Reproductive and Hormonal Factors, and Ovarian Cancer Risk for *BRCA1* and *BRCA2* Mutation Carriers: Results from the International *BRCA1/2* Carrier Cohort Study

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Abstract

Background: **Several reproductive and hormonal factors are known to be associated with ovarian cancer risk in the general population, including parity and oral contraceptive (OC) use. However, their effect on ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers has only been investigated in a small number of studies.**

Methods: **We used data on 2,281 *BRCA1* carriers and 1,038 *BRCA2* carriers from the International *BRCA1/2* Carrier Cohort Study to evaluate the effect of reproductive and hormonal factors on ovarian cancer risk for mutation carriers. Data were analyzed within a weighted Cox proportional hazards framework.**

Results: **There were no significant differences in the risk of ovarian cancer between parous and nulliparous carriers. For parous *BRCA1* mutation carriers, the risk of ovarian cancer was reduced with each additional full-term pregnancy (P trend = 0.002). *BRCA1* carriers who had ever used OC were at a significantly reduced risk of developing ovarian cancer (hazard ratio, 0.52; 95% confidence intervals, 0.37-0.73; P = 0.0002) and increasing duration of OC use was associated with a reduced ovarian cancer risk (P trend = 0.0004). The protective effect of OC use for *BRCA1* mutation carriers seemed to be greater among more recent users. Tubal ligation was associated with a reduced risk of ovarian cancer for *BRCA1* carriers (hazard ratio, 0.42; 95% confidence intervals, 0.22-0.80; P = 0.008). The number of ovarian cancer cases in *BRCA2* mutation carriers was too small to draw definitive conclusions.**

Conclusions: **The results provide further confirmation that OC use, number of full-term pregnancies, and tubal ligation are associated with ovarian cancer risk in *BRCA1* carriers to a similar relative extent as in the general population.**
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Introduction

Pathogenic mutations in *BRCA1* and *BRCA2* confer high risks of breast and ovarian cancer. The estimated ovarian cancer risk by age 70 years has been reported to be 16% to 66% in *BRCA1* mutation carriers and 11% to 27% in *BRCA2* mutation carriers (1-8). Other than age and family history, the strongest known risk factors for ovarian cancer are parity, in which risk decreases with increasing number of pregnancies, and oral contraceptive

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(OC) use, in which risk decreases with increasing duration of use (9-11). Breast-feeding and tubal ligation have also been reported to be associated with a risk of reduced ovarian cancer (10-13). However, the effect of these and other risk factors on ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers has only been investigated in a few studies (14-20), most of which have included relatively few carriers. As a result, the relative risk estimates are imprecise. Most studies have concentrated on the effect of OC use because of its potential to be used as chemoprevention for ovarian cancer risk in mutation carriers. The majority of the studies have found that OC use is associated with a reduced risk of ovarian cancer in mutation carriers (14-16, 18), although Modan et al. (17) reported no association. Parity has also been examined in several studies, and has been found to decrease the risk of ovarian cancer in *BRCA1* mutation carriers alone, or in *BRCA1* and *BRCA2* carriers combined (14, 15, 17). In the largest study to date, parous *BRCA1* mutation carriers were found be at a reduced risk of ovarian cancer (16). Surprisingly, however, parity was associated with an increased risk of ovarian cancer in *BRCA2* mutation carriers (16). The associations with other factors are yet to be established in mutation carriers.

In the general population, several of the risk factors for ovarian cancer are also risk factors for breast cancer, but the magnitude and direction of the effect may differ. In particular, OC use is protective for ovarian cancer but confers an increased risk of breast cancer (9, 21). There is some evidence that these associations may also be present in *BRCA1* and *BRCA2* carriers (16, 22). As the lifetime risks of both breast and ovarian cancer are high in *BRCA1* and, to a lesser extent, *BRCA2* carriers, it is important to establish whether OC use increases or decreases the overall risk of cancer in carriers. To answer such questions, it is important to obtain precise estimates of the effects of these risk factors using large, well-designed studies.

We have previously used data from the International *BRCA1* and *BRCA2* Carrier Cohort Study (IBCCS) to investigate the effect of reproductive and hormonal factors as well as the effect of radiation exposure on breast cancer risk in mutation carriers (22-25). The IBCCS cohort is a large series of *BRCA1* and *BRCA2* mutation carriers that is mostly independent of those used in previously published studies which investigated the ovarian cancer risk factors described above. In this report, the IBCCS data set was used to evaluate the effect of reproductive and hormonal factors on ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers.

Materials and Methods

Study Group. IBCCS was initiated in 1997 at the IARC to prospectively estimate risks of breast, ovarian, and other cancers in *BRCA1* and *BRCA2* carriers and to assess lifestyle and genetic factors that may modify the cancer risks in such individuals. One of the aims of this project is to evaluate the role of reproductive and hormonal factors as well as intervention therapies as potential modifiers of cancer risks in *BRCA1* and *BRCA2* mutation carriers. Details of the design and rationale of the study have been described elsewhere (26). Subjects are eligible to participate in IBCCS if they are carriers of pathogenic mutations in either *BRCA1* or *BRCA2*, >18 years old, capable of giving informed consent, and have been counseled as to their mutation status.

