period-specific data | 8 (5.1)     | 57 (3.9)    |          |                     | 206 (27.4)                     | 354 (20.1)  |          |                           | 343 (22.2)                  | 390 (19.8)  |          |                           |
| Missing                       | 3 (1.9)     | 33 (2.3)    |          |                     | 12 (1.6)                       | 27 (1.5)    |          |                           | 30 (1.9)                    | 36 (1.8)    |          |                           |
| P <sub>trend</sub> per year   |             |             |          | .68                 |                                |             |          | .94                       |                             |             |          | 2.2E to 04                |

(continued)

Table 5. (continued)

|                               | Prospective     |                 |                     | Retrospective "left-truncated" |                 |                           | Retrospective "full-cohort" |                 |                           |
|-------------------------------|-----------------|-----------------|---------------------|--------------------------------|-----------------|---------------------------|-----------------------------|-----------------|---------------------------|
|                               | BC+<br>No. (%)† | BC-<br>No. (%)† | HR (95% CI)‡        | BC+<br>No. (%)†                | BC-<br>No. (%)† | Weighted*<br>HR (95% CI)§ | BC+<br>No. (%)†             | BC-<br>No. (%)† | Weighted*<br>HR (95% CI)§ |
| Duration of use by FFTP       |                 |                 |                     |                                |                 |                           |                             |                 |                           |
| Before FFTP                   |                 |                 |                     |                                |                 |                           |                             |                 |                           |
| Never (<6 mo)                 | 43 (27.4)       | 390 (26.8)      | 1.00                | 237 (31.5)                     | 495 (28.1)      | 1.00                      | 603 (39.0)                  | 603 (30.6)      | 1.00                      |
| <5                            | 20 (12.7)       | 237 (16.3)      | 1.31 (0.71 to 2.39) | 106 (14.1)                     | 262 (14.9)      | 1.15 (0.85 to 1.56)       | 197 (12.7)                  | 281 (14.2)      | 1.30 (1.02 to 1.67)       |
| 5-9.99                        | 28 (17.8)       | 308 (21.2)      | 1.39 (0.78 to 2.48) | 117 (15.6)                     | 391 (22.2)      | 1.00 (0.74 to 1.35)       | 225 (14.5)                  | 413 (20.9)      | 1.38 (1.07 to 1.79)       |
| ≥10                           | 11 (7.0)        | 199 (13.7)      | 0.85 (0.39 to 1.88) | 74 (9.8)                       | 231 (13.1)      | 0.97 (0.68 to 1.38)       | 150 (9.7)                   | 250 (12.7)      | 1.64 (1.21 to 2.21)       |
| P <sub>trend</sub> per year   |                 |                 | .69                 |                                |                 | .76                       |                             |                 | .002                      |
| After FFTP, y                 |                 |                 |                     |                                |                 |                           |                             |                 |                           |
| Never (<6 mo)                 | 54 (34.4)       | 769 (52.9)      | 1.00                | 353 (46.9)                     | 921 (52.3)      | 1.00                      | 749 (48.4)                  | 1031 (52.3)     | 1.00                      |
| <5                            | 25 (15.9)       | 202 (13.9)      | 1.55 (0.91 to 2.65) | 80 (10.6)                      | 214 (12.2)      | 0.90 (0.65 to 1.23)       | 172 (11.1)                  | 239 (12.1)      | 1.06 (0.84 to 1.35)       |
| 5-9.99                        | 10 (6.4)        | 80 (5.5)        | 1.72 (0.83 to 3.58) | 55 (7.3)                       | 131 (7.4)       | 1.16 (0.81 to 1.65)       | 132 (8.5)                   | 150 (7.6)       | 1.34 (1.03 to 1.74)       |
| ≥10                           | 13 (8.3)        | 83 (5.7)        | 1.55 (0.78 to 3.09) | 46 (6.1)                       | 113 (6.4)       | 0.96 (0.63 to 1.46)       | 122 (7.9)                   | 127 (6.4)       | 1.29 (0.96 to 1.72)       |
| P <sub>trend</sub> per year   |                 |                 | .68                 |                                |                 | .98                       |                             |                 | .04                       |
| Ever, no period-specific data | 52 (33.1)       | 286 (19.7)      |                     | 206 (27.4)                     | 354 (20.1)      |                           | 343 (22.2)                  | 390 (19.8)      |                           |
| OCP or FFTP data missing      | 3 (1.9)         | 33 (2.3)        |                     | 12 (1.6)                       | 27 (1.5)        |                           | 30 (1.9)                    | 36 (1.8)        |                           |

\*Weighted to account for the oversampling of affected individuals. BC = breast cancer; CI = confidence interval; FFTP = first full-term pregnancy; HR = hazard ratio; OCP = oral contraceptive preparations.

†Distribution of variables at end of follow-up.

‡Intrinsically stratified on study (EMBRACE, GENEPSO, HEBON, kConFab, BCFR, other) and birth cohort (1920-1960, 1961-1992). Clustered on family membership.

§Intrinsically stratified on study (EMBRACE, GENEPSO, HEBON, BCFR, other) and birth cohort (1920-1952, 1953-1964, 1965-1992). Clustered on family membership.

||Duration before FFTP and after FFTP included in one multivariable model. Nulliparous women only contributed to various duration categories before FFTP and are placed in the category "never user" after FFTP. Adjusted for age at FFTP (nulliparous, ≤20, 21-25, &gt;25 years).

¶Unweighted results: Left-truncated HR = 1.03, 95% CI = 0.85 to 1.24; Full-cohort HR = 1.48, 95% CI = 1.31 to 1.68.

mutation carriers, a causal association is also not likely at those ages, but power was limited. For both BRCA1 and BRCA2 mutation carriers, prospective analyses do not support retrospective findings that BC risk is increased after long-term duration of use, especially before FFTP. These retrospective results were consistent between full-cohort and left-truncated analyses for BRCA1 mutation carriers, but not for BRCA2 mutation carriers. Inconsistent prospective and retrospective findings could be due to survival bias or a true association for younger women, who were under-represented in the prospective cohort. Therefore, despite this analysis of a large number of carriers with a prospective component, there remains uncertainty about the impact of OCP use on BC risk in carriers, and this uncertainty should be discussed with each individual woman to help her make a personalized decision about OCP use that takes into account her personal circumstances and values. Given the uncertain safety of long-term OCP use for BRCA1/2 mutation carriers, OCP use for indications other than contraception should be avoided and nonhormonal contraceptive methods (eg, copper intrauterine device) should be discussed.

Further extension and follow-up of these cohorts will provide more precise risk estimates and hence more clarity in the advice that can be provided to BRCA1 and BRCA2 mutation carriers.

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