The Influence of Number and Timing of Pregnancies on Breast Cancer Risk for Women with *BRCA1* or *BRCA2* mutations

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Running title: Pregnancies and breast cancer risks for BRCA1/2 mutation carriers.

Abstract 250/250

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 a 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 (5,707 *BRCA1* and 3,525 *BRCA2* mutation carriers) and a prospective cohort (2,276 *BRCA1* and 1,610 *BRCA2* mutation carriers), separately for each cohort and in the combined, prospective and retrospective, cohort.

Results: For *BRCA1* mutation carriers, there was no overall association with parity compared with nulliparity (Combined Hazard Ratio (HR_c)=0.99, 95%CI=0.83-1.18). Relative to being uniparous, increased number of FTPs was associated with decreased BC risk (HR_c=0.79, 95%CI=0.69-0.91; HR_c=0.70, 95%CI=0.59-0.82; HR_c=0.50, 95%CI=0.40-0.63, for 2, 3, and ≥4 FTPs, respectively, p_{trend}<0.0001) and increasing duration of breastfeeding was associated with decreased BC risk (combined cohort p_{trend}=0.0003). Relative to being nulliparous, uniparous *BRCA1* mutation carriers were at increased BC risk in the prospective cohort (HR_p=1.69, 95%CI=1.09-2.62). For *BRCA2* mutation carriers, being parous was associated with a 30% increase in BC risk (HR_c=1.33, 95%CI=1.05-1.69) and there was no apparent decrease in risk associated with multiparity except for ≥4 FTPs (HR_c=0.72, 95%CI=0.54-0.98).

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.

Text (3000/3000)

Introduction:

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%-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 (e.g.[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 a 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 start of onset of BC risk 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 [13,14] to studies supporting no association [15] to studies supporting an increased risk [16]. Though more limited in numbers, studies that examined *BRCA1 and BRCA2* mutation carriers separately have supported differences in associations by mutation type (e.g., 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 *BRCA1/2* 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 9,232 and 3,886 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 Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) Follow-Up Study, and the Breast Cancer Family Registry (BCFR) [20-24]. Eighty-four percent of the study participants were enrolled through one of the five major studies: 1) Epidemiological Study of Familial Breast Cancer [EMBRACE] in the UK 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. Ninety-four percent of the cohort participants 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 sub-cohorts for the analyses: (i) 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 (2,276 *BRCA1* and 1,610 *BRCA2* mutation carriers); and (ii) a retrospective cohort comprising both unaffected and affected women at baseline, for whom only data from the baseline questionnaire were used

(5,707 *BRCA1* and 3,525 *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 were confirmed by medical records including pathology records, or through linkage to cancer registries in 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 (i.e., parity, number of FTPs, age at first FTP, number of years since last FTP, breastfeeding history and duration of breastfeeding, IP due to either spontaneous or induced abortion, timing of IP relative to the first FTP and BC risk, both prospectively (HR_P) and retrospectively (HR_C). 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, HEBON, BCFR, 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 of 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 over-sampling 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 up 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 (e.g., linkage), age 80 years, 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 (HR_c)=0.99, 95%CI=0.83-1.18) (**Table 3**). Relative to being uniparous, multiparity was associated with decreased BC risk (HR_c=0.79, 95%CI=0.69-0.91; HR_c=0.70, 95%CI=0.59-0.82; HR_c=0.50, 95%CI=0.40-0.63, for 2, 3, and ≥4 FTPs, respectively, p_{trend}<0.0001). 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%-21%) and 26% (95%CI=14%-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 (**Supplemental-Figure 2**).

The increased risk from uniparity was only seen in the prospective cohort (Prospective Hazard Ratio (HR_p)=1.69, 95%CI=1.09-2.62). There was some suggestion that this association was stronger in women who have never breastfed (HR_p=2.01, 95%CI=1.14-3.55; HR_p=1.64, 95%=0.89-1.33 for women who did not and did breastfeed, respectively, but these HRs were not statistically different p_{het}=0.54). The increased risk, although not significant (HR_p=1.41, 95%=0.94, 2.10), for overall parity in the prospective cohort was driven mainly by the difference in nulliparity vs. uniparity between the two cohorts (HR_p=0.59, 95%CI=0.38-0.92, and HR_R=1.02, 95%CI=0.83-1.24, respectively) as the point estimates of each successive pregnancy compared with uniparity were similar for both the retrospective and prospective cohorts. **Supplemental-Figure 1** 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 cohort. Increasing duration of breastfeeding was associated with decreased BC risk (combined cohort p_{trend}=0.0003) in the retrospective cohort (p_{trend}=0.0002), but not in the prospective cohort (p_{trend}=0.28).

IP was associated with an increased BC risk compared with women without IP or FTP, in the prospective analyses (HR_p=1.72, 95%CI=1.04-2.83 and HR_p=1.77, 95%CI=1.09-2.87 for induced abortion only and miscarriage only, respectively), but not in the retrospective analysis (HR_R=1.02, 95%CI=0.82-1.27 and HR_R=0.97, 95%CI=0.78-1.21 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_p=1.64, 95%CI=1.03-2.61). There was also no difference in association whether the IP was before or after the first FTP in none of the analyses.

BRCA2 mutation carriers: In *BRCA2* mutation carriers parity was associated with a 30% increase in BC risk (HR_c=1.33, 95%CI=1.05-1.69) (**Table 4**). Multiparity was associated with a decreased BC risk (HR_c=0.72, 95%CI=0.54-0.98) but in the retrospective cohort analysis (HR_R=0.58, 95%CI=0.42-0.79 for ≥4 vs. 1 FTP, p_{trend}=0.0001), and not in the prospective analysis (HR_p=1.68, 95%CI=0.83-3.39 for ≥4 vs. 1 FTP, p_{trend}=0.41 and p_{het}=0.006) (**Figure 1)**. Multiparity was associated with a decreased BC risk only prior to age 40 (HR_R=0.29, 95%CI=0.16-0.52 for ≥4 vs. 1 FTP) (**Table 4**).

We observed an increase in risk with increasing age at first FTP in the retrospective analysis (p_{trend}=0.0003). There was some suggestion of a similar trend in the prospective cohort (p_{trend}=0.12; HR_P=1.95, 95%CI=0.95-3.98 for a first FTP at age ≥30 years vs. <20 years). Recent pregnancy was associated with BC risk (≤5 years relative to nulliparous; HR_R=1.36, 95%CI=1.03-1.78; HR_P=1.27, 95%CI=0.57-2.86; HR_c=1.37, 95%CI=1.06-1.78). Increasing duration of breastfeeding was associated with decreased BC risk in the retrospective cohort (p_{trend}=0.002), but not in the prospective cohort (p_{trend}=0.59). 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 (**Supplemental-Tables 1-3)**. Analysis based on the pseudo-incidence retrospective cohort gave also very similar estimates to those based on the entire retrospective cohort (**Supplemental-Table 4**).

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 in *BRCA1* mutation carriers but was associated with BC risk in *BRCA2* mutation carriers. Nulliparous and multiparous *BRCA1* mutation carriers had lower BC risk compared with uniparous women. Longer duration of breastfeeding also reduced risk in *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. In *BRCA2* mutation carriers, multiparity reduced risk, particularly prior to age 40 years, and late age at first FTP was associated with increased risk.

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 which 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 effect was particularly marked in the prospective cohort.

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*. (for pregnancy after age 30 years versus before 25 years RR=0.65, 95%CI=0.42-0.99) [11]. 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].

In *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, more consistent with the association seen in the general population, but in contrast to the results of the Friebel et *al.* meta-analysis which found no association [11]. We also found an association between multiparity and a reduced risk of BC particularly for women who had four of more pregnancies in the retrospective analysis. We also observed a modest increase in risk from recent pregnancies ($\leq$5 years, relative to nulliparous) in *BRCA2* mutation carriers, in both retrospective and prospective analyses (36% and 27% respectively). In *BRCA1* mutation carriers, the risk was also higher in the first 5 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 cohort where women are slightly older and no evidence that BC risk declined by time since pregnancy, and in opposite, the risk increased with time since last pregnancy in both the retrospective and prospective cohorts.

Although multiparity relative to nulliparity reduced risk in both *BRCA1* and *BRCA2* mutation carriers, late age at first FTP was only associated with increased risk in *BRCA2* mutation carriers. The differences we observed between *BRCA1* and *BRCA2* mutation carriers might reflect their difference in the ER status distribution that has been reported by mutation type [28]. We did not have hormonal receptor status for our pooled cohort, but we expect the differences we observed both reflect hormonal status as well as age-related

differences between *BRCA1* and *BRCA2* mutation carriers. For example, as we recently reported, *BRCA1* and *BRCA2* mutation carriers have different BC risk distributions. In *BRCA1* mutation carriers, there is a rapid increase in BC incidence until ages 30 to 40 years, whereas the risk in *BRCA2* mutation carriers continues to increase until approximately age 50 years, similar to the distribution in the general population [1]. Therefore, one can expect that risk factors may be different or act differently between *BRCA1* and *BRCA2* mutation carriers because of their timing. In particular, given the later peak in incidence for *BRCA2* mutation carriers, later age at FTP may increase risk in the short-term similar to the transient increase from pregnancy seen in the general population.

Retrospective cohort analyses generally have substantially more power but may be potentially biased for selected risk factors given that risk factors are ascertained after diagnosis, or might motivate study participation. Prospective cohorts have the advantage of collecting information prior to knowing the outcome, but often have more limited statistical power compared to retrospective studies. FTPs, however, are unlikely to have substantial information bias when collected retrospectively, and for prospective analyses the mean age at start of follow-up has mostly passed reproductive life period. Similar findings between the two designs also supports that selection bias may be less of a concern as selection bias operates different in retrospective and prospective studies. We were limited, however, to addressing confounding by only established risk factors that have been collected across all of the studies. We formally tested for homogeneity across the two cohorts using meta-analytic techniques and both random and fixed effects models suggested that the inferences in both retrospective and prospective cohorts were not different from each other. Thus we were able to provide more precise estimates by combining both cohorts. We also investigated heterogeneity across birth cohorts (**Supplemental-Figure 2**) and geographic study sites and observed similar inferences.

The increased risk in uniparous *BRCA1* mutation carriers (and perhaps in *BRCA2* carriers) is inconsistent with the pattern in 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 in 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 postpartum gland involution [29-33], and 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.

Conclusions: Nulliparous and multiparous *BRCA1* mutation carriers have lower BC risk compared with uniparous women. Long duration of breastfeeding decreased risk in *BRCA1* mutation carriers. In *BRCA2* mutation carriers, multiparity seems to reduce risk, particularly prior to 40 years, and late age at first FTP increased risk. These findings might help in refining the BC risk estimates and make it possible to adapt the surveillance of mutation carriers according to their reproductive life history.

