The Influence of Number and Timing of Pregnancies on Breast Cancer Risk for Women With BRCA1 or BRCA2 Mutations

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Abstract

Background: Full-term pregnancy (FTP) is associated with a reduced breast cancer (BC) risk over time, but women are at increased BC risk in the immediate years following an FTP. No large prospective studies, however, have examined whether the number and timing of pregnancies are associated with BC risk for BRCA1 and BRCA2 mutation carriers.

Methods: Using weighted and time-varying Cox proportional hazards models, we investigated whether reproductive events are associated with BC risk for mutation carriers using a retrospective cohort (5707 BRCA1 and 3525 BRCA2 mutation carriers) and a prospective cohort (2276 BRCA1 and 1610 BRCA2 mutation carriers), separately for each cohort and the combined prospective and retrospective cohort.

Results: For BRCA1 mutation carriers, there was no overall association with parity compared with nulliparity (combined hazard ratio [HRc] = 0.99, 95% confidence interval [CI] = 0.83 to 1.18). Relative to being uniparous, an increased number of FTPs...
was associated with decreased BC risk (HRc = 0.79, 95% CI = 0.69 to 0.91; HRc = 0.70, 95% CI = 0.59 to 0.82; HRc = 0.50, 95% CI = 0.40 to 0.63, for 2, 3, and >4 FTPs, respectively, \( P_{\text{trend}} < .0001 \)) and increasing duration of breastfeeding was associated with decreased BC risk (combined cohort \( P_{\text{trend}} = .0003 \)). Relative to being nulliparous, uniparous BRCA1 mutation carriers were at increased BC risk in the prospective analysis (prospective hazard ration \( [\text{HR}_p] = 1.69, 95\% \text{ CI} = 1.09 to 2.62 \)). For BRCA2 mutation carriers, being parous was associated with a 30% increase in BC risk (HRc = 1.33, 95% CI = 1.05 to 1.69), and there was no apparent decrease in risk associated with multiparity except for having at least 4 FTPs vs. 1 FTP (HRc = 0.72, 95% CI = 0.54 to 0.98).

**Conclusions:** These findings suggest differential associations with parity between BRCA1 and BRCA2 mutation carriers with higher risk for uniparous BRCA1 carriers and parous BRCA2 carriers.

Women carrying mutations in BRCA1 or BRCA2 are at high risk of developing breast cancer (BC) and ovarian cancer with cumulative BC risks to 80 years of 72% (95% CI = 65–79%) and 69% (95% CI = 61% to 77%) for BRCA1 and BRCA2 mutation carriers, respectively (1). For women in the general population, it is well established that those who had their first full-term pregnancy (FTP) at a young age (<30 years) have a lower risk of BC than nulliparous women or women who had their first FTP after age 30 years; additional FTPs are associated with even lower risks (2). The consistent association between the number of pregnancies and long-term reduction in BC risk is restricted to FTPs (3–5), as incomplete pregnancies (IP) have not been associated with BC risk [eg, (3)]. While FTPs are associated with a reduced BC risk in the long-term, a short-term increase in BC risk has been consistently observed for women following an FTP (6–8), which may be reduced by breastfeeding (4,9). Thus, in addition to being related to long-term risk reduction, breastfeeding might mitigate a short-term increase in BC risk after FTP (10).

Given the earlier age at which BC risk increases for women carrying a BRCA1 or BRCA2 (BRCA1/2) mutation, it is important to know whether the BC risk for carriers is modified by the number and timing of their pregnancies and/or by breastfeeding. However, the few studies that assessed associations with pregnancies and breastfeeding for BRCA1/2 mutation carriers have reported inconsistent results [for reviews, see (11,12)], ranging from studies supporting a decreased risk from FTP (6–8) to studies supporting no association (15) to studies supporting an increased risk (16). Although more limited in numbers, studies that examined BRCA1 and BRCA2 mutation carriers separately have supported differences in associations by mutation type [eg, higher risk for late age at first FTP or parity in general for BRCA2 mutation carriers (13,16) and lower risk for multiparity for BRCA1 mutation carriers (16) and differences based on breastfeeding (17–19)].

Most studies of BRCA1 and BRCA2 mutation carriers have been retrospective and the few prospective studies have had limited power to examine BRCA1 and BRCA2 mutation carriers separately. To address these issues, we estimated BC risk associations with reproductive history for BRCA1 and BRCA2 mutation carriers separately using an international cohort comprised of 9232 and 3886 women in the retrospective and prospective cohorts, respectively.

**Methods**

**Study Sample**

We harmonized information from three prospective cohorts, which included 21 national or center-based prospective follow-up studies conducted in Western countries: 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) (20–24). Of the study participants, 84% were enrolled through one of the five major studies: (1) Epidemiological Study of Familial Breast Cancer (EMBRACE) in the United Kingdom and Ireland; (2) Gene Etude Prospective Sein Ovaire (GENEPSO) in France; (3) Hereditary Breast and Ovarian cancer study Netherlands (HEBON) in the Netherlands; (4) kConFab in Australia and New Zealand; and (5) BCFR in North America and Australia.

**Study Participants**

Women were eligible if they were 18–80 years of age and had a known pathogenic BRCA1 or BRCA2 mutation. Of the cohort participants, 94% were tested in family clinics and 6% were tested in a research setting, and it was unknown whether or when they opted for a clinical test. We defined two subcohorts for the analyses: (1) a prospective cohort comprising women unaffected with BC at baseline, for whom reproductive history data from baseline and, if collected, follow-up questionnaires were combined (2276 BRCA1 and 1610 BRCA2 mutation carriers); and (2) a retrospective cohort comprising both unaffected and affected women at baseline, for whom only data from the baseline questionnaire were used (5707 BRCA1 and 3525 BRCA2 mutation carriers). The kConFab study women were included only in the prospective cohort.

**Data Collection**

The baseline and follow-up questionnaires collected detailed information on known or suspected risk factors for BC, including reproductive and medical history and surgical interventions. We collected family history of cancer either from the baseline questionnaire or from pedigrees provided by the genetic counselling centers. We collected information on cancer occurrences, which were confirmed by medical records including pathology records, or through linkage to cancer registries for 92% of all cases. The overall response to the follow-up questionnaires was 73% (1). Information on vital status was obtained from municipal, death, or cancer registries or from relatives. Participants provided written informed consent, and each study was approved by a relevant research ethics committee.

