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Hormonal Contraception and Breast Cancer Risk for Carriers of Germline Mutations in *BRCA1* and *BRCA2*

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ABSTRACT

PURPOSE It is uncertain whether, and to what extent, hormonal contraceptives increase breast cancer (BC) risk for germline *BRCA1* or *BRCA2* mutation carriers.

METHODS Using pooled observational data from four prospective cohort studies, associations between hormonal contraceptive use and BC risk for unaffected female *BRCA1* and *BRCA2* mutation carriers were assessed using Cox regression.

RESULTS Of 3,882 *BRCA1* and 1,509 *BRCA2* mutation carriers, 53% and 71%, respectively, had ever used hormonal contraceptives for at least 1 year (median cumulative duration of use, 4.8 and 5.7 years, respectively). Overall, 488 *BRCA1* and 191 *BRCA2* mutation carriers developed BC during median follow-up of 5.9 and 5.6 years, respectively. Although for *BRCA1* mutation carriers, neither current nor past use of hormonal contraceptives for at least 1 year was statistically significantly associated with BC risk (hazard ratio [HR], 1.40 [95% CI, 0.94 to 2.08], $P = .10$ for current use; 1.16 [0.80 to 1.69], $P = .4$, 1.40 [0.99 to 1.97], $P = .05$, and 1.27 [0.98 to 1.63], $P = .07$ for past use 1-5, 6-10, and >10 years before, respectively), ever use was associated with increased risk (HR, 1.29 [95% CI, 1.04 to 1.60], $P = .02$). Furthermore, BC risk increased with longer cumulative duration of use, with an estimated proportional increase in risk of 3% (1%-5%, $P = .002$) for each additional year of use. For *BRCA2* mutation carriers, there was no evidence that current or ever use was associated with increased BC risk (HR, 0.70 [95% CI, 0.33 to 1.47], $P = .3$ and 1.07 [0.73 to 1.57], $P = .7$, respectively).

CONCLUSION Hormonal contraceptives were associated with increased BC risk for *BRCA1* mutation carriers, especially if used for longer durations. Decisions about their use in women with *BRCA1* mutations should carefully weigh the risks and benefits for each individual.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Women with a germline mutation in *BRCA1* or *BRCA2* have high lifetime risks of breast cancer (BC). The average lifetime risk is approximately 70%, with more than half of all breast cancers in these women occurring before age 50 years.[1] Understanding whether and how use of hormonal contraception (HC) might affect these risks is important for informed decision making.

HCs include oral contraceptive pills (OCPs), hormonal implants, injections, and intrauterine devices (IUDs). They provide excellent contraceptive efficacy, and OCPs can be useful in the treatment of polycystic ovarian syndrome, premenstrual dysphoric disorder, and endometriosis, and reduce risks of ovarian and endometrial cancers.[2] In the general population, current use of HC is associated with a 20%-30% relative increase in the risk of BC compared with never having used HC.[3-5] Longer duration of use is associated

CONTEXT

Key Objective

Is hormonal contraception use associated with the risk of breast cancer (BC) for women with germline mutations in *BRCA1* and *BRCA2?*

Knowledge Generated

Hormonal contraceptive use in *BRCA1* mutation carriers was associated with increased risk of BC, with users having a proportional increase in risk of 3% for each year of hormonal contraceptive use. No evidence of association was seen between hormonal contraceptive use and BC risk for *BRCA2* mutation carriers.

Relevance *(G. Fleming)*

These results should be discussed with young women carrying a *BRCA1* mutation as they make contraceptive choices prior to prophylactic salpingo-oophorectomy.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

with higher risk and, although the relative risk reduces after cessation, it remains elevated for 5-10 years after cessation.[3–5] Most published data refer only to various formulations of the OCP, but associations are similar for progestogen-only contraceptives.[4,6]

Studies of the association between OCP use and BC risk for *BRCA1* and *BRCA2* mutation carriers have assessed ever use rather than current use, and the findings are conflicting.[7–18] Although most studies reported relative risk estimates >1 for *BRCA1*[7,8,11,13–16,18] and/or *BRCA2* mutation carriers,[7,11,14,16,18] in few studies were the findings statistically significant,[8,11,14,15,18] and these studies are inconsistent regarding whether duration of use, age at first use, and use before first childbirth influence BC risk. Most studies were small and had case-control, rather than prospective cohort, designs. No data are available regarding the risk of BC associated with the use of other types of HC, such as hormonal implants and hormonal IUDs for *BRCA1* and *BRCA2* mutation carriers.

This study assessed the association between use of any HC and BC risk for *BRCA1* and *BRCA2* mutation carriers using individual participant data from four prospective cohorts. It was hypothesized that the association between current HC use and BC risk would not differ from that for the general population[3] and that duration of use, age at first use, and use before first birth would not be associated with BC risk independently of current use and recency of use. The study protocol was prospectively registered by the Australian New Zealand Clinical Trials Registry.[19]

METHODS

Participants

This was an observational study using pooled prospective cohort data. Participants were women from Australia, New Zealand, Europe, Canada, and the United States with a germline mutation in *BRCA1* or *BRCA2* who were enrolled, between December 1991 and August 2019, in one of four cohort studies: the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer Follow-Up Project (kConFab FUP),[20,21] the Breast Cancer Family Registry (BCFR),[22,23] the Risk Factor Analysis of Hereditary Breast and Ovarian Cancer Study (RFS),[24] or the Basser Center/University of Pennsylvania Registry (UPenn Registry).[25] All cohorts included participants recruited through genetics clinics and the BCFR also included some population-based recruitment. Participants included in this analysis had follow-up information available, were at least age 18 years at cohort entry, were born after 1920, and had no personal history of cancer (except cervix carcinoma in situ or nonmelanoma skin cancer) or risk-reducing bilateral mastectomy at the time of entry into the relevant cohort. All participants provided written informed consent and all studies were approved by the relevant institutional review boards.