Authors' contributions

MBT and NA drafted the initial manuscript, while the complete writing group consisted of MBT, NA, KK, MAR and DFE. MBT, YL and NA performed and are responsible for the statistical analyses, while the complete analysis group additionally consists of JLH, HO, ACA, CE, RM, KK, MBT, YL, MAR, DFE and NA. TMM and MRB are the international database managers. MAR coordinated the collaborative study, while DEG, DFE, NA, CN, MBT, JLH, MAR initiated and coordinated the original studies. CN, BB, VM, FE, LG, EL, AH, CB, DGE, DE, JC, KRO, LI, MA, PJM, CJD, JCO, MGEMA, MK, SB, IA, EMJ, MD, MF, SAM, AO, TC, AJ, JS, CFS, YT, EO, MN, LF, AMG, BA, KO, RKS invited patients and collected data. All authors read and approved the final manuscript.

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Figure legends:

Figure 1. Probability of developing breast cancer in the Prospective Cohort by parity

1a. BRCA1

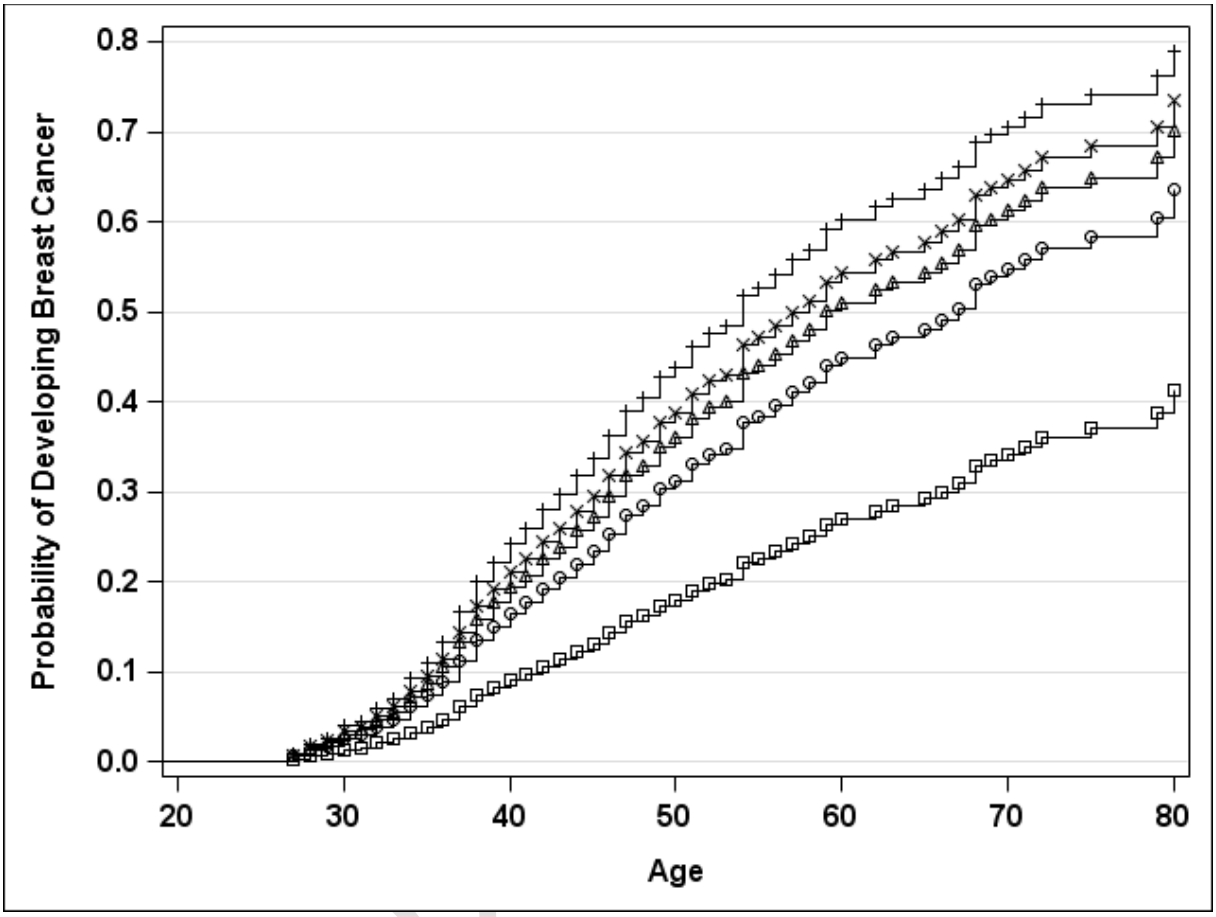
○ – Nulliparous, + – Parity=1, x – Parity=2, Δ – Parity=3, □ – Parity=4+

1b. BRCA2

○ – Nulliparous, + – Parity=1, x – Parity=2, Δ – Parity=3, □ – Parity=4

Figure 1.

1a. BRCA1



1b. BRCA2

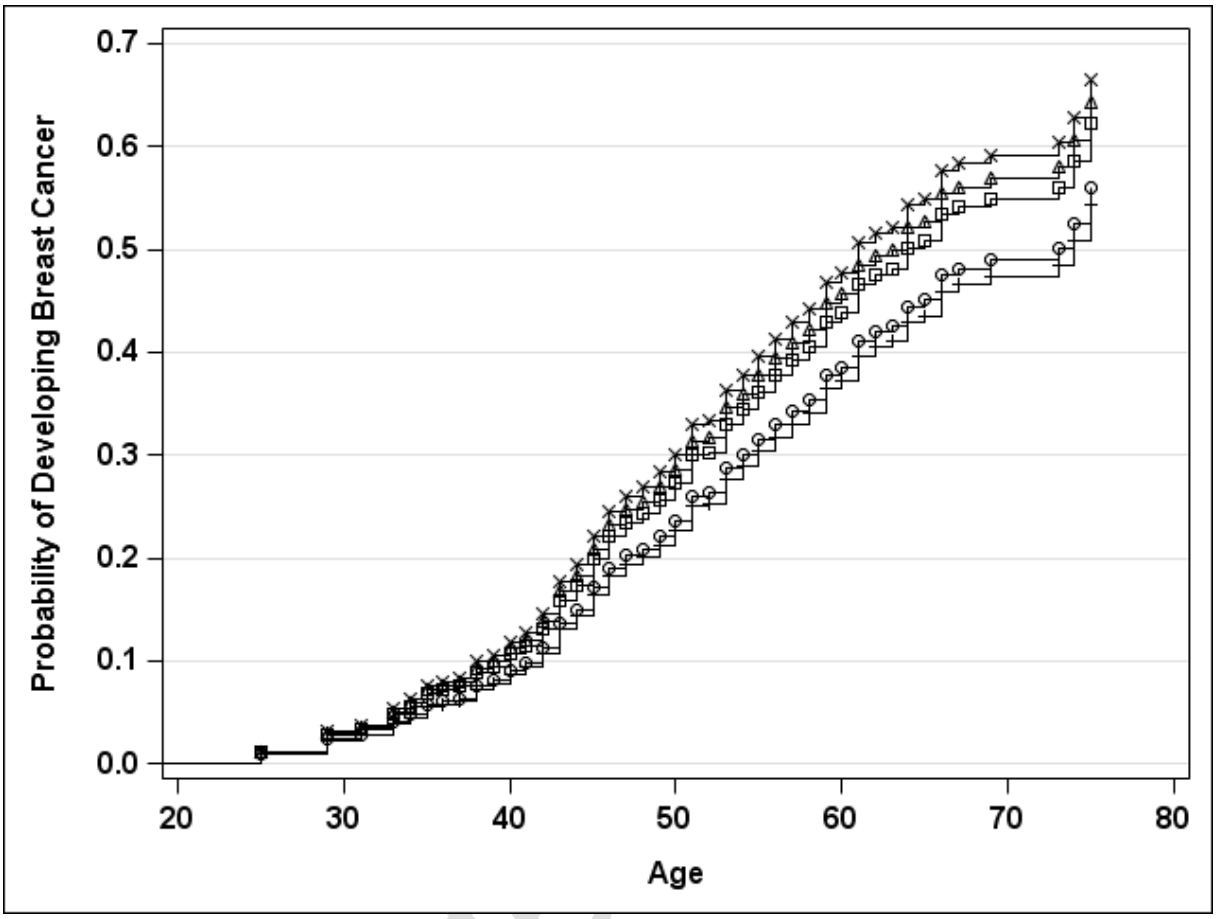


Table 1. Characteristics of the *BRCA1* mutation carriers in the retrospective and prospective cohort.

Characteristic	Women with Breast Cancer		Unaffected Women	
	retrospective (N=2544)	prospective (N=269)	retrospective (N=3163)	prospective (N=2007)
	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std
Age at Start of Follow-up		40.6 ± 10.2		37.5 ± 11.8
Age at Censure	40.1 ± 8.8	44.9 ± 10.3	39.3 ± 11.5	43.1 ± 12.3
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				
<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)

Characteristic	Women with Breast Cancer		Unaffected Women	
	retrospective (N=2544)	prospective (N=269)	retrospective (N=3163)	prospective (N=2007)
	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std
Breastfeeding Duration (months) Among Women with Full-term Pregnancy				
None	594 (29.3)	50 (22.9)	561 (25.4)	311 (22.1)
1 - 5	602 (29.7)	59 (27.1)	620 (28.0)	388 (27.6)
6 – 12	469 (23.1)	52 (23.9)	544 (24.6)	332 (23.6)
13 – 24	244 (12.0)	39 (17.9)	323 (14.6)	243 (17.3)
> 24	116 (5.7)	17 (7.8)	159 (7.2)	130 (9.3)
FTP but Stillborn	1 (0.0)	1 (0.5)	5 (0.2)	1 (0.1)
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 (72.0)
Before first FTP or no FTP	359 (14.1)	46 (17.1)	461 (14.6)	330 (16.0)
After first FTP	352 (13.8)	39 (14.5)	369 (11.7)	219 (10.0)
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)
Age at Menarche (years)				
< 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 (total number): MUV (261), MODSQUAD (228), GC-HBOC (178), Lund-BRCA (160), OUH (105), HCSC (84), INHERIT (66), NIO (98), IHCC (97), Stockholm-BRCA (71), CNIO (40), Milan Italy (33), HSP (9), DKFZ (4), Belgium (3), Dusseldorf Germany(3).