**Statistical Analysis**

We used Cox proportional hazards regression models with age as the timescale to calculate hazard ratios (HRs) to assess the association between pregnancy-related variables (ie, parity, number of FTPs, age at first FTP, number of years since last FTP, breastfeeding history and duration of breastfeeding, incomplete
### Table 1. Characteristics of the BRCA1 mutation carriers in the retrospective and prospective cohort

| Characteristic                                      | Women with breast cancer | Unaffected women |
|-----------------------------------------------------|--------------------------|------------------|
|                                                     | Retrospective (n = 2544) | Prospective (n = 269) | Retrospective (n = 3163) | Prospective (n = 2007) |
|                                                     | No. (%) or mean (SD)     | No. (%) or mean (SD) | No. (%) or mean (SD)     | No. (%) or mean (SD)   |
| Age at start of follow-up, y                        | —                        | 40.6 (10.2)        | —                        | 37.5 (11.8)           |
| Year of birth                                        |                          |                   |                          |                        |
| < 1950                                              | 805 (31.6)               | 35 (13.0)         | 526 (16.6)               | 205 (10.2)            |
| 1950–1959                                          | 843 (33.1)               | 76 (28.3)         | 646 (20.4)               | 347 (17.3)            |
| 1960–1969                                          | 665 (26.1)               | 104 (38.7)        | 943 (29.8)               | 586 (29.2)            |
| ≥ 1970                                             | 231 (9.1)                | 54 (20.1)         | 1048 (33.1)              | 869 (43.3)            |
| Study group                                         |                          |                   |                          |                        |
| EMBRACE                                            | 746 (29.3)               | 41 (15.2)         | 814 (25.7)               | 432 (21.5)            |
| GENEPSO                                            | 325 (12.8)               | 46 (17.1)         | 691 (21.8)               | 442 (22.0)            |
| HEBON                                               | 339 (13.3)               | 40 (14.9)         | 463 (14.6)               | 202 (10.1)            |
| kConFab                                             | —                        | 55 (20.4)         | —                        | 270 (13.5)            |
| BCfr                                                | 456 (17.9)               | 50 (18.6)         | 433 (13.7)               | 277 (13.8)            |
| Others*                                             | 678 (26.7)               | 37 (13.8)         | 762 (24.1)               | 384 (19.1)            |
| No. of full-term pregnancies (FTP)                   |                          |                   |                          |                        |
| Nulliparous (no FTP)                                | 518 (20.4)               | 51 (19.0)         | 951 (30.1)               | 602 (30.0)            |
| 1                                                   | 470 (18.5)               | 43 (16.0)         | 481 (15.2)               | 295 (14.7)            |
| 2                                                   | 924 (36.3)               | 113 (42.0)        | 1040 (32.9)              | 652 (32.5)            |
| 3                                                   | 430 (16.9)               | 49 (18.2)         | 467 (14.8)               | 292 (14.5)            |
| ≥ 4                                                | 202 (7.9)                | 13 (4.8)          | 224 (7.1)                | 166 (8.3)             |
| Age at 1st full-term pregnancy among parous, y       |                          |                   |                          |                        |
| < 20                                               | 286 (14.1)               | 26 (11.9)         | 244 (11.0)               | 148 (10.5)            |
| 20–24                                              | 830 (41.0)               | 73 (33.5)         | 794 (35.9)               | 482 (34.3)            |
| 25–29                                              | 620 (30.6)               | 73 (33.5)         | 776 (35.1)               | 511 (36.4)            |
| ≥ 30                                               | 290 (14.3)               | 46 (21.1)         | 398 (18.0)               | 264 (18.8)            |
| Years since last full-term pregnancy                |                          |                   |                          |                        |
| Nulliparous                                         | 518 (20.4)               | 51 (19.0)         | 951 (30.1)               | 602 (30.0)            |
| 1–5                                                | 540 (21.2)               | 43 (16.0)         | 665 (21.0)               | 291 (14.5)            |
| 6–20                                               | 1078 (42.4)              | 102 (37.9)        | 991 (31.3)               | 662 (33.0)            |
| ≥ 21                                               | 408 (16.0)               | 73 (27.1)         | 556 (17.6)               | 452 (22.5)            |
| Breastfeeding duration among women with full-term pregnancy, mo | 594 (29.3) | 50 (22.9) | 561 (25.4) | 311 (22.1) |
| None                                               | 602 (29.7)               | 59 (27.1)         | 620 (28.0)               | 388 (27.6)            |
| 1–5                                                | 469 (23.1)               | 52 (23.9)         | 544 (24.6)               | 332 (23.6)            |
| 6–12                                               | 244 (12.0)               | 39 (17.9)         | 323 (14.6)               | 243 (17.3)            |
| 13–24                                              | 116 (5.7)                | 17 (7.8)          | 159 (7.2)                | 130 (9.3)             |
| ≥ 24                                               | 408 (16.0)               | 73 (27.1)         | 556 (17.6)               | 452 (22.5)            |
| Incomplete pregnancy (IP)                           |                          |                   |                          |                        |
| No full-term pregnancy or IP                       | 437 (17.2)               | 40 (14.9)         | 825 (26.1)               | 515 (25.7)            |
| Full-term pregnancy, no IP                         | 1373 (54.0)              | 141 (52.4)        | 1473 (46.6)              | 926 (46.1)            |
| Induced abortion only                              | 281 (11.0)               | 32 (11.9)         | 334 (10.6)               | 216 (10.8)            |
| Miscarriage only                                   | 383 (15.1)               | 51 (19.0)         | 459 (14.5)               | 295 (14.7)            |
| Induced abortion and miscarriage                   | 70 (2.8)                 | 5 (1.9)           | 72 (2.3)                 | 55 (2.7)              |
| Incomplete pregnancy relative to first full-term pregnancy |            |                   |                          |                        |
| No IP                                              | 1833 (72.1)              | 184 (68.4)        | 2333 (73.8)              | 1458 (72.6)           |
| Before first FTP or no FTP                         | 359 (14.1)               | 46 (17.1)         | 461 (14.6)               | 330 (16.4)            |
| After first FTP                                    | 352 (13.8)               | 39 (14.5)         | 369 (11.7)               | 219 (10.9)            |
| Bilateral oophorectomy                             |                          |                   |                          |                        |
| No                                                 | 2342 (92.1)              | 131 (48.7)        | 2253 (71.2)              | 1215 (60.5)           |
| Yes                                                | 202 (7.9)                | 138 (51.3)        | 909 (28.7)               | 792 (39.5)            |
| Missing                                            | 0                       | 0                 | 1 (0.0)                  | 0                     |
| Oral contraceptive use                             |                          |                   |                          |                        |
| Never                                              | 605 (23.8)               | 39 (14.5)         | 653 (20.6)               | 290 (14.4)            |
| Ever                                               | 1820 (71.5)              | 226 (84.0)        | 2352 (74.4)              | 1659 (82.7)           |
| Unknown start age                                   | 69 (2.7)                 | 1 (0.4)           | 104 (3.3)                | 6 (0.3)               |
| Missing                                            | 50 (2.0)                 | 3 (1.1)           | 54 (1.7)                 | 52 (2.6)              |