The present study is a retrospective analysis of 3,319 female mutation carriers (2,281 *BRCA1* and 1,038 *BRCA2*) recruited during the period 1997 to 2005. All mutation carriers were European with the exception of 139 subjects from Quebec. Out of the 3,319 participants, 2,410 were from large ongoing national studies of *BRCA1/2* mutation carriers in the United Kingdom and Eire (EMBRACE), the Netherlands (GEO-HEBON), and France (GENEPSO). A standardized questionnaire was administered either by mail, in-person interview at the time of genetic counseling, or through telephone interview, depending on study center. The questionnaire requested detailed information on known or suspected risk factors for ovarian and breast cancer, including the timing of menarche and menopause, a detailed pregnancy history, OC and hormone replacement therapy (HRT) use, and surgical interventions (oophorectomy, hysterectomy, tubal ligation, and mastectomy). The research protocol was approved by the relevant ethics committees and all participants provided written informed consent.

Statistical Methods. The aim of the present study was to evaluate the effect of various factors on the risk of developing ovarian cancer for *BRCA1* and *BRCA2* mutation carriers. The data were analyzed within a Cox proportional hazards framework. The majority of the mutation carriers in IBCCS come from families with multiple cases of breast and ovarian cancer seen in clinical genetic centers. Thus, the selection of mutation carriers in our study is nonrandom with respect to disease status. In addition, affected and unaffected carriers are likely to be sampled with different probabilities at different ages because genetic testing is primarily targeted at affected individuals diagnosed at an early age. Therefore, the carriers in our study do not represent a true cohort. We have previously shown that under these conditions, standard Cox regression analysis leads to biased estimates of the rate ratios. To correct for this bias, we developed a weighted cohort approach (27). Briefly, this method involves assigning different weights to cancer cases and unaffected individuals such that the observed incidence rates are consistent with established incidence rates in mutation carriers. For the current analyses, we have extended this approach to take into account the potential oversampling with respect to both breast and ovarian cancer cases simultaneously (Appendix 1). The *BRCA1* and *BRCA2* weights were derived assuming the age-specific incidence rate estimates reported in Antoniou et al. (1).

In our main analyses, individuals were censored at the first of the following events: ovarian cancer diagnosis (253), breast cancer diagnosis (1,641), other cancer diagnosis (51), bilateral prophylactic oophorectomy (186), or at interview (1,188). Subjects censored at ovarian cancer diagnosis were considered affected (cases). Weights for the weighted Cox regression analysis were derived assuming this censoring process. To increase the number of ovarian cancer cases used in the analysis, additional analyses were done in which we did not censor at a breast cancer diagnosis but instead having had a breast cancer was included as a time-dependent