Data Collection

Data collection for kConFab FUP participants occurred every 3 years using self-report questionnaires. Family reports, medical records, and cancer and death registries were used to obtain data regarding deaths and cancer diagnoses. For the BCFR, invasive cancer diagnoses and mortality data were confirmed through pathology reports and cancer and national death registries. Questionnaire-based data collection on RFS participants occurred every 2 years.[26] Follow-up of UPenn Registry participants was yearly using self-report questionnaires and medical records. For RFS and kConFab, data were collected on use of all types of HCs. For BCFR, data were collected on use of OCP (including progestin-only pills), implants, and injections, but not hormone-containing IUDs. For UPenn Registry, only data on use of

the combined and progestin-only OCP (ie, not other types of HCs) were collected.

Statistical Analysis

Cox regression models were used to estimate hazard ratio (HR) and 95% CI for BC (invasive disease or ductal carcinoma in situ) associated with HC use, with age as the timescale, entry being at cohort enrollment, and censoring at the earlier of bilateral mastectomy, death, diagnosis of another cancer, or last follow-up. Separate analyses were undertaken for *BRCA1* and *BRCA2* mutation carriers; women with mutations in both were analyzed with *BRCA1* mutation carriers. The nonindependence of data from members of the same family was accounted for by clustering on family. Analyses were stratified on study (categorical, Table 1) with equal coefficients across strata but baseline hazard distinct for each stratum, and adjusted for the following predefined potential confounders[1,27]: year of birth, number of first-degree relatives with BC, parity, premenopausal bilateral oophorectomy (binary), and menopausal status (binary), the latter three modeled as time-varying covariates. Each of year of birth, number of first-degree relatives with BC, and parity were modeled with a single linear coefficient. Age at menopause was defined using self-reported data. Where self-reported age was unavailable or unreliable (eg, women who had a hysterectomy but ovaries were not removed, had a hormonal IUD, or were on OCP), the menopause age was assumed to be 50 years.

An event history of HC use over time, comprising episodes of starting and stopping use, was created on the basis of baseline and follow-up questionnaire responses. Incomplete or inconsistent information (eg, reported duration of use shorter than the difference in stop and start ages) was resolved where possible by assuming nonuse during reported pregnancies and cessation of use at natural menopause, hysterectomy, oophorectomy, or tubal ligation. Multiple imputation (10 imputations) with predictive mean matching was used to deal with missing data on HC use and family history. Gaps created by imputation of < 3 months between contiguous episodes of HC use were removed (assuming ongoing HC use). T-statistics were calculated for regression coefficients with the degrees of freedom determined using Rubin's[28] rules.

The details of specific types of HCs were not available for 78% of participants, so the exposure of interest was HC defined as any form of OCP, hormonal implant or injection, or hormone-containing IUD used for periods of 12 months or more. Exposures considered were current use, past use (categorized as time since last use), cumulative duration of use, age at first use, use before first birth, and ever use (defined as at least one episode of continuous use for at least 12 months), all modeled as time-varying covariates. Current use was defined as use within the previous year, to account for cessation of use because of BC symptoms or clinical investigation. The cumulative duration of use, age at first use, and use before first birth analyses were additionally adjusted for current use and past use categories.

Under the assumption that current users of HC are at higher risk than nonusers, and that risk returns to that of nonusers over the 10 years after cessation, as observed by the Oxford group,[3] we also fit a model with a binary parameter for current use and continuous term for time since last use that was constrained to reduce to zero (on the log-scale) over 10 years.

Model fit was compared using the Akaike information criterion (AIC). Departure from the proportional hazards assumption was assessed using Schoenfeld residuals. The following sensitivity analyses were conducted to assess the influence of potential biases: censoring observation time at age 65 years; censoring at menopause; excluding participants with unknown first-degree family history of BC; and varying the minimum time period for which gaps in HC use after imputation were removed. Separate analyses by cohort and country were also performed. Statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX). P (two-sided) <.05 was considered statistically significant.

RESULTS

Of 48,822 women enrolled in the four cohort studies, 5,391 women were included in the final analyses (Fig 1). The characteristics of the sample are summarized in Table 1. First-degree family history was not reported for 13.5% of participants. HC use history was incomplete across all questionnaire responses for 4.7% of study participants; for the cumulative duration analysis, this translated into a 2% fraction of missing information for the coefficient estimate.

For 3,882 *BRCA1* and 1,509 *BRCA2* mutation carriers, 53% and 71%, respectively, had ever used HC (for at least 1 year). The median cumulative duration of HC use was 4.8 and 5.7 years, respectively. Most HC use was after 1979 (Appendix Fig A1, online only). Incident BC was diagnosed in 488 *BRCA1* (440 invasive) and 191 *BRCA2* mutation carriers (151 invasive) during a median of 5.9 and 5.6 years of follow-up, respectively. Age at diagnosis is summarized in Figure 2.

BRCA1

Results are summarized in Table 2 and Appendix Table A1. The estimated HRs suggested there was elevated risk for both current and past HC use relative to never-use by *BRCA1* mutation carriers, but none were individually statistically significant: HR, 1.40 [95% CI, 0.94 to 2.08], P = .10 for current use within 1 year; HR, 1.16 [95% CI, 0.80 to 1.69], P = .4 for use 1-5 years before; HR, 1.40 [95% CI, 0.99 to 1.97], P = .05 for use 6-10 years before; and HR, 1.27 [95% CI, 0.98 to 1.63], P = .07 for use >10 years before. When assessed as a binary variable, ever use was associated with increased risk of BC (HR, 1.29 [95% CI, 1.04 to 1.60], P = .02). This