(continued)
Table 1. (continued)

| Characteristic          | Women with breast cancer | Unaffected women |
|-------------------------|--------------------------|------------------|
|                         | Retrospective (n = 2544) | Prospective (n = 269) | Retrospective (n = 3163) | Prospective (n = 2007) |
|                         | No. (%) or mean (SD)     | No. (%) or mean (SD) | No. (%) or mean (SD)     | No. (%) or mean (SD)     |
| Age at menarche, y      |                          |                  |                          |                  |
| <12                     | 469 (18.4)               | 34 (12.6)        | 452 (14.3)               | 270 (13.5)        |
| 12                      | 621 (24.4)               | 65 (24.2)        | 836 (26.4)               | 529 (26.4)        |
| 13                      | 594 (23.3)               | 74 (27.5)        | 745 (23.6)               | 483 (24.1)        |
| 14                      | 429 (16.9)               | 54 (20.1)        | 598 (18.9)               | 386 (19.2)        |
| ≥15                     | 380 (14.9)               | 39 (14.5)        | 474 (15.0)               | 313 (15.6)        |
| Age missing             | 51 (2.0)                 | 3 (1.1)          | 58 (1.8)                 | 26 (1.3)          |
| Never had menstrual period | 0                      | 0                | 0                        | 0                |

*Others included the following studies (at inclusion total number): Medical University of Vienna (MUV) (261), Modifier Study of Quantitative Effects on Disease (MODSQUAD) (228), German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) (178), Lund BRCA (160), Odense University Hospital (OUH) (105), Hospital Clinico San Carlos (HCSC) (84), Interdisciplinary HiHealth Research Internal Team Breast Cancer susceptibility (INHERIT) (66), National Institute of Oncology (NIO) (98), International Hereditary Cancer Center (IHCC) (97), Stockholm-BRCA (71), The Spanish National Cancer Center (CNIO) (40), Milan Italy (33), Hospital Clinico San Carlos (9), German Cancer Research Center (DKFZ) (4), Belgium (3), Dusseldorf Germany (3). EMBRACE – Epidemiological Study of Familial Breast Cancer; GENEPSO – Gene Epidemiological Study of Breast Cancer, HERON – Hereditary Breast and Ovarian cancer study Netherlands; kConFab – Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; BCRF – Breast Cancer Family Registry.

pregnancies (IP) due to either spontaneous or induced abortion, timing of IP relative to the first FTP and BC risk), both prospectively (prospective hazard ratio [HRp]) and retrospectively (retrospective hazard ratio [HRR]). We conducted separate analyses for BRCA1 and BRCA2 mutation carriers. We stratified all analyses for birth cohort (<1950, 1950–1959, 1960–1969, 1970) and for study group (EMBRACE, GENEPSO, HERON, BCRF, kConFab, and others combined) and used robust variance estimation to account for the inclusion of related women. We assessed whether the findings differed by age using attained age analyses for women based on censoring at age 40 years. We counted pregnancies that occurred at least one year before the age at right censoring to exclude pregnancies that may have occurred at the same time as diagnosis. We adjusted for bilateral oophorectomy as a time-varying covariate in all of the primary analyses and performed sensitivity analyses by including the potential confounders use of oral contraceptives (as a time-varying covariate), age at menarche, and family history of BC.

Retrospective Cohort Analysis

For retrospective analyses, we modeled time from birth to the diagnosis of first primary BC (invasive or in situ), censoring individuals at the earliest of the following events: diagnosis of any cancer, risk-reducing mastectomy (RRM), or completion of the baseline questionnaire. All covariates were constructed as time-varying covariates. All analyses of the retrospective cohort were performed using the weighted regression approach described by Antoniou et al. (25) to allow for the oversampling of affected women; cohort members were weighted so that the observed BC incidences in the study sample were consistent with established BC risk estimates for BRCA1 and BRCA2 mutation carriers (26). To evaluate potential survival bias, we also performed sensitivity analyses for the retrospective cohort using only pseudo-incident cases in which we considered only the follow-up from 5 years prior to study recruitment to age at censoring.

Prospective Cohort Analysis

For the prospective analysis, we considered follow-up from the date of the baseline questionnaire to the date of diagnosis of any cancer, RRM, last follow-up questionnaire, last information from external source (eg, linkage), age 80 years, or loss to follow-up or death, whichever came first. We included pregnancies and breastfeeding as time-varying covariates.

Combined Cohort Analyses

We also conducted a combined analysis using both retrospective and prospective data. We modeled time from birth to the date of diagnosis of any cancer, RRM, last follow-up questionnaire, last information from external source, age 80 years, loss to follow-up or death, whichever came first, with time-dependent weights as described by Antoniou et al. (25) for the retrospective period and weights equal to one for the prospective period. Statistical analyses were performed using SAS 9.4.

Results

Tables 1 and 2 summarize the descriptive information for BRCA1 and BRCA2 mutation carriers, respectively.

BRCA1 Mutation Carriers

For BRCA1 mutation carriers, there was no overall association of parity compared with nulliparity (combined hazard ratio [HRc] = 0.99, 95% CI = 0.83 to 1.18) (Table 3). Relative to being uniparous, multiparity was associated with decreased BC risk (HRc = 0.79, 95% CI = 0.69 to 0.91; HRc = 0.70, 95% CI = 0.59 to 0.82; HRc = 0.50, 95% CI = 0.40 to 0.63 for 2, 3, and ≥4 FTPs, respectively, P<.0001). The reduced risk associated with multiparity was still evident after adjusting for age at FTP and other risk factors. Each additional FTP after the first was associated with a 16% (95% CI = 11% to 21%) and 26% (95% CI = 14% to 36%) decreased risk in the retrospective and prospective analyses, respectively. Figure 1 shows the probability of developing BC for the prospective cohort. This decreasing risk with increasing parity was evident across all birth cohorts (Supplementary Figure 1, available online).