Table 1. IBCCS cohort characteristics

Characteristic	Total	*BRCA1* mutation carriers*			*BRCA2* mutation carriers*		
		Unaffected	Breast cancer	Ovarian cancer	Unaffected	Breast cancer	Ovarian cancer
Number of carriers (*n*)	3,319	970	1,110	201	455	531	52
Mean age at interview (SD)	46.5 (12.1)	40.2 (11.5)	48.9 (10.6)	54.7 (9.6)	42.9 (11.3)	51.4 (10.8)	62.4 (10.0)
Mean age at censoring (SD)	41.2 (10.0)	39.0 (10.5)	40.0 (8.7)	48.4 (8.4)	41.8 (10.6)	43.1 (8.8)	54.4 (9.9)
Person-years of follow-up	137,632	37,806	44,984	9,833	19,028	23,128	2,853
Cohort (%)							
<1940	381 (11.5)	43 (4.4)	140 (12.6)	50 (24.9)	31 (6.8)	90 (17.0)	27 (51.9)
≥1940-1949	669 (20.2)	117 (12.1)	274 (24.7)	63 (31.3)	55 (12.1)	144 (27.1)	16 (30.8)
≥1950-1959	985 (29.7)	214 (22.1)	397 (35.8)	70 (34.8)	123 (27.0)	174 (32.8)	7 (13.5)
≥1960	1,284 (38.7)	596 (61.4)	299 (26.9)	18 (9.0)	246 (54.1)	123 (23.2)	2 (3.9)
Country group † (%)							
Group 1	913 (27.5)	366 (37.7)	356 (32.1)	51 (25.4)	72 (15.8)	60 (11.3)	8 (15.4)
Group 2	234 (7.1)	87 (9.0)	69 (6.2)	24 (11.9)	28 (6.2)	24 (4.5)	2 (3.9)
Group 3	1,130 (34.0)	259 (26.7)	375 (33.8)	78 (38.8)	159 (34.9)	235 (44.3)	24 (46.2)
Group 4	1,042 (31.4)	258 (26.6)	310 (27.9)	48 (23.9)	196 (43.1)	212 (39.9)	18 (34.6)
Number of full-term pregnancies ‡ (%)							
0	693 (20.9)	275 (28.4)	211 (19.0)	15 (7.5)	107 (23.5)	82 (15.4)	3 (5.8)
1	542 (16.3)	132 (13.6)	222 (20.0)	31 (15.4)	70 (15.4)	78 (14.7)	9 (17.3)
2	1,211 (36.5)	337 (34.7)	412 (37.1)	82 (40.8)	156 (34.3)	207 (39.0)	17 (32.7)
3	593 (17.9)	152 (15.7)	181 (16.3)	51 (25.4)	90 (19.8)	108 (20.3)	11 (21.2)
≥4	259 (7.8)	67 (6.9)	80 (7.2)	21 (10.5)	27 (5.9)	52 (9.8)	12 (23.1)
Missing	21 (0.6)	7 (0.7)	4 (0.4)	1 (0.5)	5 (1.1)	4 (0.8)	0 (0)
Age at first full-term pregnancy (%)							
<20	299 (11.5)	74 (10.8)	113 (12.6)	21 (11.4)	37 (10.8)	45 (10.1)	9 (18.4)
20-24	1,050 (40.3)	260 (37.8)	393 (43.9)	82 (44.3)	118 (34.4)	175 (39.3)	22 (44.9)
25-29	886 (34.0)	256 (37.2)	287 (32.1)	53 (28.7)	119 (34.7)	160 (36.0)	11 (22.5)
≥30	370 (14.2)	98 (14.2)	102 (11.4)	29 (15.7)	69 (20.1)	65 (14.6)	7 (14.3)
Breast-feeding among parous (%)							
Never	815 (31.3)	185 (26.9)	283 (31.6)	58 (31.4)	121 (35.3)	152 (34.2)	16 (32.7)
Ever	1,790 (68.7)	503 (73.1)	612 (68.4)	127 (68.7)	222 (64.7)	293 (65.8)	33 (67.4)
Breast-feeding duration among parous, months (%)							
0	815 (31.3)	185 (26.9)	283 (31.6)	58 (31.4)	121 (35.3)	152 (34.2)	16 (32.7)
1-5	774 (29.7)	201 (29.2)	280 (31.3)	47 (25.4)	100 (29.2)	131 (29.4)	15 (30.6)
6-12	589 (22.6)	176 (25.6)	198 (22.1)	44 (23.8)	63 (18.4)	97 (21.8)	11 (22.5)
13-24	283 (10.9)	87 (12.7)	94 (10.5)	16 (8.7)	41 (12.0)	40 (9.0)	5 (10.2)
>24	106 (4.1)	32 (4.7)	28 (3.1)	11 (6.0)	14 (4.1)	20 (4.5)	1 (2.0)
Unknown	38 (1.5)	7 (1.0)	12 (1.3)	9 (4.9)	4 (1.2)	5 (1.1)	1 (2.0)
Age at menarche (%)							
<12	561 (16.9)	156 (16.1)	203 (18.3)	24 (11.9)	78 (17.1)	90 (16.9)	10 (19.2)
12-14	2,187 (65.9)	648 (66.8)	719 (64.8)	146 (72.6)	305 (67.0)	337 (63.5)	32 (61.5)
≥15	531 (16.0)	153 (15.8)	175 (15.8)	26 (12.9)	68 (15.0)	99 (18.6)	10 (19.2)
Missing	40 (1.2)	13 (1.3)	13 (1.2)	5 (2.5)	4 (0.9)	5 (0.9)	0
OC use							
Never	766 (23.1)	160 (16.5)	269 (24.2)	92 (45.8)	72 (15.8)	144 (27.1)	28 (53.9)
Ever	2,415 (72.8)	767 (79.1)	790 (71.2)	98 (48.8)	363 (79.8)	375 (70.6)	22 (42.3)
Missing	138 (4.2)	43 (4.4)	51 (4.6)	11 (5.5)	19 (4.2)	12 (2.3)	2 (3.9)
OC use duration, years (%)							
Never	766 (23.1)	160 (16.5)	269 (24.0)	92 (45.8)	73 (15.8)	144 (27.1)	28 (53.9)
>0-1	339 (10.2)	75 (7.7)	108 (9.7)	36 (17.9)	48 (10.6)	68 (12.8)	4 (7.7)
>1-3	338 (10.2)	97 (10.0)	109 (9.8)	18 (9.0)	52 (11.4)	55 (10.4)	7 (13.5)
>3-5	289 (8.7)	93 (9.6)	81 (7.3)	8 (4.0)	54 (11.9)	55 (10.4)	2 (3.9)
>5	1,248 (37.6)	412 (42.5)	437 (39.4)	33 (16.4)	176 (38.7)	183 (34.5)	7 (13.5)
Missing	339 (10.2)	137 (14.1)	106 (9.6)	14 (7.0)	52 (11.4)	26 (4.9)	4 (7.7)
HRT use (%)							
Never	2,502 (75.4)	655 (67.5)	901 (81.2)	164 (81.6)	323 (71.0)	427 (80.4)	32 (61.5)
Ever	270 (8.1)	69 (7.1)	66 (5.9)	27 (13.4)	47 (10.3)	46 (8.7)	15 (28.9)
Missing	547 (16.5)	246 (25.4)	143 (12.9)	10 (5.0)	85 (18.7)	58 (10.9)	5 (9.6)
Tubal ligation (%)							
Never	2,649 (79.8)	774 (79.8)	880 (79.3)	166 (82.6)	364 (80.0)	420 (79.1)	45 (86.5)
Yes	423 (12.7)	113 (11.6)	124 (11.2)	18 (9.0)	77 (16.9)	86 (16.2)	5 (9.6)
Missing	247 (7.4)	83 (8.6)	106 (9.55)	17 (8.5)	14 (3.1)	25 (4.7)	2 (3.8)
Hysterectomy (%)							
Never	3,178 (95.6)	944 (97.3)	1,051 (94.7)	192 (95.5)	429 (94.3)	510 (96.1)	48 (92.3)
Yes	115 (3.5)	19 (2.0)	47 (4.2)	7 (3.5)	23 (5.1)	16 (3.0)	3 (5.8)
Missing	30 (0.9)	7 (0.7)	12 (1.1)	2 (1.0)	3 (0.7)	5 (0.9)	1 (1.9)