TABLE 1. Participant Characteristics

Characteristic	*BRCA1* n = 3,882 (488 cases[a])		*BRCA2* n = 1,509 (191 cases[b])	
	Total, No. (%)	Cases, No. (%)	Total, No. (%)	Cases, No. (%)
Stratification (study/country)				
kConFab	266 (6.9)	59 (12)	240 (16)	49 (26)
BCFR	288 (7.4)	32 (6.6)	222 (15)	28 (15)
RFS Canada	524 (13)	60 (12)	408 (27)	57 (30)
RFS Poland[c]	1,731 (45)	190 (39)	23 (1.5)	1 (0.5)
RFS Norway[c]	231 (6.0)	44 (9.0)	8 (0.5)	5 (2.6)
RFS other[c]	504 (13)	64 (13)	283 (19)	27 (14)
UPenn Registry	338 (8.7)	39 (8.0)	325 (22)	24 (13)
Year of cohort entry				
1991-1999	463 (12)	98 (20)	235 (16)	60 (31)
2000-2009	2,585 (67)	342 (70)	806 (53)	105 (55)
2010-2019	834 (21)	48 (9.8)	468 (31)	26 (14)
Age at cohort entry, years[d]				
<30	1,174 (30)	78 (16)	307 (20)	16 (8.4)
30-39	1,165 (30)	162 (33)	429 (28)	52 (27)
40-49	898 (23)	156 (32)	368 (24)	53 (28)
50+	645 (17)	92 (19)	405 (27)	70 (37)
Year of birth				
1920-1939	108 (2.8)	17 (3.5)	66 (4.4)	11 (5.8)
1940-1959	969 (25)	177 (36)	488 (32)	96 (50)
1960-1979	1,972 (51)	264 (54)	709 (47)	78 (41)
1980-1999	833 (21)	30 (6.1)	246 (16)	6 (3.1)
No. of full-term pregnancies[e]				
0	1,386 (36)	137 (28)	487 (32)	42 (22)
1	669 (17)	94 (19)	191 (13)	27 (14)
2	1,134 (29)	153 (31)	454 (30)	67 (35)
3+	693 (18)	104 (21)	377 (25)	55 (29)
No. of first-degree relatives with breast cancer[e]				
0	1,532 (39)	150 (31)	578 (38)	49 (26)
1	1,469 (38)	219 (45)	595 (39)	85 (45)
2	260 (6.7)	47 (9.6)	147 (9.7)	30 (16)
3+	49 (1.3)	17 (3.5)	36 (2.4)	15 (7.9)
Unknown	572 (15)	55 (11)	153 (10)	12 (6.3)
Menopausal status[e]				
Premenopausal/perimenopausal	2,886 (74)	347 (71)	993 (66)	122 (64)
Postmenopausal	996 (26)	141 (29)	516 (34)	69 (36)
Premenopausal bilateral oophorectomy[e]				
No	3,466 (89)	422 (86)	1,352 (90)	173 (91)
Yes	416 (11)	66 (14)	157 (10)	18 (9.4)

NOTE. kConFab cases were from Australia and New Zealand; BCFR cases were from the United States, Canada, and Australia; RFS other cases were from Austria, Italy, and the United States; UPenn cases were from the United States.

Abbreviations: BCFR, Breast Cancer Family Registry; RFS, Risk Factor Analysis of Hereditary Breast and Ovarian Cancer Study.

[a]Includes 440 invasive and 48 in situ cases.

[b]Includes 151 invasive and 40 in situ cases.

[c]For *BRCA2*, these three categories were collapsed to a single stratum because of lower case numbers.

[d]Age range 18-87 years at cohort entry.

[e]At cohort entry (baseline).

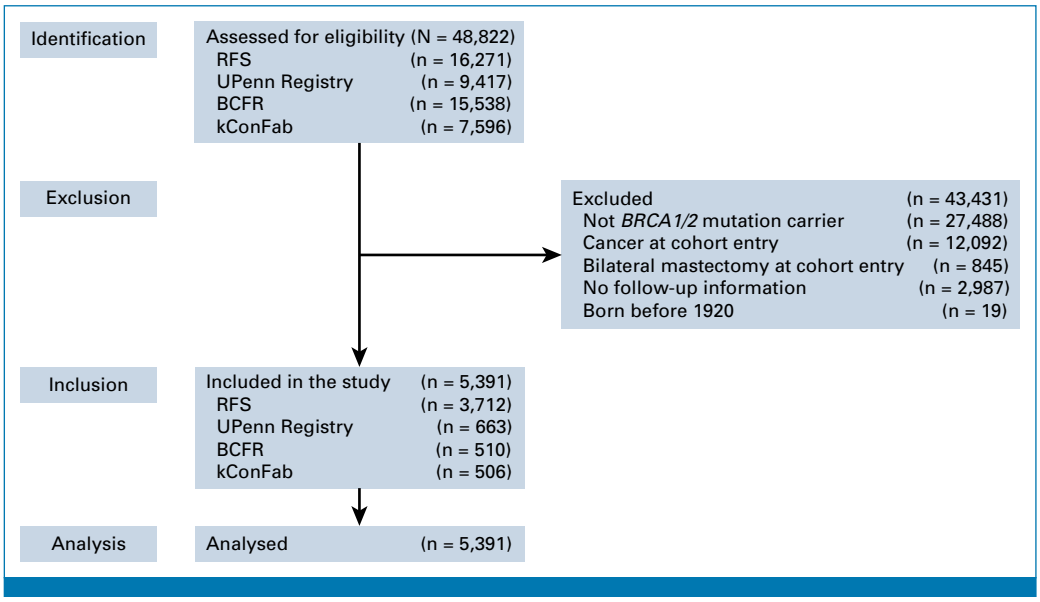

FIG 1. STROBE diagram of participant inclusion. BCFR, Breast Cancer Family Registry; RFS, Risk Factor Analysis of Hereditary Breast and Ovarian Cancer Study.

model was consistently a better fit (mean AIC across imputations 4,422.5) than that assuming any excess risk because of current use (HR, 1.20 [95% CI, 0.88 to 1.65], $P = .3$) declined to zero over 10 years since ceasing use (mean AIC 4,427.1). After adjusting for current and past use, neither younger age at first use of HC (HR, 1.01 per year [95% CI, 0.99 to 1.04], $P = .4$) nor use before first birth (HR, 1.23 [95% CI, 0.89 to 1.70], $P = .2$) was associated with BC risk, but cumulative duration of use was (HR per year of use, 1.03 [95% CI, 1.00 to 1.06], $P = .03$). Furthermore, when cumulative years of use was included in the model (mean AIC = 4,424.2), there was no evidence that risk varied with recency of use (HR, 1.08 [95% CI, 0.67 to 1.72], $P = .8$ for current use; HR, 0.92 [95% CI, 0.60 to 1.41], $P = .7$ for use 1-5 years before; HR, 1.16 [95% CI, 0.78 to 1.71], $P = .5$ for use 6-10 years before; and HR, 1.14 [95% CI, 0.87 to 1.50], $P = .3$ for use >10 years before). The model for cumulative duration of use without previous and past use was a better fit (mean AIC = 4,419.2) and gave the same HR estimate with greater precision (HR per year of use = 1.03 [95% CI, 1.01 to 1.05], $P = .002$); it was consistently the best fitting model across all imputations. Estimated HRs for categories of cumulative duration of use were consistent with a linear dose response (HR, 1.13 [95% CI, 0.88 to 1.45], $P = .3$, 1.47 [1.11 to 1.96],