The increased risk from uniparity was only seen in the prospective analysis (HRp = 1.69, 95% CI = 1.09 to 2.62). There was...
Table 2. Characteristics of the BRCA2 mutation carriers in the retrospective and prospective cohort

| Characteristic | Women with breast cancer | Unaffected women |
|----------------|--------------------------|------------------|
|                | Retrospective (n = 1560) | Prospective (n = 157) | Retrospective (n = 1965) | Prospective (n = 1453) |
|                | No. (%) or mean (SD) | No. (%) or mean (SD) | No. (%) or mean (SD) | No. (%) or mean (SD) |
| Age at start, y | 43.4 (9.1) | 45.1 (10.1) | 41.5 (12.4) | 40.0 (12.6) |
| Age at censure, y | 40.0 (12.6) | 43.4 (9.1) | 49.0 (10.3) | 45.0 (13.0) |
| Year of birth | | | | |
| <1950 | 563 (36.1) | 42 (26.8) | 386 (19.6) | 200 (13.8) |
| 1950–1959 | 513 (32.9) | 44 (28.0) | 385 (19.6) | 259 (17.8) |
| 1960–1969 | 387 (24.8) | 55 (35.0) | 570 (29.0) | 433 (29.8) |
| ≥1970 | 97 (6.2) | 16 (10.2) | 624 (31.8) | 561 (38.6) |
| Study group | | | | |
| EMBRACE | 615 (39.4) | 42 (26.8) | 740 (37.7) | 441 (30.4) |
| GENEPSO | 161 (10.3) | 18 (11.5) | 437 (22.2) | 307 (21.1) |
| HEBON | 91 (5.8) | 4 (2.5) | 146 (7.4) | 71 (4.9) |
| kConFab | — | 38 (24.2) | — | 250 (17.2) |
| BCFR | 359 (23.0) | 31 (21.0) | 322 (16.4) | 222 (15.3) |
| Others* | 334 (21.4) | 22 (14.0) | 320 (16.3) | 162 (11.1) |
| No. of full-term pregnancy (FTP) | | | | |
| Nulliparous (no FTP) | 298 (19.4) | 20 (13.4) | 406 (27.9) | 292 (20.3) |
| 1 | 224 (14.4) | 14 (9.9) | 288 (17.4) | 196 (13.5) |
| 2 | 622 (39.9) | 62 (39.5) | 631 (32.1) | 449 (30.9) |
| 3 | 284 (18.2) | 36 (22.9) | 330 (16.8) | 264 (18.2) |
| ≥4 | 152 (9.7) | 22 (14.0) | 179 (9.1) | 138 (9.5) |
| Age at 1st full-term pregnancy among parous, y | | | | |
| <20 | 154 (12.0) | 11 (8.2) | 173 (12.1) | 113 (10.8) |
| 20–24 | 503 (39.2) | 57 (42.5) | 550 (38.5) | 386 (36.9) |
| 25–29 | 408 (31.8) | 36 (26.9) | 451 (31.6) | 347 (33.1) |
| ≥30 | 217 (16.9) | 30 (22.4) | 254 (17.8) | 201 (19.2) |
| Year since last full-term pregnancy | | | | |
| Nulliparous | 278 (17.8) | 23 (14.6) | 537 (27.3) | 406 (27.9) |
| 1–5 | 280 (17.9) | 16 (10.2) | 550 (34.8) | 386 (36.9) |
| 6–20 | 669 (42.9) | 60 (41.7) | 451 (31.6) | 347 (33.1) |
| ≥21 | 333 (21.3) | 55 (35.0) | 428 (21.8) | 388 (26.7) |
| Breastfeeding duration among women with full-term pregnancy | | | | |
| None | 357 (27.8) | 26 (19.4) | 408 (26.8) | 263 (21.5) |
| 1–5 mo | 342 (26.7) | 36 (26.9) | 389 (27.2) | 255 (20.4) |
| 6–12 mo | 311 (24.3) | 34 (25.4) | 293 (20.5) | 219 (20.9) |
| 13–24 mo | 186 (14.5) | 18 (13.4) | 220 (15.4) | 186 (17.8) |
| ≥24 mo | 84 (6.6) | 20 (14.9) | 115 (8.3) | 122 (11.7) |
| FTP but stillborn | 2 (0.2) | 0 | 3 (0.2) | 2 (0.2) |
| Incomplete pregnancy (IP) | | | | |
| No full-term pregnancy or IP | 225 (14.4) | 22 (14.0) | 471 (24.0) | 343 (23.6) |
| Full-term pregnancy, no IP | 850 (54.5) | 87 (55.4) | 956 (48.7) | 680 (46.8) |
| Induced abortion only | 154 (9.9) | 10 (6.4) | 199 (10.1) | 157 (10.8) |
| Miscarriage only | 280 (17.9) | 31 (19.7) | 284 (14.5) | 225 (15.5) |
| Induced abortion and miscarriage | 51 (3.3) | 7 (4.5) | 55 (2.8) | 48 (3.3) |
| Incomplete pregnancy relative to first full-term pregnancy | | | | |
| No IP | 1087 (69.7) | 110 (70.1) | 1445 (73.5) | 1036 (71.3) |
| Before first FTP or no FTP | 256 (16.4) | 22 (14.0) | 270 (13.7) | 229 (15.8) |
| After first FTP | 217 (13.9) | 25 (15.9) | 250 (12.7) | 188 (12.9) |
| Bilateral oophorectomy | | | | |
| No | 1430 (91.7) | 95 (60.5) | 1522 (77.5) | 959 (66.0) |
| Yes | 130 (8.3) | 62 (39.5) | 443 (22.5) | 494 (34.0) |
| Missing | 0 | 0 | 0 | 0 |
| Oral contraceptive use | | | | |
| Never | 378 (24.2) | 17 (10.8) | 412 (21.0) | 214 (14.7) |
| Ever | 1106 (70.9) | 136 (86.6) | 1452 (73.9) | 1201 (82.7) |
| Unknown start age | 46 (2.9) | 1 (0.6) | 72 (3.7) | 5 (0.3) |
| Missing | 30 (1.9) | 3 (1.9) | 29 (1.5) | 33 (2.3) |

(continued)
some suggestion that this association was stronger for women who have never breastfed (HR\textsubscript{p} = 2.01, 95% CI = 1.14 to 3.55; HR\textsubscript{c} = 1.64, 95% CI = 1.00 to 2.70 for women who did not and did breastfeed, respectively), but these HRs were not statistically different (P\textsubscript{heterogeneity} = 0.54). The increased risk, although not statistically significant (HR\textsubscript{p} = 1.41, 95% CI = 0.94 to 2.10), for overall parity in the prospective cohort was driven mainly by the difference in nulliparity vs uniparity between the two analyses (HR\textsubscript{R} = 0.59, 95% CI = 0.38 to 0.92, and HR\textsubscript{R} = 1.02, 95% CI = 0.83 to 1.24, respectively) because the point estimates of each successive pregnancy compared with uniparity were similar in both the retrospective and prospective analyses. Supplementary Figure 2 (available online) illustrates the difference based on penetrance for BRCA1 mutation carriers according to different reproductive life scenarios.