*Censoring based on the first cancer diagnosis.
† Group 1: Austria, Belgium, Germany, Netherlands, Hungary, Poland; group 2: Denmark, Sweden; group 3: France, Italy, Quebec, Spain; group 4: United Kingdom and Eire.
‡ Number of live births and stillbirths by the age at censoring.

Table 2. Ovarian cancer HR estimates in *BRCA1* and *BRCA2* carriers combined and separately, under weighted cohort analysis

Factor	All		HR (95% CI)	*P*	*BRCA1*		HR (95% CI)	*P*	*BRCA2*		HR (95% CI)	*P*
	Unaffected	Ovarian cancer			Unaffected	Ovarian cancer			Unaffected	Ovarian cancer		
Parity*												
Nulliparous	675	18	1.00		486	15	1.00		189	3	1.00	
Parous	2,371	234	1.42 (0.79-2.57)	0.24	1,583	185	1.40 (0.75-2.61)	0.30	788	49	1.93 (0.51-7.39)	0.34
Full-term pregnancies (reference group: nulliparous)*												
0	675	18	1.00		486	15	1.00	0.02				
1	502	40	2.33 (1.23-4.43)	0.01	354	31	2.24 (1.13-4.43)		347	12	1.00	
2	1,112	99	1.35 (0.74-2.48)	0.33	749	82	1.35 (0.71-2.56)	0.36	363	17	0.56 (0.19-1.64)	0.29
3	531	62	1.28 (0.65-2.52)	0.48	333	51	1.30 (0.63-2.66)	0.48	198	11	0.40 (0.11-1.47)	0.17
≥4	226	33	0.76 (0.65-1.66)	0.49	147	21	0.67 (0.28-1.62)	0.38	79	12	0.54 (0.16-1.86)	0.33
Full-term pregnancies*												
0	675	18	0.43 (0.23-0.81)	0.01	486	15	0.45 (0.23-0.88)	0.02				
1	502	40	1.00		354	31	1.00		347	12	1.00	
2	1,112	99	0.58 (0.38-0.89)	0.01	749	82	0.60 (0.38-0.96)	0.03	363	17	0.56 (0.19-1.64)	0.29
3	531	62	0.55 (0.34-0.89)	0.02	333	51	0.58 (0.35-0.97)	0.04	198	11	0.40 (0.11-1.47)	0.17
≥4	226	33	0.33 (0.17-0.63)	0.001	147	21	0.30 (0.14-0.64)	0.002	79	12	0.54 (0.16-1.86)	0.33
Age at full-term pregnancy*												
<20	269	30	1.00		187	21	1.00		82	9	1.00	
20-24	946	104	1.11 (0.65-1.89)	0.71	653	82	1.21 (0.66-2.20)	0.53	293	22	0.57 (0.18-1.81)	0.34
25-29	822	64	0.84 (0.47-1.49)	0.55	543	53	0.95 (0.51-1.79)	0.88	279	11	0.28 (0.08-1.02)	0.05
≥30	334	36	1.50 (0.81-2.78)	0.19	200	29	1.60 (0.82-3.14)	0.17	134	7	1.04 (0.25-4.33)	0.96
Nulliparous	675	18	0.74 (0.35-1.56)	0.43	486	15	0.82 (0.37-1.84)	0.63	189	3	0.29 (0.06-1.45)	0.13
Breast-feeding*												
Never	741	74	1.00		468	58	1.00		273	16	1.00	
Ever	1,630	160	0.88 (0.62-1.26)	0.50	1,115	127	0.90 (0.61-1.32)	0.59	515	33	0.72 (0.27-1.91)	0.51
Nulliparous	675	18	0.70 (0.38-1.29)	0.25	486	15	0.72 (0.38-1.39)	0.33	189	3	0.42 (0.09-1.91)	0.26
Breast-feeding duration (mo)*												
Never	741	74	1.00		468	58	1.00		273	16	1.00	
1-5	712	62	0.79 (0.52-1.20)	0.27	481	47	0.81 (0.52-1.26)	0.35	231	15	0.59 (0.19-1.89)	0.38
6-12	534	55	1.06 (0.67-1.68)	0.82	374	44	1.05 (0.64-1.73)	0.84	160	11	1.07 (0.32-3.60)	0.92
13-24	262	21	0.55 (0.29-1.03)	0.06	181	16	0.52 (0.26-1.04)	0.07				
>24	94	12	0.71 (0.29-1.70)	0.44	60	11	0.71 (0.28-1.80)	0.47	115	6	0.64 (0.14-2.88)	0.56
Nulliparous	675	18	0.70 (0.38-1.28)	0.25	486	15	0.72 (0.38-1.38)	0.33	189	3	0.42 (0.09-1.93)	0.27
Age at menarche †												
<12	527	34	1.00		359	24	1.00		168	10	1.00	
12-14	2,009	178	0.92 (0.58-1.46)	0.74	1,367	146	0.94 (0.57-1.57)	0.83	642	32	0.91 (0.33-2.51)	0.86
≥15	495	36	0.65 (0.36-1.19)	0.17	328	26	0.66 (0.34-1.27)	0.21	167	10	0.86 (0.23-3.24)	0.82
OC use ‡												
Never	646	120	1.00		429	92	1.00		217	28	1.00	
Ever	2,295	120	0.55 (0.40-0.76)	0.0003	1,557	98	0.52 (0.37-0.73)	0.0002	738	22	1.04 (0.42-2.54)	0.94
OC duration of use (y) ‡												
Never	646	120	1.00		429	92	1.00		217	28	1.00	
>0-1	299	40	1.04 (0.66-1.62)	0.88	183	36	1.03 (0.64-1.65)	0.91				
>1-3	313	25	0.60 (0.35-1.03)	0.06	206	18	0.51 (0.28-0.93)	0.03	332	13	1.33 (0.52-3.39)	0.56
>3-5	279	10	0.41 (0.19-0.87)	0.02	170	8	0.40 (0.17-0.91)	0.03				
>5	1,208	40	0.35 (0.22-0.55)	5×10^{-6}	849	33	0.34 (0.21-0.54)	6×10^{-6}	359	7	0.59 (0.16-2.24)	0.44
OC start age ‡												
Never	646	120	1.72 (1.05-2.82)	0.03	429	92	1.75 (1.05-2.90)	0.03	217	28	1.25 (0.31-5.08)	0.76