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)
	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std
Age at Start		45.1 ± 10.1		40.0 ± 12.6
Age at Censure	43.4 ± 9.1	49.0 ± 10.3	41.5 ± 12.4	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)	33 (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)	278 (17.8)	23 (14.6)	537 (27.3)	406 (27.9)
1	224 (14.4)	14 (8.9)	288 (14.7)	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				
<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)	410 (20.9)	175 (12.0)
6 - 20	669 (42.9)	63 (40.1)	590 (30.0)	484 (33.3)
≥21	333 (21.3)	55 (35.0)	428 (21.8)	388 (26.7)

Characteristic	Women with Breast Cancer		Unaffected Women	
	retrospective (N=1560)	prospective (N=157)	retrospective (N=1965)	prospective (N=1453)
	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std	N(%) or Mean±Std
Breastfeeding Duration Among Women with Full-term Pregnancy				
None	357 (27.8)	26 (19.4)	408 (28.6)	263 (25.1)
1 - 5 mo	342 (26.7)	36 (26.9)	389 (27.2)	255 (24.4)
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 (8.1)	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)
Age at Menarche (years)				
< 12	238 (15.3)	29 (18.5)	337 (17.2)	237 (16.3)
12	365 (23.4)	40 (25.5)	503 (25.6)	353 (24.3)
13	404 (25.9)	37 (23.6)	454 (23.1)	377 (25.9)
14	274 (17.6)	24 (15.3)	336 (17.1)	246 (16.9)
>=15	247 (15.8)	27 (17.2)	303 (15.4)	214 (14.7)
Age Missing	31 (2.0)	0	30 (1.5)	24 (1.7)
Never had menstrual period	1 (0.1)	0	2 (0.1)	2 (0.1)

§ Others included the following studies (total number): MUV (100), MODSQUAD (80), GC-HBOC (105), Lund-BRCA (58), OUH (62), HCSC (65), INHERIT (74), NIO (31), IHCC (0), Stockholm-BRCA (13), CNIO (44), Milan Italy (12), HSP (10).

Table 3. Retrospective, prospective and combined analyses for the *BRCA1* mutation carriers

Characteristic	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Parous (at least 1 Full-term Pregnancy)[a]						
No	Reference		Reference		Reference	
Yes	0.87 (0.72, 1.05)		1.41 (0.94, 2.10)		0.99 (0.83, 1.18)	
No. of Full-term Pregnancy[a] (FTP)						
Nulliparous (no FTP)	Reference		Reference		Reference	
1	0.98 (0.81, 1.20)		1.69 (1.09, 2.62)		1.11 (0.92, 1.34)	
2	0.77 (0.63, 0.95)	<.0001	1.25 (0.81, 1.95)	<.0001	0.88 (0.73, 1.07)	
3	0.68 (0.53, 0.86)		1.15 (0.70, 1.90)		0.77 (0.62, 0.97)	<.0001
≥4	0.54 (0.40, 0.73)		0.52 (0.27, 1.02)		0.56 (0.42, 0.74)	
1	Reference		Reference		Reference	
2	0.78 (0.68, 0.91)	<.0001	0.74 (0.51, 1.08)	<.0001	0.79 (0.69, 0.91)	
3	0.69 (0.58, 0.82)		0.68 (0.44, 1.05)		0.70 (0.59, 0.82)	<.0001
≥4	0.55 (0.43, 0.70)		0.31 (0.17, 0.57)		0.50 (0.40, 0.63)	
Nulliparous	1.02 (0.83, 1.24)		0.59 (0.38, 0.92)		0.90 (0.75, 1.09)	
No. of Full-term Pregnancy By Attained Age[a]						
<40 years						
1	Reference		Reference		Reference	
2	0.73 (0.61, 0.87)	<.0001	1.08 (0.61, 1.91)	0.22	0.79 (0.66, 0.94)	<.0001
3	0.68 (0.55, 0.85)		0.35 (0.12, 1.09)		0.65 (0.52, 0.82)	
≥4	0.63 (0.45, 0.87)		0.67 (0.20, 2.27)		0.64 (0.46, 0.89)	
≥40 years						
1	Reference		Reference		Reference	
2	0.82 (0.66, 1.03)	<.0001	0.61 (0.38, 0.99)	<.0001	0.78 (0.64, 0.96)	<.0001
3	0.68 (0.54, 0.87)		0.69 (0.41, 1.16)		0.70 (0.56, 0.88)	
≥4	0.52 (0.39, 0.70)		0.24 (0.12, 0.48)		0.46 (0.34, 0.61)	

Characteristic	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age at 1st Full-term Pregnancy[b]						
<20	Reference		Reference		Reference	
20 - 24	0.98 (0.81, 1.19)	0.03	0.84 (0.54, 1.30)	0.95	0.95 (0.80, 1.13)	0.06
25 - 29	0.87 (0.71, 1.06)		0.80 (0.52, 1.23)		0.85 (0.71, 1.02)	
≥30	0.82 (0.65, 1.04)		0.95 (0.59, 1.55)		0.86 (0.70, 1.07)	
Year Since Last Full-term Pregnancy[c]						
0 - 5	Reference		Reference		Reference	
6 - 20	1.19 (1.03, 1.36)	0.04	0.89 (0.59, 1.34)	0.002	1.14 (0.99, 1.30)	0.0002
≥21	1.48 (1.17, 1.87)		1.12 (0.63, 1.98)		1.44 (1.15, 1.81)	
Nulliparous	1.05 (0.86, 1.29)		0.55 (0.33, 0.88)		0.92 (0.76, 1.11)	
Nulliparous	Reference		Reference		Reference	
0 - 5	0.95 (0.78, 1.16)		1.84 (1.13, 2.99)		1.09 (0.90, 1.32)	
6 - 20	1.13 (0.90, 1.41)	0.04	1.64 (1.02, 2.64)	0.002	1.24 (1.01, 1.52)	0.0002
≥21	1.41 (1.06, 1.87)		2.06 (1.12, 3.79)		1.57 (1.20, 2.06)	
Year Since Last Full-term Pregnancy by number of Full-term pregnancy[a]						
1 FTP, 0 – 5	Reference		Reference		Reference	
≥2 FTP, 0 - 5	0.65 (0.53, 0.80)		0.75 (0.38, 1.47)		0.68 (0.55, 0.84)	
1 FTP, 6 - 20	0.94 (0.73, 1.20)		0.96 (0.47, 1.95)		0.95 (0.75, 1.21)	
≥2 FTP, 6 - 20	0.84 (0.67, 1.04)		0.65 (0.33, 1.30)		0.82 (0.66, 1.03)	
1 FTP, ≥21	1.55 (1.09, 2.21)		1.22 (0.48, 3.07)		1.55 (1.11, 2.17)	
≥2 FTP, ≥21	0.96 (0.72, 1.30)		0.81 (0.36, 1.84)		0.98 (0.73, 1.31)	
BreastFeeding Duration[d]						
None	Reference		Reference		Reference	
1 - 5 mo	0.96 (0.82, 1.12)		1.07 (0.73, 1.56)		0.97 (0.84, 1.11)	
6 - 12 mo	0.81 (0.69, 0.95)	0.0002	1.04 (0.70, 1.54)	0.28	0.84 (0.72, 0.97)	0.0003
13 - 24 mo	0.75 (0.61, 0.91)		1.05 (0.68, 1.63)		0.80 (0.67, 0.95)	
> 24 mo	0.64 (0.48, 0.86)		0.75 (0.44, 1.31)		0.66 (0.50, 0.87)	

Characteristic	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
No. of Full-term Pregnancy and Breastfeeding[a]						
Nulliparous	Reference		Reference		Reference	
1 FTP, Never Breastfeeding	1.15 (0.89, 1.49)		2.01 (1.14, 3.55)		1.33 (1.04, 1.70)	
≥2 FTP, Never Breastfeeding	0.85 (0.67, 1.07)		1.15 (0.67, 1.96)		0.94 (0.76, 1.18)	
1 FTP, Ever Breastfeeding	0.97 (0.78, 1.19)		1.64 (1.00, 2.70)		1.09 (0.89, 1.33)	
≥2 FTP, Ever Breastfeeding	0.73 (0.59, 0.89)		1.22 (0.79, 1.90)		0.84 (0.69, 1.02)	
Incomplete Pregnancy[c] (IP)						
No full-term or Incomplete pregnancy	Reference		Reference		Reference	
Full-term pregnancy, no IP	0.96 (0.79, 1.16)		1.64 (1.03, 2.61)		1.08 (0.90, 1.29)	
Induced abortion only	1.02 (0.82, 1.27)		1.72 (1.04, 2.83)		1.15 (0.93, 1.41)	
Miscarriage only	0.97 (0.78, 1.21)		1.77 (1.09, 2.87)		1.11 (0.91, 1.36)	
Induced abortion and miscarriage	1.09 (0.77, 1.55)		1.09 (0.40, 2.94)		1.11 (0.80, 1.55)	
Incomplete Pregnancy Relative To First Full-term Pregnancy[c]						
No IP	Reference		Reference		Reference	
Before first FTP or no FTP	1.05 (0.90, 1.22)		1.02 (0.74, 1.41)		1.04 (0.91, 1.19)	
After first FTP	1.03 (0.89, 1.20)		1.32 (0.93, 1.88)		1.09 (0.94, 1.25)	

[a] Adjusted for Bilateral Oophorectomy (Yes, No), Age at 1st full-term pregnancy (<30, ≥30+nulliparous), Strata By Birth year and Study site
[b] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), Strata By Birth year and Study site
[c] 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
[d] Adjusted for Bilateral Oophorectomy, Number of live birth (0-1, ≥2), Age at 1st full-term pregnancy, Strata By Birth year and Study site
[e] Nulliparous Excluded, Risk Factor As Continuous

Table 4. Retrospective, prospective and combined analyses for the *BRCA2* mutation carriers