Relative to a recent pregnancy, longer time since last FTP was associated with higher risk in the retrospective analysis. Increasing duration of breastfeeding was associated with decreased BC risk (combined cohort P\textsubscript{trend} = .0003) in the retrospective analysis (P\textsubscript{trend} = .0002), but not in the prospective analysis (P\textsubscript{trend} = .28).

IP was associated with an increased BC risk compared with women without IP or FTP in the prospective analysis (HR\textsubscript{p} = 1.72, 95% CI = 1.04 to 2.83 and HR\textsubscript{p} = 1.77, 95% CI = 1.09 to 2.87 for induced abortion only and miscarriage only, respectively), but not in the retrospective analysis (HR\textsubscript{R} = 1.02, 95% CI = 0.82 to 1.27 and HR\textsubscript{R} = 0.97, 95% CI = 0.78 to 1.21 for induced abortion only and miscarriage only, respectively). The magnitude of the association with IP was similar to the association for any FTP without IP (HR\textsubscript{R} = 1.64, 95% CI = 1.03 to 2.61). There was also no difference in association whether the IP was before or after the first FTP in all of the analyses.

### BRCA2 Mutation Carriers

For BRCA2 mutation carriers, parity was associated with a 30% increase in BC risk (HR\textsubscript{R} = 1.33, 95% CI = 1.05 to 1.69) (Table 4). Multiparity was associated with a decreased BC risk (HR\textsubscript{p} = 0.72, 95% CI = 0.54 to 0.98 for \( \geq 4 \) vs 1 FTP in the retrospective analysis (HR\textsubscript{R} = 0.58, 95% CI = 0.42 to 0.79 for \( \geq 4 \) vs 1 FTP, P\textsubscript{trend} = .0001), but not in the prospective cohort (HR\textsubscript{p} = 1.68, 95% CI = 0.83 to 3.39 for \( \geq 4 \) vs 1 FTP, P\textsubscript{trend} = 41 and P\textsubscript{heterogeneity} = 0.06) (Figure 1). Multiparity was associated with a decreased BC risk only prior to age 40 years (HR\textsubscript{R} = 0.29, 95% CI = 0.16 to 0.52 for \( \geq 4 \) vs 1 FTP) (Table 4).

We observed an increase in risk with increasing age at first FTP in the retrospective analysis (P\textsubscript{trend} = .0003). There was some suggestion of a similar trend in the prospective cohort (P\textsubscript{trend} = .12; HR\textsubscript{R} = 1.95, 95% CI = 0.95 to 3.98 for a first FTP at age \( \geq 30 \) years vs \(< 20 \) years). Recent pregnancy was associated with BC risk (≤5 years relative to nulliparous; HR\textsubscript{R} = 1.36, 95% CI = 1.03 to 1.78; HR\textsubscript{p} = 1.27, 95% CI = 0.57 to 2.86; HR\textsubscript{c} = 1.37, 95% CI = 1.06 to 1.78). Increasing duration of breastfeeding was associated with decreased BC risk in the retrospective analysis (P\textsubscript{trend} = .002), but not in the prospective cohort (P\textsubscript{trend} = .59). Any pregnancy, including IP, was associated with BC risk but only in the retrospective cohort (Table 4).

We performed sensitivity analyses that further adjusted for age at menarche, oral contraceptive use, and family history of BC or excluding in situ BC. The estimates were very similar to those in the main analysis (Supplementary Tables 1–3, available online). Analysis based on the pseudo-incidence retrospective cohort also gave very similar estimates to those based on the entire retrospective cohort (Supplementary Table 4, available online).