(*Continued on the following page*)

Table 2. Ovarian cancer HR estimates in *BRCA1* and *BRCA2* carriers combined and separately, under weighted cohort analysis (Cont'd)

Factor	All		HR (95% CI)	*P*	*BRCA1*		HR (95% CI)	*P*	*BRCA2*		HR (95% CI)	*P*
	Unaffected	Ovarian cancer			Unaffected	Ovarian cancer			Unaffected	Ovarian cancer		
<20	1,181	36	1.00		844	32	1.00		590	10	1.00	
20-24	707	41	0.88 (0.51-1.50)	0.63	454	35	0.86 (0.49-1.50)	0.59				
≥25	407	43	0.96 (0.53-1.73)	0.89	259	31	0.87 (0.46-1.65)	0.67	148	12	1.46 (0.35-6.01)	0.60
OC: Calendar year at start ‡												
Never	646	120	2.18 (1.50-3.18)	5×10^{-5}	429	92	2.40 (1.58-3.61)	3×10^{-5}	217	28	0.98 (0.40-2.41)	0.40
<1975	790	73	1.00		527	57	1.00		263	16	1.00	
≥1975	1,505	47	1.63 (0.95-2.81)	0.08	1,030	41	1.74 (0.98-3.10)	0.06	475	6	1.16 (0.27-5.01)	0.84
OC: Time since last use ‡												
Never	646	120	1.00		429	92	1.00		217	28	1.00	
Current or <10 y	1,077	24	0.29 (0.18-0.48)	1×10^{-6}	790	20	0.28 (0.17-0.48)	2×10^{-6}	287	4	0.38 (0.10-1.45)	0.16
≥10 y	1,218	96	0.85 (0.59-1.21)	0.36	767	78	0.80 (0.55-1.18)	0.26	451	18	1.76 (0.63-4.94)	0.63
HRT use †												
Never	2,306	196	1.00		1,556	164	1.00		750	32	1.00	
Ever	228	42	0.89 (0.53-1.47)	0.64	135	27	0.89 (0.48-1.63)	0.70	93	15	1.06 (0.45-2.51)	0.90
HRT by duration (y) †												
Never	2,306	196	1.00		1,556	164	1.00		750	32	1.00	
>0-5	137	21	1.18 (0.63-2.21)	0.60	87	18	1.30 (0.65-2.60)	0.45	93	15	1.06 (0.45-2.51)	0.90
>5-10	51	11	0.74 (0.29-1.89)	0.53	48	9	0.51 (0.19-1.39)	0.19				
>10	40	10	0.47 (0.19-1.20)	0.12								
Tubal ligation †												
Never	2,438	211	1.00		1,654	166	1.00		784	45	1.00	
Yes	400	23	0.43 (0.24-0.75)	0.003	237	18	0.42 (0.22-0.80)	0.008	163	5	0.47 (0.18-1.21)	0.12
Age at tubal ligation †												
Never	2,438	211	3.40 (1.45-7.99)	0.005	1,654	166	4.60 (1.51-13.96)	0.007	784	45	1.00	
≤35	232	9	1.00		138	5	1.00		163	5	0.47 (0.18-1.21)	0.12
>35	168	14	2.00 (0.68-5.86)	0.21	99	13	3.14 (0.87-11.28)	0.08				
Hysterectomy †												
Never	2,934	240	1.00		1,955	192	1.00		939	48	1.00	
Yes	105	10	0.59 (0.22-1.57)	0.29	66	7	0.68 (0.22-2.12)	0.51	39	3	0.35 (0.08-1.58)	0.17