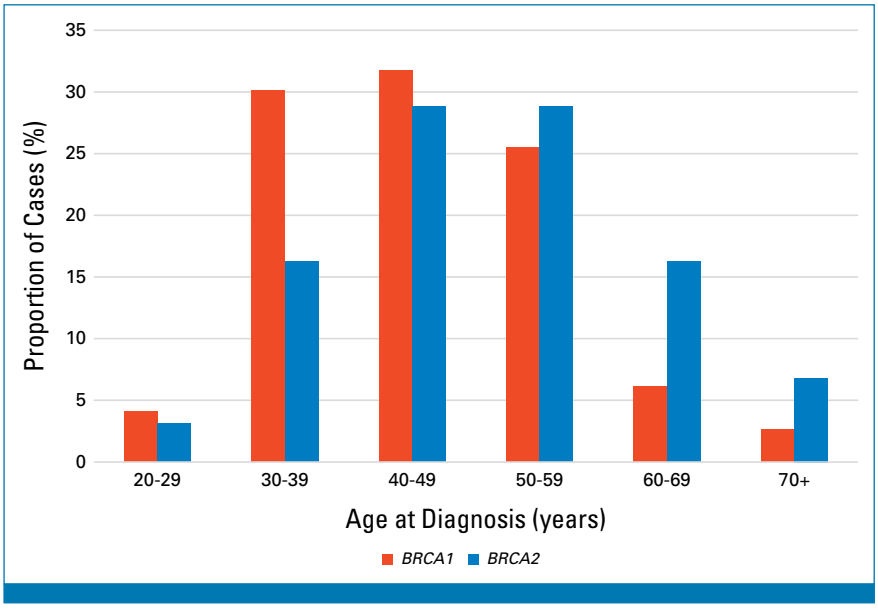

FIG 2. Age at breast cancer diagnosis of 488 *BRCA1* and 191 *BRCA2* mutation carriers.

TABLE 2. Associations Between Hormonal Contraception Use and Breast Cancer Risk for Carriers of a *BRCA1* Mutation

Hormonal Contraceptive Use	Person-Years	Cases, No.	Cases per 1,000 Person-Years	HR[a]	95% CI	*P*
Ever use						
Never used	12,365	201	16.3	1 (ref)		
Ever used	13,409	287	21.4	1.29	1.04 to 1.60	.02
Current or past use						
Never used	12,365	201	16.3	1 (ref)		
Current use[b]	2,629	43	16.4	1.40	0.94 to 2.08	.10
Past use: 1-5 years before	2,747	45	16.4	1.16	0.80 to 1.69	.4
Past use: 6-10 years before	2,412	59	24.5	1.40	0.99 to 1.97	.05
Past use >10 years before	5,621	140	24.9	1.27	0.98 to 1.63	.07
Cumulative duration of use[c]						
Cumulative duration, per year	25,774	488	18.9	1.03	1.00 to 1.06	.03
Age at first use[c]						
Younger age, per year	25,774	488	18.9	1.01	0.99 to 1.04	.4
Use before first birth[c]						
No use before first birth	15,927	278	17.5	1 (ref)		
Used before first birth	9,847	210	21.3	1.23	0.89 to 1.70	.2

Abbreviations: HR, hazard ratio; ref, reference.
[a]Estimated using Cox regression, including year of birth, parity, number of first-degree relatives with breast cancer, menopausal status, and premenopausal bilateral oophorectomy as covariates, stratified by study.
[b]Includes use in the past year.
[c]Additionally adjusted for current or past use.

P = .007, and 1.56 [1.13 to 2.17], *P* = .007 for 1-5, 6-10, and >10 years of use, respectively).

These results were largely consistent in sensitivity analyses and in stratified analyses by cohort and by country (Appendix Table A2), particularly those for cumulative duration of use. The HR estimate per additional year of use was between 1.03 and 1.05 for each cohort and country. It was 1.04 (95% CI, 1.01 to 1.07, *P* = .02) when censoring at menopause (thus excluding any potential influence of hormone therapy use).

BRCA2

Results are summarized in Table 3 and Appendix Table A3. Current HC use was not associated with increased BC risk (HR, 0.70 [95% CI, 0.33 to 1.47], *P* = .3) nor was past use (HR, 0.80 [95% CI, 0.40 to 1.61], *P* = .5 for use 1-5 years before; HR, 1.08 [95% CI, 0.57 to 2.05], *P* = .8 for use 6-10 years before; and HR, 1.15 [95% CI, 0.77 to 1.70], *P* = .5 for use >10 years before). There was no evidence of association with BC risk for ever use (HR, 1.07 [95% CI, 0.73 to 1.57], *P* = .7), cumulative duration of use (HR per year of use, 0.99 [95% CI, 0.96 to 1.03], *P* = .6), age at first use of HC (HR, 0.99 per year [95% CI, 0.95 to 1.03], *P* = .5), or use before first birth (HR, 1.16 [95% CI, 0.64 to 2.12], *P* = .6). Assuming any excess risk because of current use declined to zero over 10 years since ceasing use, the estimated HR for current use of 0.66 (95% CI, 0.38 to 1.14) was statistically significantly lower than 1.24, as estimated by the Oxford group for the general population (*P* = .02).[3] These results were broadly consistent in sensitivity and stratified analyses (data not shown).