Characteristic	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Parous (at least 1 Full-term Pregnancy)[a]						
No	Reference		Reference		Reference	
Yes	1.26 (0.99, 1.62)		1.44 (0.83, 2.49)		1.33 (1.05, 1.69)	
No. of Full-term Pregnancy[a] (FTP)						
Nulliparous	Reference		Reference		Reference	
1	1.28 (0.98, 1.67)		1.08 (0.55, 2.14)		1.29 (1.01, 1.66)	
2	1.32 (1.00, 1.73)	0.0001	1.63 (0.91, 2.92)	0.41	1.42 (1.09, 1.85)	0.005
3	1.04 (0.76, 1.44)		1.72 (0.89, 3.34)		1.22 (0.89, 1.66)	
≥4	0.73 (0.51, 1.07)		1.82 (0.91, 3.64)		0.93 (0.66, 1.33)	
1	Reference		Reference		Reference	
2	1.03 (0.83, 1.28)	0.0001	1.51 (0.85, 2.66)	0.41	1.10 (0.90, 1.35)	0.005
3	0.82 (0.63, 1.06)		1.59 (0.83, 3.04)		0.94 (0.74, 1.20)	
≥4	0.58 (0.42, 0.79)		1.68 (0.83, 3.39)		0.72 (0.54, 0.98)	
Nulliparous	0.78 (0.60, 1.02)		0.92 (0.47, 1.82)		0.78 (0.60, 0.99)	
No. of Full-term Pregnancy By Attained Age[a]						
<40 years						
1	Reference		Reference		Reference	
2	0.81 (0.62, 1.06)	<.0001	2.36 (0.47, 11.83)	0.98	0.88 (0.67, 1.16)	0.0008
3	0.79 (0.56, 1.13)		1.25 (0.14, 11.55)		0.81 (0.56, 1.19)	
≥4	0.29 (0.16, 0.52)		1.31 (0.09, 19.54)		0.33 (0.17, 0.63)	
≥40 years						
1	Reference		Reference		Reference	
2	1.28 (0.95, 1.73)	0.005	1.33 (0.71, 2.48)	0.39	1.26 (0.97, 1.65)	0.04
3	0.96 (0.69, 1.34)		1.51 (0.77, 2.96)		1.07 (0.79, 1.45)	
≥4	0.77 (0.53, 1.12)		1.57 (0.76, 3.25)		0.90 (0.64, 1.26)	

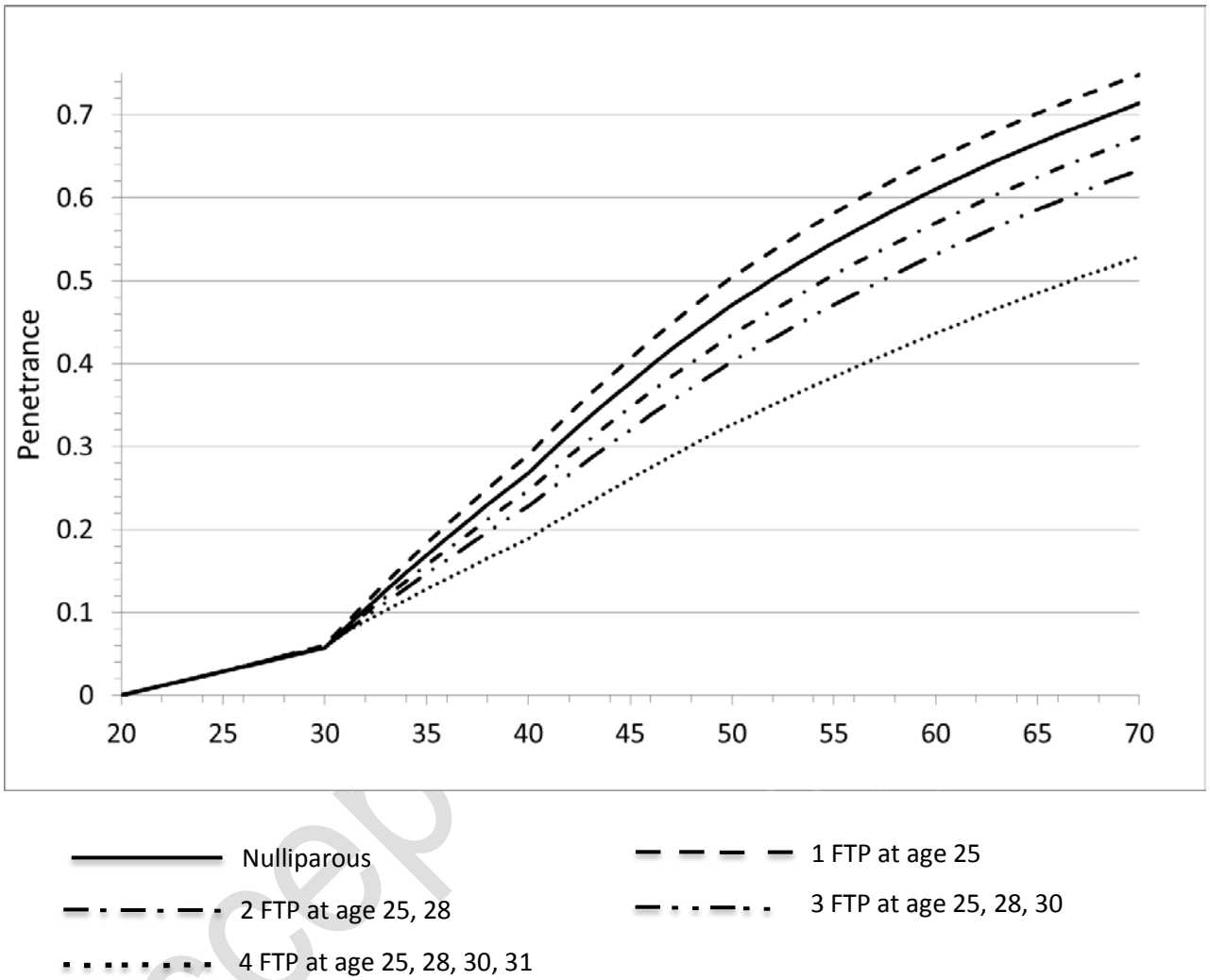
Characteristic	retrospective HR (95% CI)	Trend[e]	prospective HR (95% CI)	Trend[e]	combined HR (95% CI)	Trend[e]
Age at 1st Full-term Pregnancy[b]						
<20	Reference		Reference		Reference	
20 - 24	1.13 (0.87, 1.47)	0.0003	1.60 (0.85, 2.98)	0.12	1.25 (0.97, 1.60)	<.0001
25 - 29	1.39 (1.05, 1.84)		1.26 (0.63, 2.51)		1.39 (1.06, 1.83)	
≥30	1.64 (1.20, 2.24)		1.95 (0.95, 3.98)		1.77 (1.30, 2.40)	
Year Since Last Full-term Pregnancy[c]						
0 - 5	Reference		Reference		Reference	
6 - 20	0.97 (0.79, 1.18)	0.54	0.82 (0.42, 1.59)	0.06	0.96 (0.79, 1.17)	0.40
≥21	0.92 (0.67, 1.25)		0.71 (0.31, 1.64)		0.88 (0.65, 1.19)	
Nulliparous	0.74 (0.56, 0.97)		0.79 (0.35, 1.77)		0.73 (0.56, 0.94)	
Nulliparous	Reference		Reference		Reference	
0 - 5	1.36 (1.03, 1.78)		1.27 (0.57, 2.86)		1.37 (1.06, 1.78)	
6 - 20	1.31 (0.98, 1.76)	0.54	1.04 (0.51, 2.14)	0.06	1.32 (1.01, 1.74)	0.40
≥21	1.24 (0.86, 1.79)		0.90 (0.38, 2.15)		1.21 (0.86, 1.70)	
BreastFeeding Duration[d]						
None	Reference		Reference		Reference	
1 - 5 mo	1.00 (0.82, 1.24)		1.14 (0.69, 1.88)		1.05 (0.87, 1.27)	
6 - 12 mo	1.16 (0.93, 1.43)	0.002	1.28 (0.77, 2.13)	0.59	1.17 (0.96, 1.43)	0.01
13 - 24 mo	0.85 (0.66, 1.09)		0.74 (0.40, 1.35)		0.82 (0.64, 1.03)	
> 24 mo	0.61 (0.43, 0.86)		1.03 (0.58, 1.81)		0.74 (0.55, 1.00)	
No. of Full-term Pregnancy and Breastfeeding[a]						
Nulliparous	Reference		Reference		Reference	
1 FTP, Never Breastfeeding	1.33 (0.91, 1.93)		1.90 (0.77, 4.72)		1.45 (1.02, 2.06)	
≥2 FTP, Never Breastfeeding	1.25 (0.91, 1.72)		1.32 (0.66, 2.65)		1.31 (0.98, 1.77)	
1 FTP, Ever Breastfeeding	1.33 (1.00, 1.78)		0.79 (0.35, 1.80)		1.27 (0.98, 1.66)	
≥2 FTP, Ever Breastfeeding	1.19 (0.90, 1.57)		1.71 (0.97, 3.03)		1.35 (1.03, 1.76)	

Characteristic	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Incomplete Pregnancy[c] (IP)						
No full-term or Incomplete pregnancy	Reference		Reference		Reference	
Full-term pregnancy, no IP	1.35 (1.05, 1.75)		0.82 (0.40, 1.68)		1.28 (1.00, 1.64)	
Induced abortion only	1.38 (1.01, 1.89)		0.47 (0.18, 1.17)		1.15 (0.85, 1.56)	
Miscarriage only	1.52 (1.13, 2.04)		0.88 (0.43, 1.79)		1.40 (1.06, 1.84)	
Induced abortion and miscarriage	1.87 (1.19, 2.92)		0.87 (0.35, 2.15)		1.61 (1.07, 2.42)	
Incomplete Pregnancy Relative To First Full-term Pregnancy[c]						
No IP	Reference		Reference		Reference	
Before first FTP or no FTP	1.34 (1.10, 1.63)		0.78 (0.50, 1.21)		1.17 (0.97, 1.40)	
After first FTP	1.01 (0.82, 1.24)		0.99 (0.65, 1.53)		0.99 (0.82, 1.20)	