### Discussion

Using data from the largest international cohort study of BRCA1 and BRCA2 mutation carriers to date, we found that overall parity was not associated with BC risk for BRCA1 mutation carriers but was associated with BC risk for BRCA2 mutation carriers. Nulliparous and multiparous BRCA1 mutation carriers had lower BC risk compared with uniparous women. Longer duration of breastfeeding also was associated with a reduced risk for BRCA1 mutation carriers. There was some suggestion that uniparous women who subsequently breastfed may have a decrease in BC risk compared with those that did not. For BRCA2 mutation carriers, multiparity reduced risk, particularly prior to age 40 years, and late age at first FTP was associated with increased risk.
| Characteristic                                      | Retrospective | Prospective | Combined |
|----------------------------------------------------|---------------|-------------|----------|
|                                                    | HR (95% CI)   | HR (95% CI) | HR (95% CI) |
|                                                    | $P_{\text{trend}}^*$ | $P_{\text{trend}}^*$ | $P_{\text{trend}}^*$ |
| Parous (at least 1 full-term pregnancy)†           |               |             |          |
| No                                                 | 0.87 (0.72 to 1.05) | 1.41 (0.94 to 2.10) | 0.99 (0.83 to 1.18) |
| Yes                                                | 0.98 (0.81 to 1.20) | <.0001 | 1.69 (1.09 to 2.62) | <.0001 | 1.11 (0.92 to 1.34) | <.0001 |
| No. of full-term pregnancy† (FTP)                  |               |             |          |
| Nulliparous (no FTP)                               |               |             |          |
| 1                                                  | 0.73 (0.61 to 0.87) | <.0001 | 1.08 (0.61 to 1.91) | .22 | 0.79 (0.66 to 0.94) | <.0001 |
| 2                                                  | 0.68 (0.55 to 0.85) | 0.35 (0.12 to 1.09) | 0.65 (0.52 to 0.82) |             |          |
| 3                                                  | 0.63 (0.45 to 0.87) | 0.67 (0.20 to 2.27) | 0.64 (0.46 to 0.89) |             |          |
| ≥4                                                 | 0.52 (0.39 to 0.70) | 0.24 (0.12 to 0.48) | 0.46 (0.34 to 0.61) |             |          |
| Nulliparous                                        | 1.02 (0.83 to 1.24) | 0.59 (0.38 to 0.92) | 0.90 (0.75 to 1.09) |             |          |
| No. of full-term pregnancy by attained age†         |               |             |          |
| <40 years                                          |               |             |          |
| 1                                                  | 0.73 (0.61 to 0.87) | <.0001 | 1.08 (0.61 to 1.91) | .22 | 0.79 (0.66 to 0.94) | <.0001 |
| 2                                                  | 0.68 (0.55 to 0.85) | 0.35 (0.12 to 1.09) | 0.65 (0.52 to 0.82) |             |          |
| 3                                                  | 0.63 (0.45 to 0.87) | 0.67 (0.20 to 2.27) | 0.64 (0.46 to 0.89) |             |          |
| ≥4                                                 | 0.52 (0.39 to 0.70) | 0.24 (0.12 to 0.48) | 0.46 (0.34 to 0.61) |             |          |
| ≥40 years                                          |               |             |          |
| 1                                                  | 0.82 (0.66 to 1.03) | <.0001 | 0.61 (0.38 to 0.99) | <.0001 | 0.78 (0.64 to 0.96) | <.0001 |
| 2                                                  | 0.68 (0.54 to 0.87) | 0.69 (0.41 to 1.16) | 0.70 (0.56 to 0.88) |             |          |
| 3                                                  | 0.52 (0.39 to 0.70) | 0.24 (0.12 to 0.48) | 0.46 (0.34 to 0.61) |             |          |
| Age at 1st full-term pregnancy, y‡                  |               |             |          |
| <20                                                |               |             |          |
| 20–24                                              | 0.98 (0.81 to 1.19) | .03 | 0.84 (0.54 to 1.30) | .95 | 0.95 (0.80 to 1.13) | .06 |
| 25–29                                              | 0.87 (0.71 to 1.06) | 0.80 (0.52 to 1.23) | 0.85 (0.71 to 1.02) |             |          |
| ≥30                                                | 0.82 (0.65 to 1.04) | 0.95 (0.59 to 1.55) | 0.86 (0.70 to 1.07) |             |          |
| Year since last full-term pregnancy§               |               |             |          |
| 0–5                                                |               |             |          |
| 6–20                                               | 1.19 (1.03 to 1.36) | .02 | 0.89 (0.59 to 1.35) | .002 | 1.14 (0.99 to 1.30) | .0002 |
| ≥21                                                | 1.48 (1.17 to 1.87) | 1.12 (0.63 to 1.98) | 1.44 (1.15 to 1.81) |             |          |
| Nulliparous                                        | 1.05 (0.86 to 1.29) | 0.55 (0.33 to 0.89) | 0.92 (0.76 to 1.11) |             |          |
| Nulliparous (FTP)                                  |               |             |          |
| 0–5                                                | 0.95 (0.78 to 1.16) | 0.2 | 1.84 (1.13 to 2.99) | .002 | 1.09 (0.90 to 1.32) | .0002 |
| 6–20                                               | 1.13 (0.90 to 1.41) | 1.64 (1.02 to 2.64) | 1.24 (1.01 to 1.52) |             |          |
| ≥21                                                | 1.41 (1.06 to 1.87) | 2.06 (1.12 to 3.79) | 1.57 (1.20 to 2.06) |             |          |
| Year since last full-term pregnancy by number of FTP†|               |             |          |
| 1 FTP, 0–5                                         |               |             |          |
| ≥2 FTP, 0–5                                       | 0.65 (0.53 to 0.80) | 0.75 (0.38 to 1.47) | 0.68 (0.55 to 0.84) |             |          |
| 1 FTP, 6–20                                       | 0.94 (0.73 to 1.20) | 0.96 (0.47 to 1.95) | 0.95 (0.75 to 1.21) |             |          |
| ≥2 FTP, 6–20                                      | 0.84 (0.67 to 1.04) | 0.65 (0.33 to 1.30) | 0.82 (0.66 to 1.03) |             |          |
| 1 FTP, ≥21                                        | 1.55 (1.09 to 2.21) | 1.22 (0.48 to 3.07) | 1.55 (1.11 to 2.17) |             |          |
| ≥2 FTP, ≥21                                       | 0.96 (0.72 to 1.30) | 0.81 (0.36 to 1.84) | 0.98 (0.73 to 1.31) |             |          |
| Breastfeeding duration†                             |               |             |          |
| None                                               |               |             |          |
| 1–5 mo                                             | 0.96 (0.82 to 1.12) | .0002 | 1.07 (0.73 to 1.56) | .28 | 0.97 (0.84 to 1.11) | .0003 |
| 6–12 mo                                            | 0.81 (0.69 to 0.95) | 1.04 (0.70 to 1.54) | 0.84 (0.72 to 0.97) |             |          |
| 13–24 mo                                           | 0.75 (0.61 to 0.91) | 1.05 (0.68 to 1.63) | 0.80 (0.67 to 0.95) |             |          |
| > 24 mo                                            | 0.64 (0.48 to 0.86) | 0.75 (0.44 to 1.31) | 0.66 (0.50 to 0.87) |             |          |
| No. of full-term pregnancy and breastfeeding†       |               |             |          |
| Nulliparous                                        |               |             |          |
| 1 FTP, never breastfeeding                         | 1.15 (0.89 to 1.49) | 2.01 (1.14 to 3.55) | 1.33 (1.04 to 1.70) |             |          |
| ≥2 FTP, never breastfeeding                        | 0.85 (0.67 to 1.07) | 1.15 (0.67 to 1.96) | 0.94 (0.76 to 1.18) |             |          |
| 1 FTP, ever breastfeeding                          | 0.97 (0.78 to 1.21) | 1.64 (1.00 to 2.70) | 1.09 (0.89 to 1.33) |             |          |
| ≥2 FTP, ever breastfeeding                         | 0.73 (0.59 to 0.89) | 1.22 (0.79 to 1.90) | 0.84 (0.69 to 1.02) |             |          |
Previous epidemiological studies investigating modifiable factors for BRCA1 and BRCA2 mutation carriers have had limited power to examine gene-specific associations and have primarily been retrospective (8,11,19). Our cohort provides the first large-scale prospective evaluation of parity separately for BRCA1 and BRCA2 mutation carriers. Overall, we found that increasing parity beyond the first child was associated with a decrease in BC risk for BRCA1 mutation carriers in both the retrospective and prospective analyses. This association with multiparity in BRCA1 mutation carriers was consistent with a meta-analysis that reported a 17% decrease for each additional birth (11). Curiously, however, nulliparity was associated with a reduced risk of BC in comparison with uniparity; this association was particularly marked in the prospective analysis.

Increasing age at FTP was associated with reduced BC risk for BRCA1 mutation carriers but only in the retrospective analysis. Moreover, the effect size was smaller than that reported in the meta-analysis by Friebel et al. (11) for pregnancy after age 30 years vs before 25 years, relative risk [RR] = 0.65, 95% CI = 0.42 to 0.99. The pattern of association is clearly different from that seen in the general population, where increased age at first FTP is associated with increased BC risk (27).