DISCUSSION

The results of this study suggest that HC increases risk of BC for *BRCA1* mutation carriers. Use of HC for at least one continuous episode of 12 months was associated with an average 29% increased relative risk of BC compared with never use, but this varied with cumulative duration of use, with a proportional increase of 3% per year for each year of use. Risk was not associated with earlier age at first use or use before first birth. By contrast, we found no evidence of an increased risk for BC associated with use of HC by *BRCA2* mutation carriers. However, the analysis for *BRCA2* was based on only 191 BC cases and the confidence intervals were wide.

When counseling women, absolute risks are more useful than relative risks. Table 4 shows the risk estimates for a hypothetical *BRCA1* mutation carrier if she started to use HCs at age 18 years and continued them for 5, 10, and 15 years. These absolute risks will be different for different women, so incorporating our findings into risk prediction models such as CanRisk[29-32] would assist in providing personalized estimates.

BRCA1 and *BRCA2* mutation carriers also have very high lifetime risks of tubo-ovarian cancer, with their risk rising over that of the general population from about the late 30s

TABLE 3. Associations Between Hormonal Contraception Use and Breast Cancer (BC) Risk for Carriers of a *BRCA2* Mutation

Hormonal Contraceptive Use	Person-Years	Cases, No.	Cases per 1,000 Person-Years	HR[a]	95% CI	*P*
Ever use						
Never used	2,872	51	17.8	1 (ref)		
Ever used	7,057	140	19.8	1.07	0.73 to 1.57	.7
Current or past use						
Never used	2,873	51	17.8	1 (ref)		
Current use[b]	1,165	11	9.4	0.70	0.33 to 1.47	.3
Past use: 1-5 years before	1,168	14	12.0	0.80	0.40 to 1.61	.5
Past use: 6-10 years before	1,041	20	19.2	1.08	0.57 to 2.05	.8
Past use >10 years before	3,682	95	25.8	1.15	0.77 to 1.70	.5
Cumulative duration of use[c]						
Cumulative duration, per year	9,929	191	19.2	0.99	0.96 to 1.03	.6
Age at first use[c]						
Younger age, per year	9,929	191	19.2	0.99	0.95 to 1.03	.5
Use before first birth[c]						
No use before first birth	4,096	80	19.5	1 (ref)		
Used before first birth	5,833	111	19.0	1.16	0.64 to 2.12	.6

Abbreviations: HR, hazard ratio; ref, reference.

[a]Estimated using Cox regression, including year of birth, parity, number of first-degree relatives with BC, menopausal status, and premenopausal bilateral oophorectomy as covariates, and stratified by study/country (see Table 1).

[b]Includes use in the past year.

[c]Additionally adjusted for current or past use.

and the mid 40s, respectively.[1] Guidelines recommend bilateral salpingo-oophorectomy by age 35-40 years and 40-45 years, respectively,[33] which virtually eliminates this risk. Thus, although OCPs substantially reduce tubo-ovarian cancer risk,[34] this benefit is redundant when bilateral salpingo-oophorectomy guidelines are followed.

Major strengths of this study include the large sample size of *BRCA1* mutation carriers, the prospective design (HC use reported before cancer diagnosis), systematic data collection, and use of multiple imputation to address missing data. The consistency of HR estimates for cumulative duration of HC use in *BRCA1* mutation carriers across cohorts and countries supports the generalizability of this result. The most important limitation of this study is its observational design, which may have resulted in important biases. Few women in the study had used HC for more than 15 years; thus, the results should not be extrapolated beyond 15 years. Another limitation is that the completeness of data on HC type varied between studies; thus, some participants who used HCs other than the OCP will have been either misclassified as never users or have underreported duration of use, which could have biased our study toward a null result. Use of the OCP will have driven the study results as this was the most common HC. There is emerging evidence of possible differences in BC risk associated with different formulations of the OCP, particularly regarding type of progestogen.[5,35] We did not have data on the formulation of OCP used, and also cannot account for changing formulations over time, noting that older formulations generally had higher doses of estrogen compared with newer formulations.

Our finding of increased BC risk with increasing duration of HC use for *BRCA1* mutation carriers is interesting, given that BC in *BRCA1* mutation carriers is usually of the triple-negative phenotype.[36] However, it is consistent with a recent meta-analysis of risk factors for triple-negative BC. That study found that although ever use of the OCP was not statistically significantly associated with increased risk of triple-negative BC (odds ratio [OR], 1.16 [95% CI, 0.92 to 1.46]), use for 10 years or longer was associated with about a 30% relative increase in the risk of triple-negative BC (OR, 1.29 [95% CI, 1.08 to 1.55]).[37] *BRCA1* mutation status of participants in the studies that were meta-analyzed was not known.

Two recent meta-analyses have both shown an increased risk of BC for women with *BRCA1* and *BRCA2* mutations who used the OCP.[38,39] Park et al[38] estimated a relative risk of 1.24 [95% CI, 1.08 to 1.41] and the results were similar for *BRCA1* and *BRCA2* mutation carriers when analyzed separately. Statistically significant associations were only seen for more than 5 years of use. van Bommel et al also showed an association between HC use and increased BC risk for *BRCA1* and *BRCA2* mutation carriers in cohort studies (HR, 1.55 [95% CI, 1.36 to 1.76]).[39] Past use more than 10 years before was also associated with increased risk (HR, 1.40 [95% CI, 1.13 to 1.73]).

TABLE 4. Example of Estimated Absolute Risk of BC Associated With Use of HC by Cumulative Duration of Use for a US *BRCA1* Mutation Carrier With One First-Degree Relative With BC Who Starts HC at Age 18 Years

	Estimated Absolute Risk of BC (%)						
Duration of HC Use	To Age 23 Years (5-year risk)	To Age 28 Years (10-year risk)	To Age 38 Years (20-year risk)	To Age 48 Years (30-year risk)	To Age 58 Years (40-year risk)	To Age 68 Years (50-year risk)	To Age 80 Years (lifetime risk)
Age 18 years at start of HC							
No HC use	0.2	1.6	13.1	32.5	51.3	65.6	76.5
5 years of HC use	0.2	1.9	15.1	36.7	56.6	71.1	81.4
10 years of HC use	0.2	2.0	17.1	41.1	62.0	76.3	85.8
15 years of HC use	0.2	2.0	18.9	45.5	67.3	81.1	89.6