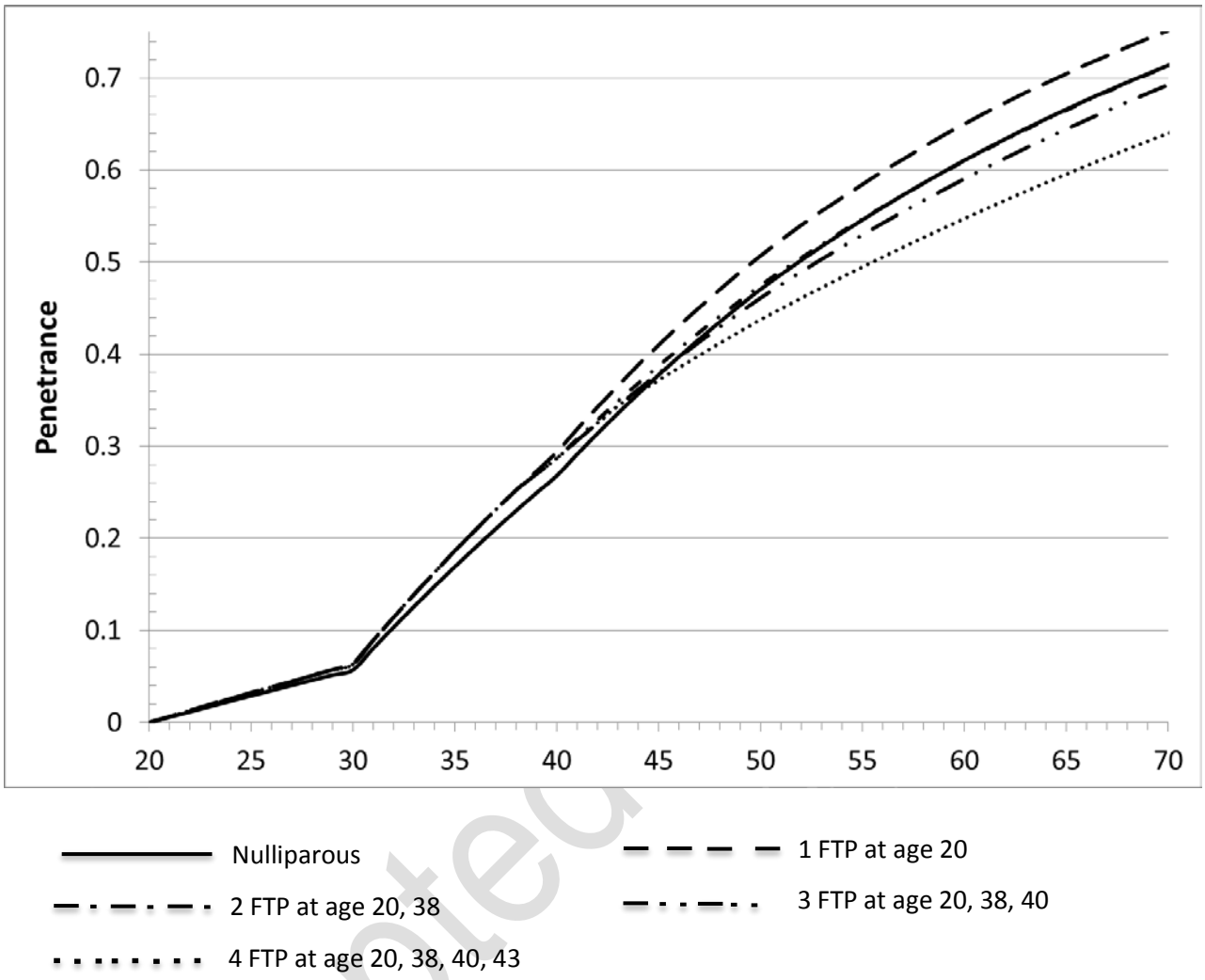
[a] Adjusted for Bilateral Oophorectomy (Yes, No), Age at 1st Full-term pregnancy (<30, ≥30+nulliparous), Strata By Birth year and Study site
[b] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), Strata By Birth year and Study site
[c] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), Age at 1st Full-term pregnancy, Strata By Birth year and Study site
[d] Adjusted for Bilateral Oophorectomy, Number of live birth (0-1, ≥2), Age at 1st Full-term pregnancy, Strata By Birth year and Study site
[e] Nulliparous Excluded, Risk Factor As Continuous

Supplemental Figure 1: Penetrance for *BRCA1* mutation carriers according to different reproductive life scenarios (using breast cancer incidences estimated by Kuchenbaecker KB et al. [1], HRs from combined analyses and frequencies of number of full-term pregnancies by age range in the prospective cohort).

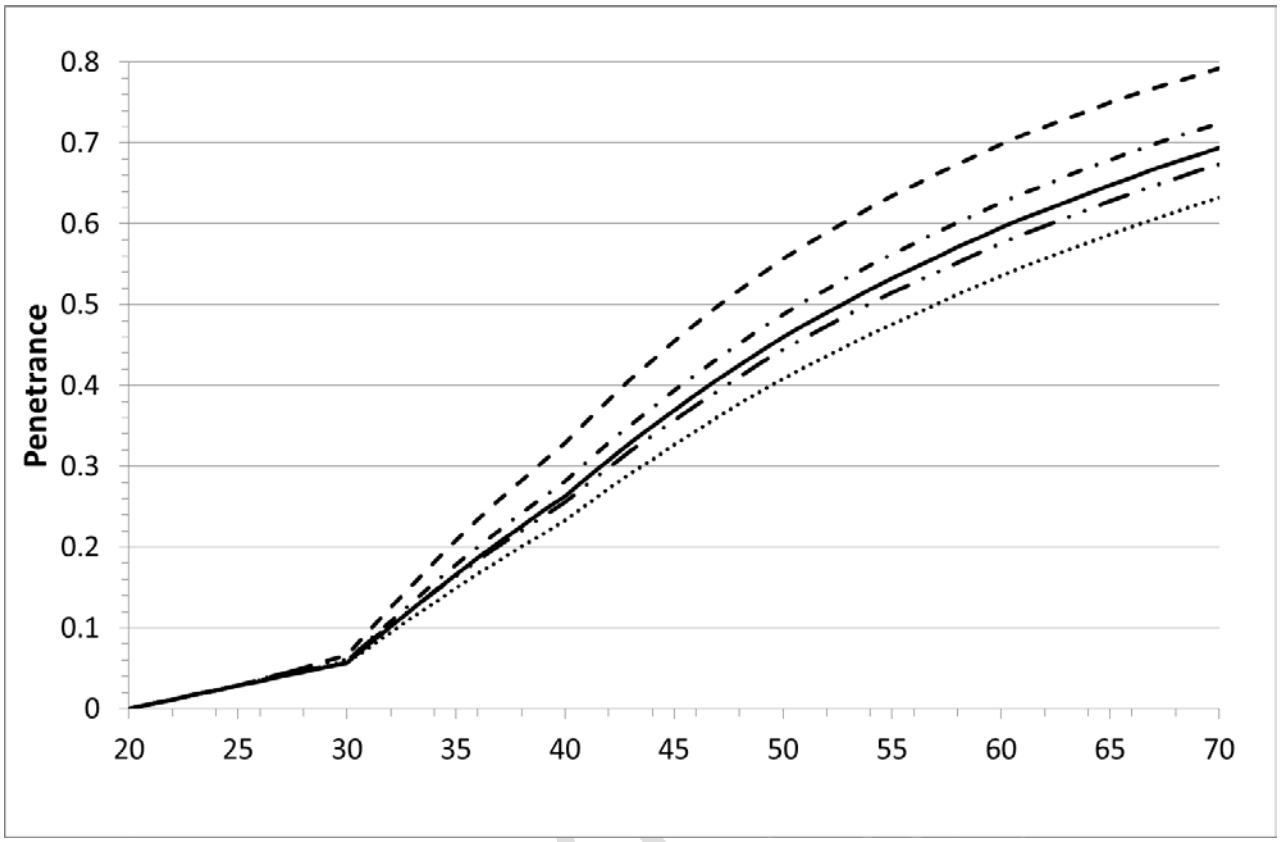
A - Mean age at 1st, 2d, 3rd and 4th Full-term Pregnancy calculated in the retro- and prospective cohort: 25, 28, 30 and 31 years respectively



B – Higher risk scenario: age at 1st, 2d, 3rd and 4th Full-term Pregnancy at 20, 38, 40 and 43 years respectively



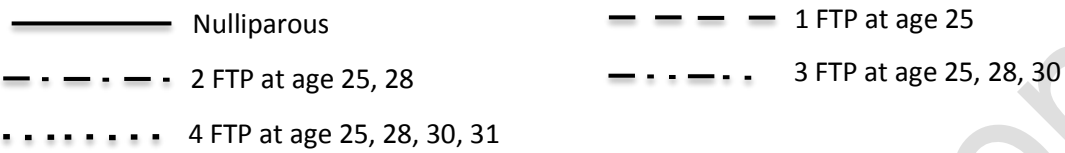
C- Effect of breastfeeding according to the number of Full-term Pregnancy at age 25 and 28 for the 1st and 2d Full-term Pregnancy respectively.



Legends :

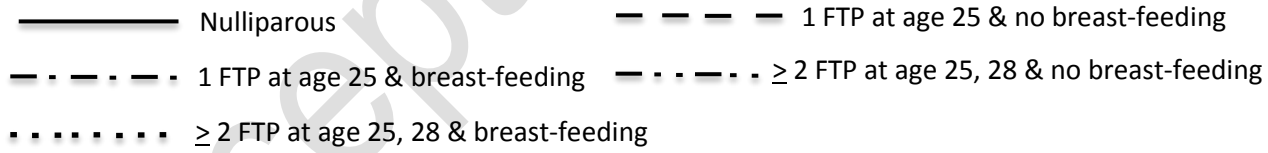
Supplemental Figure 1: Penetrance for *BRCA1* mutation carriers according to different reproductive life scenarios (using breast cancer incidences estimated by Kuchenbaecker KB et al. [1], HRs from combined analyses and frequencies of number of full-term pregnancies by age range in the prospective cohort).

A - Mean age at 1st, 2d, 3rd and 4th Full-term Pregnancy calculated in the retro- and prospective cohort: 25, 28, 30 and 31 years respectively

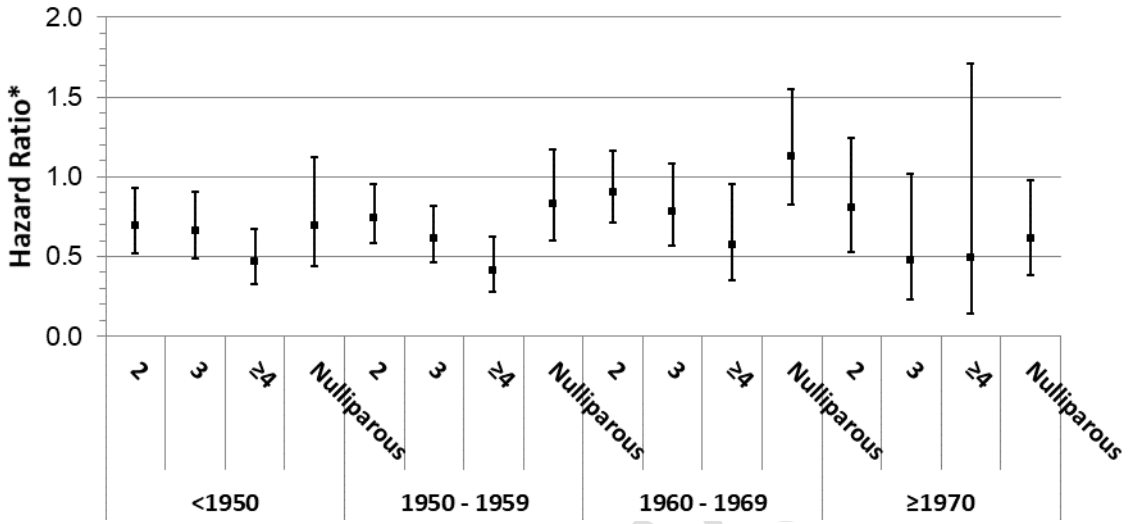


B – Higher risk scenario: age at 1st, 2d, 3rd and 4th Full-term Pregnancy at 20, 38, 40 and 43 years respectively

C- Effect of breastfeeding according to the number of Full-term Pregnancy at age 25 and 28 for the 1st and 2d Full-term Pregnancy respectively.