*Adjusted for duration of OC use.
† Adjusted for duration of OC use and number of full-term pregnancies.
‡ Adjusted for full-term pregnancy.

covariate. In this analysis, all subjects were allocated disease-specific weights as above. These analyses should be valid provided that the ascertainment depends on the first, but not a subsequent, cancer diagnosis.

With the exception of age at menarche, all the risk factors were analyzed as time-dependent covariates. Women for whom the age at which the covariates changed were unknown were included in an unknown category for the relevant analyses. Pregnancy-related variables were considered up to 1 year prior to the censoring age, in line with previous IBCCS analyses (23). All analyses were stratified by birth cohort (<1940, 1940-1949, 1950-1959, 1960+) and country grouping (group 1: Austria, Belgium, Germany, Netherlands, Hungary, and Poland; group 2: Denmark, Sweden; group 3: France, Italy, Quebec, Spain; group 4: United Kingdom and Eire). Stratification by country was done to reflect potential differences in ovarian cancer incidence and risk factor prevalence. Each of the large studies (United Kingdom, France, and the Netherlands) were assigned to separate groups. The combined analyses that included both *BRCA1* and *BRCA2* mutation carriers were stratified for these genes. Analyses were adjusted for duration of OC use (never, ≤5 years, >5 years, missing data) and number of full-term pregnancies (nulliparous, 1, 2, ≥3). Analyses were further complicated by the fact that more than one mutation carrier could come from the same family and could not therefore be considered independent. Although Cox regression provides unbiased estimates of the rate ratios, in this case, the SEs and confidence intervals (CI) would be underestimated. To allow for the fact that the data set included related individuals, a robust variance approach was used to compute the variance of the rate ratio estimates (28). This adjusts for potential correlations between family members without modeling the dependence explicitly. All analyses were done using the STATA statistical software, version 8 for Unix systems (Statacorp).

Results

The cohort characteristics are summarized in Table 1. In the primary analysis, 1,641 *BRCA1* and *BRCA2* mutation carriers were censored at breast cancer diagnosis, 253 at ovarian cancer diagnosis, 51 at another cancer diagnosis, 186 at bilateral prophylactic oophorectomy, and the remaining 1,188 at the age at interview. The majority of the ovarian cancer cases were *BRCA1* mutation carriers (201 versus 52 *BRCA2* mutation carriers). The mean age at interview was lower for unaffected carriers in both *BRCA1* and *BRCA2* mutation carriers, although the differences in the mean age at censoring between affected and unaffected were smaller.

The estimated hazard ratios (HR) for the risk of developing ovarian cancer using weighted Cox regression analysis are shown in Table 2. Mutation carriers with at least one full-term pregnancy did not have a significantly different ovarian cancer risk compared with nulliparous carriers. The HR estimates for the combined and separate analyses of *BRCA1* and *BRCA2* mutation carriers were all in excess of 1. However, *BRCA1* mutation carriers with two, three, and four or more full-term pregnancies were at a lower ovarian cancer risk compared with *BRCA1* mutation carriers with a single full-term pregnancy (P = 0.03, P = 0.04, and P = 0.002, respectively; P trend = 0.002). Furthermore, there was evidence that nulliparous *BRCA1* carriers were are at a significantly decreased risk compared with carriers with only one full-term pregnancy (HR, 0.45; 95% CI, 0.23-0.88; P = 0.02). We repeated this analysis using a more refined stratification by birth cohort (<1935, 1935-1939, . . ., 1965-1969, ≥1970), to investigate whether this effect was confounded by changes in parity by birth cohort, but the estimates were virtually identical (HR for nulliparous compared with women with a single pregnancy, 0.42; 95% CI, 0.21-0.88; P = 0.02). The estimated HRs by parity in *BRCA1* and *BRCA2* carriers were very similar. However, none of the estimates were significant in *BRCA2* carriers due to the small number of events. There was no significant evidence that the age at first full-term pregnancy was associated with ovarian cancer risk.