NOTE. For this particular *BRCA1* mutation carrier, the estimated absolute 5-year, 10-year, 20-year, and lifetime (to age 80 years) risk of BC would increase by 0%, 0.3%, 2%, and 4.9%, respectively, with 5 years of HC use. With 10 years of use, the corresponding increases would be 0%, 0.4%, 4%, and 9.3%, and with 15 years of use, they would be 0%, 0.4% 5.8%, and 13.1%. Estimates are based on CanRisk[28,29,30,31] for an 18-year-old US female *BRCA1* mutation carrier with a 60-year-old mother who had BC at age 40 years, and two maternal aunts without BC. CanRisk cumulative risk estimates by age were converted to annual incidence by age, which was then used to derive annual incidence estimates for mutually exclusive categories of HC use such that (1) the estimates for never users were multiplied by a HR of 1.03 for each year of HC use and (2) the weighted average annual incidence across all categories of users and nonusers (weighted by the proportion of carriers in each category) was equal to the CanRisk annual incidence. Categories of use were never use, 5 years, 10 years, or 15 years of continuous use, with carrier population prevalence of 40%, 45%, 10%, and 5%, respectively.
Abbreviations: BC, breast cancer; HC, hormonal contraception; HR, hazard ratio.

HC use increases BC risk for the general population. The Oxford Collaborative Group pooled epidemiologic study data on 153,536 women and showed an increased risk of BC while women were taking the OCP (relative risk [RR], 1.24 [95% CI, 1.15 to 1.33]), which gradually resolved over the 10 years after stopping.[3] After recency of use was accounted for, duration of use, age at first use, and whether OCP use began before or after first childbirth made little difference to the estimates. The Nurses' Health Study of 116,429 women found that current users of the OCP had a relative risk of BC of 1.31 (95% CI, 1.09 to 1.58) compared with never users and risk decreased with time since cessation.[5] A study using Danish national registry data from 1.8 million women reported similar findings for all types of contemporary HC, including the hormonal IUD.[4] The estimated relative risk of BC was 1.20 (95% CI, 1.14 to 1.26) for current and recent users of HC relative to never users, and risk increased with duration of use (RR, 1.38 [95% CI, 1.26 to 1.51] for more than 10 years of use *v* never use) and remained elevated more than 5 years after cessation. There was some evidence that commencing HC at a younger age was associated with increased BC risk.

Our findings are consistent with HC use in *BRCA1* mutation carriers being associated with similar increases in the relative risk of BC as seen in the general population. Furthermore, we observed evidence of a dose response of increasing BC risk with increasing cumulative duration of use. However, the higher baseline BC risks for *BRCA1* mutation carriers mean that the relative risks translate into higher absolute risks for carriers than for women in the general population.

Given the relatively small number of events, and inconsistent evidence from other studies, our findings for *BRCA2* mutation carriers should be interpreted with caution and should not be used to advise women that HC use does not increase their BC risk.

Decisions about use of HC in women at increased risk for BC due to *BRCA1* mutations need to carefully weigh the absolute risks and benefits; while shorter-term use may result in only small increases, prolonged cumulative use may result in larger increases in absolute BC risk that may not be acceptable to some women.

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DATA SHARING STATEMENT

The dataset generated for the current study is not publicly available due to compliance with participant informed consent and human research ethics committee approvals, but can be requested by contacting the corresponding author.