Supplemental Figure 2. Estimated hazard ratio for the number of full-term pregnancies, after the first full-term pregnancy, among *BRCA1* mutation carriers according to birth cohort (combined analysis)



*: HR adjusted for the oophorectomy, age at 1st FTP (<30, ≥30+nulliparous) and stratified by study

Supplemental Table 1: Retrospective (weighted), Prospective, Combined and Pseudo-incident models adjusted for Bilateral Oophorectomy, OC Use, Family History and Age at Menarche for *BRCA1* mutation carriers.

	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]	pseudo-incident retrospective	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Parous[a]								
No	Reference		Reference		Reference		Reference	
Yes	0.86 (0.71, 1.04)		1.44 (0.97, 2.16)		0.99 (0.83, 1.18)		0.93 (0.75, 1.16)	
No. of Full-term Pregnancy[a] (FTP)								
Nulliparous (no FTP)	Reference		Reference		Reference		Reference	
1	0.97 (0.79, 1.18)		1.73 (1.11, 2.70)		1.11 (0.92, 1.34)		1.05 (0.83, 1.33)	
2	0.77 (0.63, 0.95)	<.0001	1.30 (0.83, 2.01)	<.0001	0.89 (0.73, 1.08)	<.0001	0.84 (0.66, 1.07)	0.001
3	0.67 (0.52, 0.85)		1.17 (0.71, 1.92)		0.77 (0.62, 0.97)		0.79 (0.59, 1.04)	
≥4	0.58 (0.42, 0.78)		0.56 (0.28, 1.11)		0.59 (0.45, 0.79)		0.65 (0.45, 0.94)	
1	Reference		Reference		Reference		Reference	
2	0.80 (0.69, 0.92)	<.0001	0.75 (0.52, 1.09)	<.0001	0.80 (0.70, 0.92)	<.0001	0.80 (0.67, 0.96)	0.001
3	0.69 (0.58, 0.82)		0.68 (0.44, 1.04)		0.70 (0.59, 0.83)		0.75 (0.60, 0.93)	
≥4	0.60 (0.46, 0.76)		0.32 (0.17, 0.61)		0.53 (0.42, 0.67)		0.62 (0.46, 0.85)	
Nulliparous	1.03 (0.85, 1.27)		0.58 (0.37, 0.90)		0.90 (0.75, 1.09)		0.95 (0.75, 1.20)	
No. of Full-term Pregnancy By Attained Age[a]								
<40 years								
1	Reference		Reference		Reference		Reference	
2	0.73 (0.62, 0.87)	<.0001	1.04 (0.58, 1.86)	0.14	0.80 (0.67, 0.95)	<.0001	0.65 (0.49, 0.88)	0.004
3	0.68 (0.54, 0.85)		0.33 (0.11, 1.02)		0.65 (0.52, 0.82)		0.65 (0.44, 0.97)	
≥4	0.66 (0.48, 0.92)		0.68 (0.20, 2.29)		0.67 (0.48, 0.93)		0.56 (0.32, 0.96)	
≥40 years								
1	Reference		Reference		Reference		Reference	
2	0.84 (0.68, 1.05)	<.0001	0.61 (0.38, 1.00)	0.0001	0.79 (0.65, 0.98)	<.0001	0.81 (0.63, 1.05)	0.01
3	0.69 (0.54, 0.88)		0.69 (0.41, 1.16)		0.70 (0.56, 0.88)		0.70 (0.52, 0.94)	
≥4	0.56 (0.42, 0.77)		0.24 (0.11, 0.50)		0.48 (0.36, 0.64)		0.57 (0.38, 0.85)	

	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]	pseudo-incident retrospective	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age at 1st Full-term Pregnancy[b]								
<20	Reference		Reference		Reference		Reference	
20 - 24	1.02 (0.84, 1.24)	0.051	0.85 (0.55, 1.31)	0.99	0.98 (0.82, 1.17)	0.10	0.92 (0.73, 1.15)	0.21
25 - 29	0.91 (0.74, 1.11)		0.81 (0.53, 1.24)		0.88 (0.74, 1.06)		0.84 (0.67, 1.07)	
≥30	0.85 (0.67, 1.08)		0.98 (0.60, 1.59)		0.90 (0.72, 1.11)		0.82 (0.63, 1.07)	
Year Since Last Full-term Pregnancy[c]								
Nulliparous	Reference		Reference		Reference		Reference	
0 - 5	0.93 (0.76, 1.14)		1.89 (1.16, 3.09)		1.09 (0.90, 1.32)		1.02 (0.80, 1.30)	
6 - 20	1.10 (0.88, 1.38)	0.04	1.66 (1.03, 2.69)	0.003	1.22 (1.00, 1.51)	0.0005	1.13 (0.86, 1.47)	0.34
≥21	1.38 (1.03, 1.84)		2.07 (1.12, 3.81)		1.55 (1.18, 2.04)		1.41 (1.01, 1.96)	
0 - 5	Reference		Reference		Reference		Reference	
6 - 20	1.18 (1.03, 1.36)	0.04	0.88 (0.58, 1.33)	0.003	1.13 (0.98, 1.29)	0.0005	1.11 (0.91, 1.35)	0.34
≥21	1.48 (1.17, 1.87)		1.09 (0.62, 1.92)		1.43 (1.14, 1.79)		1.38 (1.03, 1.86)	
Nulliparous	1.08 (0.88, 1.32)		0.53 (0.32, 0.87)		0.92 (0.76, 1.12)		0.98 (0.77, 1.26)	
Year Since Last Full-term Pregnancy by number of Full-term pregnancy[a]								
1 FTP, 0 - 5	Reference		Reference		Reference		Reference	
≥2 FTP, 0 - 5	0.65 (0.53, 0.80)		0.73 (0.37, 1.45)		0.68 (0.55, 0.84)		0.67 (0.50, 0.90)	
1 FTP, 6 - 20	0.92 (0.72, 1.18)		0.91 (0.44, 1.86)		0.94 (0.74, 1.19)		0.87 (0.62, 1.24)	
≥2 FTP, 6 - 20	0.84 (0.68, 1.05)		0.64 (0.32, 1.27)		0.82 (0.66, 1.03)		0.82 (0.60, 1.11)	
1 FTP, ≥21	1.51 (1.06, 2.15)		1.19 (0.47, 2.99)		1.52 (1.08, 2.13)		1.35 (0.87, 2.09)	
≥2 FTP, ≥21	0.98 (0.73, 1.31)		0.78 (0.35, 1.75)		0.97 (0.73, 1.31)		0.96 (0.65, 1.40)	
Breast-Feeding Duration[d]								
None or < 1 month	Reference		Reference		Reference		Reference	
1 - 5 mo	0.97 (0.84, 1.14)		1.06 (0.72, 1.56)		0.98 (0.85, 1.13)		0.90 (0.74, 1.09)	
6 - 12 mo	0.82 (0.69, 0.96)	0.001	1.07 (0.73, 1.58)	0.40	0.84 (0.72, 0.98)	0.001	0.86 (0.70, 1.05)	0.02
13 - 24 mo	0.76 (0.62, 0.92)		1.10 (0.71, 1.71)		0.81 (0.68, 0.97)		0.74 (0.58, 0.95)	
> 24 mo	0.66 (0.49, 0.89)		0.82 (0.48, 1.43)		0.69 (0.52, 0.90)		0.70 (0.51, 0.96)	

	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]	pseudo-incident retrospective	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
No. of Full-term Pregnancy and Breast-feeding[a]								
Nulliparous	Reference		Reference		Reference		Reference	
1 FTP, Never Breast-feeding	1.14 (0.88, 1.48)		2.03 (1.14, 3.61)		1.34 (1.05, 1.71)		1.23 (0.90, 1.69)	
≥2 FTP, Never Breast-feeding	0.83 (0.65, 1.05)		1.15 (0.68, 1.96)		0.93 (0.75, 1.17)		0.96 (0.72, 1.27)	
1 FTP, Ever Breast-feeding	0.94 (0.76, 1.16)		1.67 (1.01, 2.77)		1.08 (0.88, 1.31)		1.02 (0.80, 1.31)	
≥2 FTP, Ever Breast-feeding	0.73 (0.59, 0.90)		1.26 (0.81, 1.96)		0.85 (0.69, 1.03)		0.81 (0.64, 1.03)	
Incomplete Pregnancy[c] (IP)								
No full-term or Incomplete pregnancy	Reference		Reference		Reference		Reference	
Full-term pregnancy, no IP	0.94 (0.77, 1.15)		1.67 (1.05, 2.67)		1.07 (0.89, 1.29)		0.98 (0.77, 1.24)	
Induced abortion only	0.99 (0.79, 1.23)		1.72 (1.03, 2.87)		1.12 (0.91, 1.38)		1.03 (0.79, 1.33)	
Miscarriage only	0.93 (0.74, 1.16)		1.79 (1.10, 2.90)		1.08 (0.88, 1.32)		0.98 (0.75, 1.29)	
Induced abortion and miscarriage	1.04 (0.73, 1.47)		1.16 (0.44, 3.03)		1.08 (0.78, 1.50)		1.46 (1.03, 2.06)	
Incomplete Pregnancy Relative To First Full-term Pregnancy[c]								
No IP	Reference		Reference		Reference		Reference	
Before first FTP or no FTP	1.01 (0.87, 1.17)		1.00 (0.72, 1.38)		1.01 (0.88, 1.16)		1.09 (0.92, 1.29)	
After first FTP	1.00 (0.86, 1.17)		1.35 (0.95, 1.92)		1.07 (0.93, 1.23)		1.07 (0.89, 1.29)	

[a] Adjusted for Bilateral Oophorectomy (Yes, No), Age at 1st full-term pregnancy (<30, ≥30+nulliparous), OC Use (Ever, Never, Ever Unknown Start Age, Missing), Family History (0, 1 ,≥2, Unknown), Age at Menarche (<12, ≥12 - <13, ≥13 - <14, ≥14 - <15, >=15, Age Missing or Never had menstrual period), Strata By Birth year and Study site

[b] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), OC Use, Family History, Age at Menarche, Strata By Birth year and Study site

[c] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), Age at 1st full-term pregnancy, OC Use, Family History, Age at Menarche, Strata By Birth year and Study site

[d] Adjusted for Bilateral Oophorectomy, Number of live birth (0-1, ≥2), Age at 1st full-term pregnancy, OC Use, Family History, Age at Menarche, Strata By Birth year and Study site

[e] Nulliparous Excluded, Risk Factor As Continuous

Supplemental Table 2: Retrospective (weighted), Prospective, Combined and Pseudo-incident models adjusted for Bilateral Oophorectomy, OC Use, Family History and Age at Menarche for *BRCA2* mutation carriers.