For parous mutation carriers, there was some indication that breast-feeding may be protective for ovarian cancer but the results were not significant (*BRCA1*: HR, 0.90; 95% CI, 0.61-1.32; *BRCA2*: HR, 0.72; 95% CI, 0.27-1.91). There was no apparent trend in risk with increasing duration of breast-feeding. Similarly, the HR estimates decreased with increasing age at menarche, but none of the associations were statistically significant (P trend = 0.20 and 0.82 for *BRCA1* and *BRCA2*, respectively).

Mutation carriers who had ever used OCs were at a significantly reduced risk of developing ovarian cancer (HR, 0.55; 95% CI, 0.40-0.76; P = 0.0003 in *BRCA1* and *BRCA2* combined). The effect was restricted to *BRCA1* mutation carriers only (HR, 0.52; 95% CI, 0.37-0.73; P = 0.0002). Increasing duration of OC use was also associated with a reduced risk of ovarian cancer with HR estimates of 0.60 (95% CI, 0.35-1.03), 0.41 (95% CI, 0.19-0.87), 0.35 (95% CI, 0.22-0.55) for durations of use 1 to 3 years, 3 to 5 years, and more than 5 years, respectively, for *BRCA1* and *BRCA2* mutation carriers combined (P trend = 0.0003). The effect was mainly driven by *BRCA1* mutation carriers (P trend = 0.0004), but the number of *BRCA2* mutation carriers in individual categories was too small to draw reliable conclusions. There was no evidence that the age at first OC use was associated with ovarian cancer risk. There was some indication that *BRCA1* carriers who started taking OCs after 1975 were at higher risk, but the difference in risk by year of first use was not statistically significant and no such effect was apparent in *BRCA2* carriers. The protective effect of OCs for *BRCA1* mutation carriers seemed to be greater for more recent users. The HR for ovarian cancer for *BRCA1* mutation carriers who were current users or used OCs within the past 10 years (with respect to the age at censoring) was estimated to be 0.28 (95% CI, 0.17-0.48) compared with 0.80 (95% CI, 0.55-1.18) for *BRCA1* mutation carriers who last used OCs more than 10 years ago (P_{Het} = 0.0002). A similar pattern was observed for *BRCA2* (P_{Het} = 0.04).

Tubal ligation was associated with a reduced risk of ovarian cancer for *BRCA1* and *BRCA2* mutation carriers combined (HR, 0.43; 95% CI, 0.24-0.75; P = 0.003) and for *BRCA1* carriers alone (HR, 0.42; 95% CI, 0.22-0.80). The HR for *BRCA2* mutation carriers was very similar to that in *BRCA1* carriers but it was not significant. There was no significant evidence that the protective effect of tubal

ligation varies with the age at which the surgery took place.

Duration of HRT use was not associated with ovarian cancer risk for *BRCA1* or *BRCA2* mutation carriers (P = 0.70 and 0.90, respectively). Similarly, there was no association between past hysterectomy and the risk of ovarian cancer in *BRCA1* or *BRCA2* mutation carriers (HR, 0.68; 95% CI, 0.22-2.12 and HR, 0.35; 95% CI, 0.08-1.58, respectively), although the number of women who had had a previous hysterectomy was small.

We repeated the above analyses, including follow-up after a first breast cancer diagnosis. In this analysis, mutation carriers who were previously censored at a breast cancer diagnosis were followed until the first of the subsequent events occurred: contralateral breast cancer diagnosis (392), bilateral prophylactic oophorectomy (210), ovarian cancer diagnosis (64), other cancer diagnosis (53), or at interview (922). This analysis thus added an additional 64 events and 9,729 person-years of follow-up. The results were virtually identical to the analysis in which *BRCA1* and *BRCA2* mutation carriers were censored at the first breast cancer diagnosis. In particular, the observed pattern of risk seen with the number of full-term pregnancies remained the same, a single full-term pregnancy was associated with an increased risk of ovarian cancer compared with nulliparous carriers (HR, 2.35; 95% CI, 1.25-4.41; P = 0.008 in *BRCA1* mutation carriers), but increasing number of pregnancies were associated with a reduced ovarian cancer risk (HR, 0.61; 95% CI, 0.41-0.92; HR, 0.59; 95% CI, 0.37-0.94; HR, 0.31; 95% CI, 0.16-0.61, for two, three, and four or more pregnancies, respectively, compared with *BRCA1* carriers with a single pregnancy; P trend = 0.002). Similarly, increasing duration of OC use was also associated with a reduced risk of ovarian cancer (HR, 0.92; 95% CI, 0.60-1.41; HR, 0.48; 95% CI, 0.27-0.83; HR, 0.36; 95% CI, 0.16-0.77; HR, 0.37; 95% CI, 0.24-0.56 for durations of 0-1, >1-3, >3-5, and >5 years, respectively). The estimated HRs were also similar for the other risk factors, but the significances of the associations in *BRCA1* carriers were slightly stronger. None of the HR estimates were significantly different from 1.0 in *BRCA2* carriers, in line with the primary analysis.