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REFERENCES

1. Kuchenbaecker KB, Hopper JL, Barnes DR, et al: Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 317:2402-2416, 2017
2. Iversen L, Sivasubramaniam S, Lee AJ, et al: Lifetime cancer risk and combined oral contraceptives: The Royal College of General Practitioners' oral contraception study. Am J Obstet Gynecol 216: 580.e1-580.e9, 2017
3. Collaborative Group on Hormonal Factors in Breast Cancer: Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 347:1713-1727, 1996
4. Morch LS, Skovlund CW, Hannaford PC, et al: Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 377:2228-2239, 2017
5. Burchardt NA, Eliassen AH, Shafrir AL, et al: Oral contraceptive use by formulation and breast cancer risk by subtype in the Nurses' Health study II: A prospective cohort study. Am J Obstet Gynecol 226:821.e1-821.e26, 2022
6. Fitzpatrick D, Pirie K, Reeves G, et al: Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis. PLoS Med 20:e1004188, 2023
7. Heimdal K, Skovlund E, Møller P: Oral contraceptives and risk of familial breast cancer. Cancer Detect Prev 26:23-27, 2002
8. Narod SA, Dubé MP, Klijn J, et al: Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 94:1773-1779, 2002
9. Gronwald J, Byrski T, Huzarski T, et al: Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. Breast Cancer Res Treat 95:105-109, 2006
10. Haile RW, Thomas DC, McGuire V, et al: BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 15:1863-1870, 2006
11. Brohet RM, Goldgar DE, Easton DF, et al: Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: A report from EMBRACE, GENEPSO, GEOHEBON, and the IBCCS collaborating group. J Clin Oncol 25:3831-3836, 2007
12. Lee E, Ma H, McKean-Cowdin R, et al: Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: Results from a population-based study. Cancer Epidemiol Biomarkers Prev 17:3170-3178, 2008
13. Figueiredo JC, Haile RW, Bernstein L, et al: Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among BRCA1 and BRCA2 mutation carriers and noncarriers: The WECARE Study. Breast Cancer Res Treat 120:175-183, 2010
14. Bernholtz S, Laitman Y, Kaufman B, et al: Cancer risk in Jewish BRCA1 and BRCA2 mutation carriers: Effects of oral contraceptive use and parental origin of mutation. Breast Cancer Res Treat 129: 557-563, 2011
15. Kotsopoulos J, Lubinski J, Moller P, et al: Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. Breast Cancer Res Treat 143:579-586, 2014
16. Lecarpentier J, Noguès C, Mouret-Fourme E, et al: Breast cancer risk associated with estrogen exposure and truncating mutation location in BRCA1/2 carriers. Cancer Epidemiol Biomarkers Prev 24:698-707, 2015
17. Park B, Hopper JL, Win AK, et al: Reproductive factors as risk modifiers of breast cancer in BRCA mutation carriers and high-risk non-carriers. Oncotarget 8:102110-102118, 2017
18. Schrijver LH, Olsson H, Phillips KA, et al: Oral contraceptive use and breast cancer risk: Retrospective and prospective analyses from a BRCA1 and BRCA2 mutation carrier cohort study. JNCI Cancer Spectr 2:pky023, 2018
19. Australian New Zealand Clinical Trials Registry: Assessing the Association between Hormonal Contraception and Breast Cancer Risk for BRCA1 and BRCA2 Mutation Carriers Using Prospective Data. Sydney, NSW, NHMRC Clinical Trials Centre, University of Sydney (Australia), 2022. 2022 – Identifier ACTRN 12622000991718; [1 page] www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=383041&isReview=true
20. Phillips KA, Butow P, Stewart A, et al: Predictors of participation in clinical and psychosocial follow-up of the kConFab breast cancer family cohort. Fam Cancer 4:105-113, 2005
21. kConFab: kConFab clinical follow-up project. https://www.kconfab.org/FollowUp
22. Terry MB, Phillips KA, Daly MB, et al: Cohort profile: The breast cancer prospective family study cohort (ProF-SC). Int J Epidemiol 45:683-692, 2016
23. John EM, Hopper JL, Beck JC, et al: The Breast Cancer Family Registry: An infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast Cancer Res 6:R375-R389, 2004
24. Kotsopoulos J, Huzarski T, Gronwald J, et al: Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 109:20, 2017
25. Domchek SM, Jhaveri K, Patil S, et al: Risk of metachronous breast cancer after BRCA mutation–associated ovarian cancer. Cancer 119:1344-1348, 2013
26. Kotsopoulos J, Huzarski T, Gronwald J, et al; Hereditary Breast Cancer Clinical Study Group: Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 109:djw177, 2017
27. Milne RL, Antoniou AC: Modifiers of breast and ovarian cancer risks for BRCA1 and BRCA2 mutation carriers. Endocr Relat Cancer 23:T69-T84, 2016
28. Rubin DB: Multiple Imputation for Nonresponse in Surveys. Hoboken, NJ, Wiley, 1987. pp 91-93
29. Lee A, Mavaddat N, Wilcox AN, et al: BOADICEA: A comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med 21:1708-1718, 2019
30. Carver T, Hartley S, Lee A, et al: CanRisk tool-A web interface for the prediction of breast and ovarian cancer risk and the likelihood of carrying genetic pathogenic variants. Cancer Epidemiol Biomarkers Prev 30:469-473, 2021
31. University of Cambridge: CanRisk. https://www.canrisk.org/
32. Archer S, Babb de Villiers C, Scheibl F, et al: Evaluating clinician acceptability of the prototype CanRisk tool for predicting risk of breast and ovarian cancer: A multi-methods study. PLoS ONE 15: e0229999, 2020
33. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 2.2024. 2023
34. Schrijver LH, Antoniou AC, Olsson H, et al: Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers: An International Cohort Study. Am J Obstet Gynecol 225:51.e1-51.e17, 2021
35. Shamseddin M, De Martino F, Constantin C, et al: Contraceptive progestins with androgenic properties stimulate breast epithelial cell proliferation. EMBO Mol Med 13:e14314, 2021
36. Sokolova A, Johnstone KJ, McCart Reed AE, et al: Hereditary breast cancer: Syndromes, tumour pathology and molecular testing. Histopathology 82:70-82, 2023
37. Kumar N, Ehsan S, Banerjee S, et al: The unique risk factor profile of triple negative breast cancer: A comprehensive meta-analysis. J Natl Cancer Inst 116:1210-1219, 2024
38. Park J, Huang D, Chang YJ, et al: Oral contraceptives and risk of breast cancer and ovarian cancer in women with a BRCA1 or BRCA2 mutation: A meta-analysis of observational studies. Carcinogenesis 43:231-242, 2022
39. van Bommel MHD, IntHout J, Veldmate G, et al: Contraceptives and cancer risk in BRCA1/2 pathogenic variant carriers: A systematic review and meta-analysis. Hum Reprod Update 29:197-217, 2022

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Hormonal Contraception and Breast Cancer Risk for Carriers of Germline Mutations in *BRCA1* and *BRCA2*

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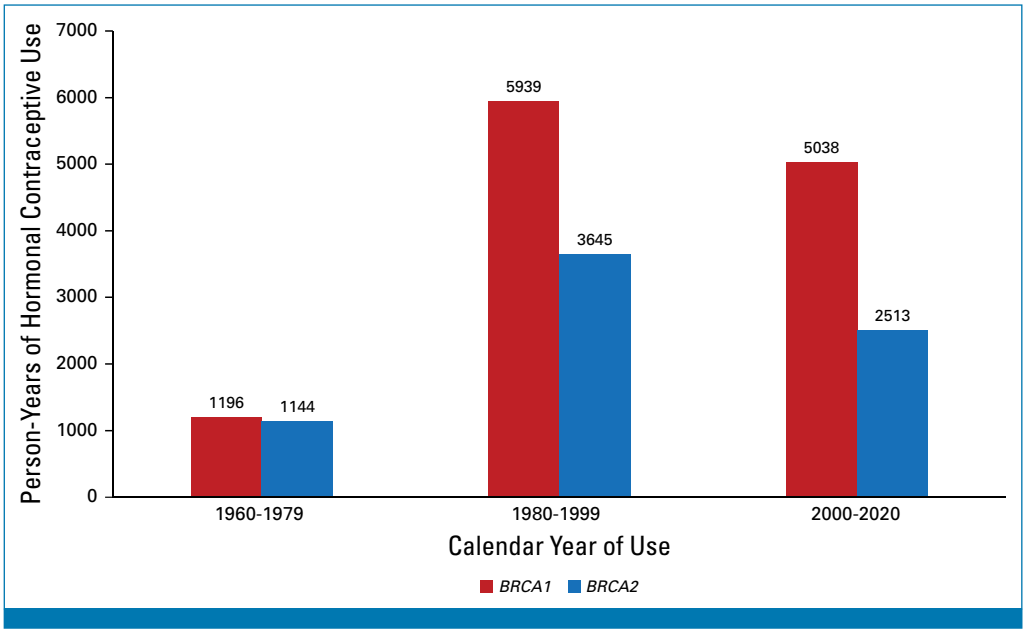

FIG A1. Person-years of hormonal contraception by calendar year for 3882 *BRCA1* and 1509 *BRCA2* mutation carriers.