	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]	pseudo-incident retrospective	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Parous[a]								
No	Reference		Reference		Reference		Reference	
Yes	1.18 (0.91, 1.52)		1.30 (0.76, 2.21)		1.24 (0.98, 1.58)		1.14 (0.86, 1.52)	
No. of Full-term Pregnancy[a] (FTP)								
Nulliparous (no FTP)	Reference		Reference		Reference		Reference	
1	1.20 (0.92, 1.59)		1.01 (0.52, 1.98)		1.22 (0.94, 1.57)		1.20 (0.89, 1.63)	
2	1.22 (0.92, 1.62)	0.0002	1.45 (0.82, 2.55)	0.45	1.32 (1.01, 1.72)	0.005	1.17 (0.85, 1.61)	<.0001
3	0.94 (0.68, 1.30)		1.54 (0.81, 2.93)		1.09 (0.79, 1.50)		0.80 (0.55, 1.16)	
≥4	0.70 (0.48, 1.03)		1.58 (0.80, 3.09)		0.88 (0.61, 1.25)		0.55 (0.34, 0.90)	
1	Reference		Reference		Reference		Reference	
2	1.01 (0.81, 1.26)	0.0002	1.43 (0.80, 2.55)	0.45	1.08 (0.88, 1.33)	0.005	0.97 (0.75, 1.26)	<.0001
3	0.78 (0.60, 1.01)		1.52 (0.79, 2.92)		0.89 (0.70, 1.15)		0.66 (0.48, 0.91)	
≥4	0.58 (0.42, 0.80)		1.56 (0.77, 3.13)		0.72 (0.53, 0.97)		0.46 (0.30, 0.71)	
Nulliparous	0.83 (0.63, 1.09)		0.99 (0.51, 1.93)		0.82 (0.64, 1.06)		0.83 (0.61, 1.13)	
No. of Full-term Pregnancy By Attained Age[a]								
<40 years								
1	Reference		Reference		Reference		Reference	
2	0.80 (0.61, 1.05)	<.0001	3.06 (0.43, 21.75)	0.90	0.88 (0.67, 1.15)	0.0008	1.00 (0.65, 1.54)	0.0002
3	0.79 (0.55, 1.12)		1.50 (0.14, 16.52)		0.81 (0.55, 1.19)		0.72 (0.39, 1.34)	
≥4	0.29 (0.16, 0.53)		1.71 (0.09, 31.79)		0.33 (0.18, 0.63)		0.12 (0.03, 0.45)	
≥40 years								
1	Reference		Reference		Reference		Reference	
2	1.25 (0.92, 1.70)	0.007	1.32 (0.69, 2.52)	0.43	1.25 (0.95, 1.64)	0.04	0.96 (0.66, 1.39)	0.001
3	0.90 (0.64, 1.27)		1.53 (0.76, 3.08)		1.01 (0.74, 1.37)		0.64 (0.42, 0.96)	
≥4	0.78 (0.53, 1.13)		1.50 (0.71, 3.14)		0.88 (0.63, 1.24)		0.52 (0.32, 0.85)	

	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]	pseudo-incident retrospective	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age at 1st Full-term Pregnancy[b]								
<20	Reference		Reference		Reference		Reference	
20 - 24	1.09 (0.84, 1.43)	0.0006	1.60 (0.86, 2.98)	0.12	1.22 (0.95, 1.56)	0.0002	0.84 (0.62, 1.13)	0.62
25 - 29	1.38 (1.04, 1.84)		1.29 (0.65, 2.56)		1.39 (1.05, 1.83)		0.88 (0.64, 1.20)	
≥30	1.55 (1.13, 2.13)		1.96 (0.96, 4.00)		1.70 (1.25, 2.31)		0.96 (0.67, 1.38)	
Year Since Last Full-term Pregnancy[c]								
Nulliparous	Reference		Reference		Reference		Reference	
0 - 5	1.28 (0.97, 1.69)		1.29 (0.58, 2.84)		1.31 (1.00, 1.70)		1.24 (0.90, 1.70)	
6 - 20	1.23 (0.91, 1.66)	0.46	0.96 (0.48, 1.95)	0.047	1.24 (0.94, 1.64)	0.50	1.22 (0.86, 1.73)	0.02
≥21	1.19 (0.81, 1.72)		0.76 (0.31, 1.84)		1.14 (0.80, 1.61)		1.48 (0.94, 2.31)	
0 - 5	Reference		Reference		Reference		Reference	
6 - 20	0.96 (0.79, 1.18)	0.46	0.75 (0.39, 1.45)	0.047	0.95 (0.79, 1.15)	0.50	0.99 (0.74, 1.30)	0.02
≥21	0.93 (0.68, 1.27)		0.59 (0.25, 1.40)		0.87 (0.64, 1.18)		1.19 (0.79, 1.81)	
Nulliparous	0.78 (0.59, 1.03)		0.78 (0.35, 1.72)		0.77 (0.59, 1.00)		0.81 (0.59, 1.12)	
Breast-Feeding Duration[d]								
None or < 1 month	Reference		Reference		Reference		Reference	
1 - 5 mo	0.97 (0.79, 1.20)		1.17 (0.71, 1.93)		1.03 (0.85, 1.26)		0.82 (0.63, 1.05)	
6 - 12 mo	1.09 (0.88, 1.36)	0.001	1.29 (0.79, 2.12)	0.55	1.12 (0.91, 1.37)	0.01	0.95 (0.73, 1.23)	0.03
13 - 24 mo	0.82 (0.63, 1.06)		0.73 (0.40, 1.33)		0.79 (0.62, 1.02)		0.72 (0.54, 0.98)	
> 24 mo	0.58 (0.41, 0.83)		1.11 (0.64, 1.91)		0.71 (0.53, 0.96)		0.59 (0.40, 0.88)	
No. of Full-term Pregnancy and Breastfeeding[a]								
Nulliparous	Reference		Reference		Reference		Reference	
1 FTP, Never Breastfeeding	1.27 (0.87, 1.88)		1.61 (0.63, 4.09)		1.38 (0.96, 1.99)		1.56 (1.00, 2.44)	
≥2 FTP, Never Breastfeeding	1.19 (0.86, 1.65)		1.16 (0.59, 2.30)		1.24 (0.92, 1.68)		1.24 (0.86, 1.79)	
1 FTP, Ever Breastfeeding	1.25 (0.93, 1.68)		0.77 (0.34, 1.75)		1.20 (0.92, 1.57)		1.17 (0.84, 1.63)	
≥2 FTP, Ever Breastfeeding	1.09 (0.82, 1.45)		1.52 (0.87, 2.64)		1.24 (0.94, 1.62)		1.02 (0.73, 1.41)	

	retrospective	Trend[e]	prospective	Trend[e]	combined	Trend[e]	pseudo-incident retrospective	Trend[e]
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Incomplete Pregnancy[c] (IP)								
No full-term or Incomplete pregnancy	Reference		Reference		Reference		Reference	
Full-term pregnancy, no abortion	1.28 (0.99, 1.67)		0.75 (0.37, 1.52)		1.21 (0.94, 1.56)		1.19 (0.88, 1.61)	
Induced abortion only	1.34 (0.97, 1.84)		0.41 (0.17, 1.02)		1.11 (0.82, 1.51)		1.47 (1.04, 2.07)	
Miscarriage only	1.40 (1.03, 1.89)		0.77 (0.38, 1.56)		1.27 (0.96, 1.69)		1.24 (0.87, 1.77)	
Induced abortion and miscarriage	1.81 (1.15, 2.85)		0.79 (0.32, 1.95)		1.53 (1.01, 2.32)		1.40 (0.83, 2.36)	
Incomplete Pregnancy Relative To First Full-term Pregnancy[c]								
No IP	Reference		Reference		Reference		Reference	
Before first FTP or no FTP	1.29 (1.06, 1.58)		0.73 (0.46, 1.15)		1.12 (0.93, 1.36)		1.23 (0.98, 1.55)	
After first FTP	1.01 (0.82, 1.25)		0.95 (0.62, 1.48)		0.99 (0.82, 1.20)		1.10 (0.86, 1.40)	

[a] Adjusted for Bilateral Oophorectomy (Yes, No), Age at 1st full-term pregnancy (<30, ≥30+nulliparous), OC Use (Ever, Never, Ever Unknown Start Age, Missing), Family History (0, 1 ,≥2, Unknown), Age at Menarche (<12, ≥12 - <13, ≥13 - <14, ≥14 - <15, >=15, Age Missing or Never had menstrual period), Strata By Birth year and Study site

[b] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), OC Use, Family History, Age at Menarche, Strata By Birth year and Study site

[c] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), Age at 1st full-term pregnancy, OC Use, Family History, Age at Menarche, Strata By Birth year and Study site

[d] Adjusted for Bilateral Oophorectomy, Number of live birth (0-1, ≥2), Age at 1st full-term pregnancy, OC Use, Family History, Age at Menarche, Strata By Birth year and Study site

[e] Nulliparous Excluded, Risk Factor As Continuous

Supplemental Table 3. Prospective analyses excluding in-situ breast cancers by gene

	*BRCA*1	Trend[d]	*BRCA*2	Trend[d]
	HR (95% CI)		HR (95% CI)	
Parous (at least 1 Full-term Pregnancy)[a]				
No	Reference		Reference	
Yes	1.40 (0.93, 2.10)		1.44 (0.80, 2.59)	
No. of Full-term Pregnancy[a] (FTP)				
Nulliparous	Reference		Reference	
1	1.76 (1.13, 2.73)	<.0001	1.25 (0.62, 2.51)	0.74
2	1.18 (0.75, 1.86)		1.56 (0.83, 2.91)	
3	1.13 (0.67, 1.89)		1.57 (0.76, 3.23)	
≥4	0.50 (0.25, 0.99)		1.67 (0.79, 3.54)	
1	Reference		Reference	
2	0.67 (0.46, 0.99)		1.24 (0.70, 2.21)	
3	0.64 (0.41, 1.00)	<.0001	1.25 (0.64, 2.46)	0.74
≥4	0.28 (0.15, 0.53)		1.34 (0.65, 2.75)	
Nulliparous	0.57 (0.37, 0.88)		0.80 (0.40, 1.60)	
No. of Full-term Pregnancy By Attained Age[a]				
<40 years				
1	Reference		Reference	
2	1.03 (0.58, 1.84)	0.26	2.25 (0.45, 11.35)	0.79
3	0.36 (0.12, 1.11)		1.32 (0.15, 11.58)	
≥4	0.70 (0.20, 2.38)		1.46 (0.10, 22.46)	
≥40 years				
1	Reference		Reference	
2	0.53 (0.33, 0.86)	<.0001	1.07 (0.57, 2.02)	0.79
3	0.63 (0.37, 1.06)		1.15 (0.57, 2.33)	
≥4	0.20 (0.10, 0.42)		1.20 (0.57, 2.54)	