For BRCA2 mutation carriers, we observed a positive association with overall parity in both the retrospective and prospective analyses not driven by uniparity as observed for BRCA1 mutation carriers. We also observed an increased risk of BC with later age at first FTP, which is more consistent with the association seen in the general population, but in contrast to the results of the Friebel et al. (11) meta-analysis, which found no association. We also found an association between multiparity and a reduced risk of BC particularly for women who had four or more pregnancies in the retrospective analysis. We also observed a modest increase in risk associated with recent pregnancies (<5 years, relative to nulliparous) in BRCA2 mutation carriers in both retrospective and prospective analyses (36% and 27%, respectively). For BRCA1 mutation carriers, the risk was also higher in the first five years, relative to nulliparous women, but this was observed only in the prospective cohort. However, there was no difference by attained age even in the prospective analysis where women are slightly older and no evidence that

Table 3. (continued)

| Characteristic                  | Retrospective HR (95% CI) | Retrospective PTrend* | Prospective HR (95% CI) | Prospective PTrend* | Combined HR (95% CI) | Combined PTrend* |
|--------------------------------|---------------------------|-----------------------|-------------------------|---------------------|----------------------|-----------------|
| Incomplete pregnancy§ (IP)     |                           |                       |                         |                     |                      |                 |
| No full-term or incomplete pregnancy | Referent                 | Referent              | Reference               | Reference           |                      |                 |
| Full-term pregnancy, no IP     | 0.96 (0.79 to 1.16)       | 1.64 (1.03 to 2.61)   | 1.08 (0.90 to 1.29)     |                     |                      |                 |
| Induced abortion only          | 1.02 (0.82 to 1.27)       | 1.72 (1.04 to 2.83)   | 1.15 (0.93 to 1.41)     |                     |                      |                 |
| Miscarriage only               | 0.97 (0.78 to 1.21)       | 1.77 (1.09 to 2.87)   | 1.11 (0.91 to 1.36)     |                     |                      |                 |
| Induced abortion and miscarriage | 1.09 (0.77 to 1.55)      | 1.09 (0.40 to 2.94)   | 1.11 (0.80 to 1.55)     |                     |                      |                 |

*Nulliparous excluded, risk factor as continuous.
†Adjusted for bilateral oophorectomy (Yes, No), age at 1st full-term pregnancy (<30, ≥30 - nulliparous), strata by birth year and study site.
‡Adjusted for bilateral oophorectomy, number of full-term pregnancies (0–1, ≥2), strata by birth year and study site.
§Adjusted for bilateral oophorectomy, number of full-term pregnancies (0–1, ≥2), age at 1st full-term pregnancy, strata by birth year and study site.
∥Adjusted for bilateral oophorectomy, number of live births (0–1, ≥2), age at 1st full-term pregnancy, strata by birth year and study site.

Figure 1. Probability of developing breast cancer in the prospective cohort by parity. A) BRCA1. B) BRCA2. Circles – nulliparous; plus sign, parity = 1; x, parity = 2; triangles, parity = 3; squares, parity = 4 or more.
Table 4. Retrospective, prospective, and combined analyses for the BRCA2 mutation carriers