TABLE A1. Unadjusted Associations Between Hormonal Contraception Use and Breast Cancer Risk for Carriers of a *BRCA1* Mutation

Hormonal Contraceptive Use	Person-Years	Cases, No.	Cases Per 1,000 Person-Years	HR[a]	95% CI	*P*
Ever use						
Never used	12,365	201	16.3	1 (ref)		
Ever used	13,409	287	21.4	1.26	1.05 to 1.52	.01
Current or past use						
Never used	12,365	201	16.3	1 (ref)		
Current use[b]	2,629	43	16.4	1.37	0.93 to 2.00	.11
Past use: 1-5 years before	2,747	45	16.4	1.20	0.84 to 1.71	.3
Past use: 6-10 years before	2,412	59	24.5	1.44	1.05 to 1.96	.02
Past use >10 years before	5,621	140	24.9	1.20	0.96 to 1.51	.11
Cumulative duration of use[c]						
Cumulative duration, per year	25,774	488	18.9	1.03	1.00 to 1.05	.02
Age at first use[c]						
Younger age, per year	25,774	488	18.9	1.01	0.99 to 1.03	.3
Use before first birth[c]						
No use before first birth	15,927	278	17.5	1 (ref)		
Used before first birth	9,847	210	21.3	1.20	0.91 to 1.58	.2

Abbreviations: HR, hazard ratio; ref, reference.
[a]Estimated using Cox regression, unadjusted (unless otherwise indicated).
[b]Includes use in the past year.
[c]Adjusted for current or past use.

TABLE A2. Associations Between Hormonal Contraception Use and Breast Cancer Risk for Carriers of a *BRCA1* Mutation, by Cohort and by Country

Stratification Factor	Hormonal Contraceptive Use	Person-Years	Cases, No.	Case Per 1,000 Person-Years	HR[a]	95% CI	*P*
Cohort	Ever use						
BCFR and kConFab	Never used	1,286	15	11.7	1 (ref)		
	Ever used	3,488	76	21.8	1.75	0.94 to 3.26	.08
RFS	Never used	10,403	168	16.1	1 (ref)		
	Ever used	8,945	190	21.2	1.23	0.99 to 1.53	.06
UPenn Registry	Never used	675	18	26.7	1 (ref)		
	Ever used	977	21	21.5	0.88	0.42 to 1.87	.7
Cohort	Cumulative duration of use						
BCFR and kConFab	Cumulative duration, per year	4,774	91	19.1	1.05	1.01 to 1.08	.009
RFS	Cumulative duration, per year	19,348	358	18.5	1.03	1.00 to 1.05	.02
UPenn Registry	Cumulative duration, per year	1,652	39	23.6	1.03	0.96 to 1.10	.4
Country	Ever use						
Australia/New Zealand	Never used	391	7	17.9	1 (ref)		
	Ever used	2,056	59	28.7	1.03	0.47 to 2.25	.9
United States	Never used	2,352	41	17.4	1 (ref)		
	Ever used	4,185	78	18.6	1.19	0.75 to 1.88	.5
Canada	Never used	972	11	11.3	1 (ref)		
	Ever used	2,327	52	22.3	1.94	0.93 to 4.04	.08
Poland	Never used	7,862	121	15.4	1 (ref)		
	Ever used	3,427	69	20.1	1.33	0.97 to 1.82	.08
Other	Never used	787	21	26.7	1 (ref)		
	Ever used	1,415	29	20.5	1.01	0.55 to 1.88	.97
Country	Cumulative duration of use						
Australia/New Zealand	Cumulative duration, per year	2,447	66	27.0	1.03	0.99 to 1.07	.18
United States	Cumulative duration, per year	6,537	119	18.2	1.03	1.00 to 1.07	.09
Canada	Cumulative duration, per year	3,299	63	19.1	1.05	0.99 to 1.11	.09
Poland	Cumulative duration, per year	11,289	190	16.8	1.03	0.99 to 1.08	.12
Other	Cumulative duration, per year	2,202	50	22.7	1.04	0.98 to 1.11	.18

Abbreviations: BCFR, Breast Cancer Family Registry; HR, hazard ratio; RFS, Risk Factor Analysis of Hereditary Breast and Ovarian Cancer Study.
[a]Estimated using Cox regression, including as covariates year of birth, parity, number of first-degree relatives with breast cancer, menopausal status, and premenopausal bilateral oophorectomy.

TABLE A3. Unadjusted Associations Between Hormonal Contraception Use and Breast Cancer Risk for Carriers of a *BRCA2* Mutation

Hormonal Contraceptive Use	Person-Years	Cases, No.	Cases per 1,000 Person-Years	HR[a]	95% CI	*P*
Ever use						
Never used	2,873	51	17.8	1 (ref)		
Ever used	7,057	140	19.8	1.15	0.80 to 1.64	.4
Current or past use						
Never used	2,873	51	17.8	1 (ref)		
Current use[b]	1,165	11	9.4	0.75	0.37 to 1.55	.4
Past use: 1-5 years before	1,168	14	12.0	0.87	0.44 to 1.69	.7
Past use: 6-10 years before	1,041	20	19.2	1.14	0.61 to 2.13	.7
Past use >10 years before	3,682	95	25.8	1.24	0.86 to 1.80	.3
Cumulative duration of use[c]						
Cumulative duration, per year	9,929	191	19.2	1.00	0.96 to 1.03	.8
Age at first use[c]						
Younger age, per year	9,929	191	19.2	0.99	0.96 to 1.03	.7
Use before first birth[c]						
No use before first birth	4,096	80	19.5	1 (ref)		
Used before first birth	5,833	111	19.0	1.05	0.64 to 1.73	.8

Abbreviations: HR, hazard ratio; ref, reference.

[a]Estimated using Cox regression, unadjusted (unless otherwise indicated).

[b]Includes use in the past year.

[c]Adjusted for current or past use.