	*BRCA*1	Trend[d]	*BRCA*2	Trend[d]
	HR (95% CI)		HR (95% CI)	
Age at 1st Full-term Pregnancy[b]				
<20	Reference		Reference	
20 - 24	0.78 (0.50, 1.21)	0.74	1.36 (0.73, 2.54)	0.28
25 - 29	0.69 (0.44, 1.07)		1.09 (0.55, 2.18)	
≥30	0.90 (0.55, 1.47)		1.54 (0.75, 3.17)	
Year Since Last Full-term Pregnancy[c]				
0 - 5	Reference		Reference	
6 - 20	0.91 (0.60, 1.40)	0.001	0.69 (0.35, 1.38)	0.09
≥21	1.20 (0.67, 2.15)		0.60 (0.25, 1.46)	
Nulliparous	0.53 (0.33, 0.87)		0.61 (0.27, 1.40)	
Nulliparous	Reference		Reference	
0 - 5	1.88 (1.15, 3.06)		1.64 (0.72, 3.76)	
6 - 20	1.71 (1.06, 2.78)	0.001	1.14 (0.54, 2.38)	0.09
≥21	2.24 (1.21, 4.17)		0.99 (0.41, 2.41)	
Year Since Last Full-term Pregnancy by number of Full-term pregnancy[a]				
1 FTP, 0 - 5	Reference			
≥2 FTP, 0 - 5	0.72 (0.36, 1.43)			
1 FTP, 6 - 20	1.02 (0.50, 2.08)			
≥2 FTP, 6 - 20	0.63 (0.31, 1.27)			
1 FTP, ≥21	1.35 (0.53, 3.43)			
≥2 FTP, ≥21	0.82 (0.36, 1.88)			
Breast Feeding Duration[cbis]				
None	Reference		Reference	
1 - 5 mo	0.98 (0.66, 1.46)		1.00 (0.59, 1.70)	
6 - 12 mo	1.01 (0.67, 1.52)	0.43	1.26 (0.74, 2.16)	0.48
13 - 24 mo	1.09 (0.69, 1.71)		0.78 (0.42, 1.45)	
> 24 mo	0.79 (0.45, 1.37)		0.90 (0.49, 1.65)	
No Live Birth	0.58 (0.35, 0.95)		0.80 (0.36, 1.80)	

	*BRCA*1	Trend[d]	*BRCA*2	Trend[d]
	HR (95% CI)		HR (95% CI)	
No. of Full-term Pregnancy and Breastfeeding[a]				
Nulliparous	Reference		Reference	
1 FTP, Never Breastfeeding	2.07 (1.17, 3.66)		2.25 (0.90, 5.60)	
≥2 FTP, Never Breastfeeding	1.14 (0.66, 1.97)		1.31 (0.61, 2.78)	
1 FTP, Ever Breastfeeding	1.72 (1.05, 2.81)		0.92 (0.40, 2.11)	
≥2 FTP, Ever Breastfeeding	1.16 (0.74, 1.82)		1.61 (0.87, 2.98)	
Incomplete Pregnancy[c]				
No full-term pregnancy or abortion	Reference		Reference	
Full-term pregnancy, no abortion	1.72 (1.08, 2.74)		0.98 (0.47, 2.05)	
Induced abortion only	1.73 (1.05, 2.86)		0.60 (0.23, 1.58)	
Miscarriage only	1.81 (1.11, 2.95)		1.04 (0.50, 2.16)	
Induced abortion and miscarriage	1.19 (0.44, 3.21)		1.08 (0.41, 2.86)	
Incomplete Pregnancy Relative To First Full-term Pregnancy[c]				
No abortion	Reference		Reference	
Before first full-term pregnancy or no Full-term Pregnancy	1.03 (0.74, 1.43)		0.89 (0.56, 1.42)	
After first full-term pregnancy	1.28 (0.88, 1.85)		1.01 (0.63, 1.61)	

[a] Adjusted for Bilateral Oophorectomy (Yes, No), Age at 1st full-term pregnancy (<30, ≥30+nulliparous), Strata By Birth year and Study site
[b] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), Strata By Birth year and Study site
[c] 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
[d] Adjusted for Bilateral Oophorectomy, Number of live birth (0-1, ≥2), Age at 1st full-term pregnancy, Strata By Birth year and Study site
[e] Nulliparous Excluded, Risk Factor As Continuous

Supplemental Table 4. Pseudo-incident retrospective analysis by gene

	BRCA1		BRCA2	
	HR (95% CI)	**Trend[e]**	**HR (95% CI)**	**Trend[e]**
Parous[a]				
No	Reference		Reference	
Yes	0.94 (0.76, 1.17)		1.15 (0.87, 1.53)	
No. of Full-term Pregnancy[a] (FTP)				
Nulliparous (no FTP)	Reference		Reference	
1	1.06 (0.84, 1.34)		1.22 (0.90, 1.65)	
2	0.84 (0.66, 1.07)	0.001	1.16 (0.85, 1.59)	<.0001
3	0.80 (0.60, 1.05)		0.83 (0.58, 1.20)	
≥4	0.64 (0.45, 0.92)		0.55 (0.34, 0.88)	
1	Reference		Reference	
2	0.79 (0.66, 0.95)	0.001	0.95 (0.74, 1.23)	<.0001
3	0.75 (0.60, 0.93)		0.68 (0.50, 0.93)	
≥4	0.61 (0.45, 0.82)		0.45 (0.30, 0.68)	
Nulliparous	0.94 (0.75, 1.19)		0.82 (0.61, 1.11)	
No. of Full-term Pregnancy By Attained Age[a]				
<40 years				
1	Reference		Reference	
2	0.66 (0.49, 0.88)	0.004	0.94 (0.62, 1.43)	0.0002
3	0.67 (0.45, 0.99)		0.71 (0.40, 1.28)	
≥4	0.57 (0.33, 0.98)		0.14 (0.04, 0.49)	
≥40 years				
1	Reference		Reference	
2	0.81 (0.62, 1.05)	0.02	0.96 (0.67, 1.37)	0.001
3	0.71 (0.53, 0.96)		0.67 (0.45, 0.99)	
≥4	0.57 (0.39, 0.85)		0.52 (0.32, 0.83)	
Age at 1st Full-term Pregnancy[b]				
<20	Reference		Reference	
20 - 24	0.90 (0.72, 1.13)	0.14	0.84 (0.62, 1.13)	0.64
25 - 29	0.82 (0.65, 1.03)		0.88 (0.64, 1.21)	
≥30	0.80 (0.62, 1.05)		0.97 (0.68, 1.38)	
Year Since Last Full-term Pregnancy[c]				
Nulliparous	Reference		Reference	
0 - 5	1.04 (0.81, 1.33)		1.28 (0.93, 1.77)	
6 - 20	1.13 (0.87, 1.47)	0.46	1.21 (0.86, 1.71)	0.053
≥21	1.38 (0.99, 1.93)		1.42 (0.92, 2.19)	
0 - 5	Reference		Reference	
6 - 20	1.09 (0.89, 1.34)	0.46	0.95 (0.72, 1.25)	0.053
≥21	1.33 (0.99, 1.79)		1.11 (0.74, 1.66)	
Nulliparous	0.97 (0.76, 1.23)		0.78 (0.57, 1.08)	

	BRCA1		BRCA2	
	HR (95% CI)	Trend[e]	HR (95% CI)	Trend[e]
Year Since Last Full-term Pregnancy by number of Full-term pregnancy[a]				
1 FTP, 0 - 5	Reference		-	
≥2 FTP, 0 - 5	0.68 (0.51, 0.92)		-	
1 FTP, 6 - 20	0.89 (0.63, 1.26)		-	
≥2 FTP, 6 - 20	0.81 (0.59, 1.10)		-	
1 FTP, ≥21	1.34 (0.86, 2.08)		-	
≥2 FTP, ≥21	0.93 (0.63, 1.37)		-	
Breast-Feeding Duration[d]				
None or < 1 month	Reference		Reference	
1 - 5 mo	0.88 (0.72, 1.06)		0.85 (0.66, 1.09)	
6 - 12 mo	0.84 (0.68, 1.03)	0.02	0.98 (0.75, 1.28)	0.03
13 - 24 mo	0.76 (0.59, 0.97)		0.73 (0.54, 0.98)	
> 24 mo	0.69 (0.51, 0.95)		0.63 (0.43, 0.92)	
No. of Full-term Pregnancy and Breast-feeding[a]				
Nulliparous	Reference		Reference	
1 FTP, Never Breast-feeding	1.23 (0.90, 1.70)		1.56 (1.01, 2.41)	
≥2 FTP, Never Breast-feeding	0.98 (0.74, 1.29)		1.22 (0.85, 1.76)	
1 FTP, Ever Breast-feeding	1.04 (0.81, 1.33)		1.19 (0.86, 1.66)	
≥2 FTP, Ever Breast-feeding	0.80 (0.63, 1.02)		1.04 (0.75, 1.43)	
Incomplete Pregnancy[c] (IP)				
No full-term or Incomplete pregnancy	Reference		Reference	
Full-term pregnancy, no IP	0.98 (0.77, 1.24)		1.21 (0.90, 1.63)	
Induced abortion only	1.04 (0.81, 1.34)		1.52 (1.08, 2.13)	
Miscarriage only	1.00 (0.77, 1.30)		1.33 (0.94, 1.89)	
Induced abortion and miscarriage	1.53 (1.08, 2.16)		1.35 (0.80, 2.28)	
Incomplete Pregnancy Relative To First Full-term Pregnancy[c]				
No IP	Reference		Reference	
Before first FTP or no FTP	1.10 (0.93, 1.30)		1.27 (1.01, 1.59)	
After first FTP	1.09 (0.91, 1.31)		1.13 (0.89, 1.44)	

[a] Adjusted for Bilateral Oophorectomy (Yes, No), Age at 1st full-term pregnancy (<30, ≥30+nulliparous), Strata By Birth year and Study site

[b] Adjusted for Bilateral Oophorectomy, Number of full-term pregnancies (0-1, ≥2), Strata By Birth year and Study site

[c] 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

[d] Adjusted for Bilateral Oophorectomy, Number of live birth (0-1, ≥2), Age at 1st full-term pregnancy, Strata By Birth year and Study site

[e] Nulliparous Excluded, Risk Factor As Continuous