| Characteristic | Retrospective HR (95% CI) | Retrospective $P_{trend}$ | Prospective HR (95% CI) | Prospective $P_{trend}$ | Combined HR (95% CI) | Combined $P_{trend}$ |
|----------------|---------------------------|---------------------------|-------------------------|-------------------------|----------------------|---------------------|
| Parous (at least 1 full-term pregnancy)† | | | | | | |
| No | Referent | Referent | Referent | Referent | Referent | Referent |
| Yes | 1.26 (0.99 to 1.62) | 1.44 (0.83 to 2.49) | 1.33 (1.05 to 1.69) |
| No. of full-term pregnancy† (FTP) | | | | | | |
| Nulliparous | Referent | Referent | Referent | Referent | Referent | Referent |
| 1 | 1.28 (0.98 to 1.67) | .0001 | 1.08 (0.55 to 2.14) | .41 | 1.29 (1.01 to 1.66) | .005 |
| 2 | 1.32 (1.00 to 1.73) | | 1.63 (0.91 to 2.92) | | 1.42 (1.09 to 1.85) | |
| 3 | 1.04 (0.76 to 1.44) | | 1.72 (0.89 to 3.34) | | 1.22 (0.89 to 1.66) | |
| ≥4 | 0.73 (0.51 to 1.07) | | 1.82 (0.91 to 3.64) | | 0.93 (0.66 to 1.33) | |
| 1 | Referent | Referent | Referent | Referent | Referent | Referent |
| 2 | 1.03 (0.83 to 1.28) | .0001 | 1.51 (0.85 to 2.66) | .41 | 1.10 (0.90 to 1.35) | .005 |
| 3 | 0.82 (0.63 to 1.06) | | 1.59 (0.83 to 3.04) | | 0.94 (0.74 to 1.20) | |
| ≥4 | 0.58 (0.42 to 0.79) | | 1.68 (0.83 to 3.39) | | 0.72 (0.54 to 0.98) | |
| Nulliparous | 0.78 (0.60 to 1.02) | | 0.92 (0.47 to 1.82) | | 0.78 (0.60 to 0.99) | |
| No. of full-term pregnancy by attained age† | | | | | | |
| <40 years | | | | | | |
| 1 | Referent | Referent | Referent | Referent | Referent | Referent |
| 2 | 0.81 (0.62 to 1.06) | <.0001 | 2.36 (0.47 to 11.83) | .98 | 0.88 (0.67 to 1.16) | .0008 |
| 3 | 0.79 (0.56 to 1.13) | | 1.25 (0.14 to 11.55) | | 0.81 (0.56 to 1.19) | |
| ≥4 | 0.29 (0.16 to 0.52) | | 1.31 (0.09 to 19.54) | | 0.33 (0.17 to 0.63) | |
| ≥40 years | | | | | | |
| 1 | Referent | Referent | Referent | Referent | Referent | Referent |
| 2 | 1.28 (0.95 to 1.73) | .005 | 1.33 (0.71 to 2.48) | .39 | 1.26 (0.97 to 1.65) | .04 |
| 3 | 0.96 (0.69 to 1.34) | | 1.51 (0.77 to 2.96) | | 1.07 (0.79 to 1.45) | |
| ≥4 | 0.77 (0.53 to 1.12) | | 1.57 (0.76 to 3.25) | | 0.90 (0.64 to 1.26) | |
| Age at 1st full-term pregnancy, y‡ | | | | | | |
| <20 | Referent | Referent | Referent | Referent | Referent | Referent |
| 20–24 | 1.13 (0.87 to 1.47) | .0003 | 1.60 (0.85 to 2.98) | .12 | 1.25 (0.97 to 1.60) | <.0001 |
| 25–29 | 1.39 (1.05 to 1.84) | | 1.26 (0.63 to 2.51) | | 1.39 (1.06 to 1.83) | |
| ≥30 | 1.64 (1.20 to 2.24) | | 1.95 (0.95 to 3.98) | | 1.77 (1.30 to 2.40) | |
| Year since last full-term pregnancy§ | | | | | | |
| 0–5 | Referent | Referent | Referent | Referent | Referent | Referent |
| 6–20 | 0.97 (0.79 to 1.18) | .57 | 0.82 (0.42 to 1.59) | .06 | 0.96 (0.79 to 1.17) | .40 |
| ≥21 | 0.92 (0.67 to 1.25) | | 0.71 (0.31 to 1.64) | | 0.88 (0.65 to 1.19) | |
| Nulliparous | 0.74 (0.56 to 0.97) | | 0.79 (0.35 to 1.77) | | 0.73 (0.56 to 0.94) | |
| Nulliparous | Referent | Referent | Referent | Referent | Referent | Referent |
| 0–5 | 1.36 (1.03 to 1.78) | | 1.27 (0.57 to 2.86) | | 1.37 (1.06 to 1.78) | .40 |
| 6–20 | 1.31 (0.98 to 1.76) | .57 | 1.04 (0.51 to 2.14) | | 1.32 (1.01 to 1.74) | |
| ≥21 | 1.24 (0.86 to 1.79) | | 0.90 (0.38 to 2.15) | | 1.21 (0.86 to 1.70) | |
| Breastfeeding duration§ | | | | | | |
| None | Referent | Referent | Referent | Referent | Referent | Referent |
| 1–5 mo | 1.00 (0.82 to 1.24) | .002 | 1.14 (0.69 to 1.88) | .59 | 1.05 (0.87 to 1.28) | .01 |
| 6–12 mo | 1.16 (0.93 to 1.43) | | 1.28 (0.77 to 2.13) | | 1.17 (0.96 to 1.43) | |
| 13–24 mo | 0.85 (0.66 to 1.09) | | 0.74 (0.40 to 1.35) | | 0.82 (0.64 to 1.04) | |
| ≥24 mo | 0.61 (0.43 to 0.86) | | 1.03 (0.58 to 1.81) | | 0.74 (0.55 to 1.00) | |
| No. of full-term pregnancy and breastfeeding† | | | | | | |
| Nulliparous | Referent | Referent | Referent | Referent | Referent | Referent |
| 1 FTP, never breastfeeding | 1.33 (0.91 to 1.93) | | 1.90 (0.77 to 4.72) | | 1.45 (1.02 to 2.06) | |
| ≥2 FTP, never breastfeeding | 1.25 (0.91 to 1.72) | | 1.32 (0.66 to 2.65) | | 1.31 (0.98 to 1.77) | |
| 1 FTP, ever breastfeeding | 1.33 (1.00 to 1.78) | | 0.79 (0.35 to 1.80) | | 1.27 (0.98 to 1.66) | |
| ≥2 FTP, ever breastfeeding | 1.19 (0.90 to 1.57) | | 1.71 (0.97 to 3.03) | | 1.35 (1.03 to 1.76) | |
| Incomplete pregnancy (IP)§ | | | | | | |
| No full-term or incomplete pregnancy | Referent | Referent | Referent | Referent | Referent | Referent |
| Full-term pregnancy, no IP | 1.35 (1.05 to 1.75) | | 0.82 (0.40 to 1.68) | | 1.28 (1.00 to 1.64) | |
| Induced abortion only | 1.38 (1.01 to 1.89) | | 0.47 (0.18 to 1.17) | | 1.15 (0.85 to 1.56) | |
| Miscarriage only | 1.52 (1.13 to 2.04) | | 0.88 (0.43 to 1.79) | | 1.40 (1.06 to 1.84) | |
| Induced abortion and miscarriage | 1.87 (1.19 to 2.92) | | 0.87 (0.35 to 2.15) | | 1.61 (1.07 to 2.42) | |

(continued)
Incomplete pregnancy relative to first full-term pregnancy§  

| Characteristic | Retrospective HR (95% CI) | $P_{\text{trend}}^*$ | Prospective HR (95% CI) | $P_{\text{trend}}^*$ | Combined HR (95% CI) | $P_{\text{trend}}^*$ |
|----------------|---------------------------|-----------------------|-------------------------|-----------------------|----------------------|-----------------------|
| No IP          |                           |                       |                         |                       |                      |                       |
| Before first FTP or no FTP | 1.34 (1.10 to 1.63)     |                       | 0.78 (0.50 to 1.21)     |                       | 1.17 (0.97 to 1.40)  |                       |
| After first FTP | 1.01 (0.82 to 1.24)      |                       | 0.99 (0.65 to 1.53)     |                       | 0.99 (0.82 to 1.20)  |                       |

*Nulliparous excluded, risk factor as continuous.
†Adjusted for bilateral oophorectomy, number of live births (0–1, ≥2), strata by birth year and study site.
‡Adjusted for bilateral oophorectomy, number of full-term pregnancies (0–1, ≥2), strata by birth year and study site.
§Adjusted for bilateral oophorectomy, number of live births (0–1, ≥2), age at 1st full-term pregnancy, strata by birth year and study site.
∥Adjusted for bilateral oophorectomy, number of live births (0–1, ≥2), age at 1st full-term pregnancy, strata by birth year and study site.

The increased risk for uniparous BRCA1 mutation carriers (and perhaps for BRCA2 carriers) is inconsistent with the pattern for the general population. However, the lack of a protective effect of parity in BRCA1 mutation carriers who develop primarily ER-negative tumor is consistent with the weaker association with parity and age at first FTP observed for ER-negative BC in the general population (28). It suggests that many of the key driver events may have already occurred in adolescence, such that the first FTP increases the risk of BC due to stimulation of partially transformed mammary cells. This risk may be stronger for first pregnancy for those most susceptible based on prior exposures and then decline after FTP given increased cell differentiation in the late phase of pregnancy and lactation and post-partum gland involution (29–33), thus the lower risk for the uniparous women who breastfeed than women who do not may be explained by the differential rates of mammary gland involution.

Nulliparous and multiparous BRCA1 mutation carriers have lower BC risk compared with uniparous women. Long duration of breastfeeding decreased risk for BRCA1 mutation carriers. For BRCA2 mutation carriers, multiparity seems to reduce risk, although this was limited to the retrospective cohort analyses, and late age at first FTP increased risk. These findings might help refine the BC risk estimates and make it possible to adapt the surveillance of mutation carriers according to their reproductive life history.

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