Discussion

We used data on 3,319 *BRCA1* and *BRCA2* mutation carriers from the IBCCS study to investigate the effect of reproductive and hormonal factors on the risk of ovarian cancer risk in mutation carriers. We found evidence that increasing number of full-term pregnancies among parous women, OC use, and tubal ligation are associated with a reduced risk of ovarian cancer for *BRCA1* mutation carriers. The number of ovarian cancer cases in *BRCA2* mutation carriers was too small to draw definitive conclusions for the associations in this group of carriers. We found no significant evidence that breastfeeding, age at menarche, HRT, or hysterectomy are associated with ovarian cancer risk in *BRCA1* or *BRCA2* mutation carriers. Our data comes from a large series of *BRCA1* and *BRCA2* mutation carriers that are largely independent from those already published. Some overlap may exist with the study of McLaughlin et al. (16), but the exact number of carriers that are common between the two studies is difficult to establish. Based on the reported country of residence of mutation carriers in that report and in the IBCCS cohort, the maximum potential overlap between our study and the McLaughlin et al. study would be 297 carriers, or 8.9% of our data set, but the true overlap is likely to be much smaller.

The data were analyzed within a Cox proportional hazards framework, using differential weighting of carriers censored at a breast cancer diagnosis, an ovarian cancer diagnosis and those who were unaffected, to reflect the nonrandom sampling of mutation carriers with respect to their disease phenotypes which includes both the cancer site and age at diagnosis or censoring (for unaffected). The main advantages of this approach over other approaches (e.g., a matched case-control design) are that testing bias is optimally adjusted for and all *BRCA1* and *BRCA2* mutation carriers in the IBCCS cohort were used in the analysis, and therefore, the power of the study was not compromised (27). *BRCA1* and *BRCA2* mutation carriers with a first breast cancer diagnosis were assumed to be unaffected in our analysis. A potential bias in the estimated HRs for ovarian cancer could arise if the risk factor under investigation is also associated with breast cancer risk in mutation carriers (which in this case, many are). However, in our analyses, mutation carriers censored at breast cancer diagnosis were assigned breast cancer–specific weights which were lower than the weights assigned to mutation carriers censored at the age at interview (reflecting the oversampling of affected carriers). Therefore, our weighting scheme would correct for such a bias if the associations are in the same direction for breast and ovarian cancer. In addition, we carried out further analyses which included the follow-up time after the first breast cancer diagnosis, treating the first breast cancer diagnosis as a time-dependent covariate, and the results were virtually identical to those in the primary analyses.

This is one of the largest studies of risk factors for ovarian cancer in *BRCA1* and *BRCA2* carriers to date. Nevertheless, the number of carriers diagnosed with ovarian cancer in our study is still relatively small, particularly among *BRCA2* mutation carriers. Therefore, our study is underpowered to detect the effect of risk factors which confer a small increase or decrease in ovarian cancer risk. The analysis which included the follow-up time after the first breast cancer diagnosis increased power somewhat, but no further significant associations were detected. Larger studies of *BRCA2* mutation carriers will be necessary to address the associations between these factors and ovarian cancer risk with certainty.

Both prevalent and incident ovarian cancer cases were considered in our analysis. The mean time between an ovarian cancer diagnosis and the age at interview in our study was 6.7 years. The inclusion of prevalent cases could potentially bias our estimates if the risk factors under investigation were also associated with survival after an ovarian cancer diagnosis. A study by McLaughlin et al., which investigated the effect of reproductive and hormonal factors on ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers, found that their results were similar between analyses which included both prevalent and incident cases and analyses which were restricted to incident ovarian cancer cases (16). Furthermore, studies in the general population have not found

an association between reproductive or hormonal factors and survival except from breast-feeding (29). Women who had ever breast fed were found to have a better prognosis in the general population. If the same is true for carriers, this might have attenuated a real protective effect. These considerations suggest that our remaining results are unlikely to have been influenced by the inclusion of prevalent ovarian cancer cases.

One potential source of bias in our analyses was that 61.7% of the mutation carriers censored upon diagnosis of ovarian cancer were born before the year 1950, whereas this was true for only 29.2% of the remaining women. In our main analysis, birth cohort was categorized in 10-year intervals, and we suspected that this categorization might be too broad to fully adjust for the cohort effect. We therefore repeated the analysis using 5-year birth cohort categories, but the results were similar.

We found a curious pattern of risk associated with parity. Among parous women, we saw a clear reduction in risk by number of full-term pregnancies in both *BRCA1* and *BRCA2* carriers. These results are in line with studies of ovarian cancer in the general population in which parity is associated with a reduced risk of ovarian cancer (10). However, nulliparous women were at a lower risk of ovarian cancer than women with one pregnancy, so that overall nulliparity was associated with a slight, although nonsignificant reduction in risk. This latter effect is not consistent with the effects seen in the general population. Previous studies in *BRCA1* mutation carriers alone or *BRCA1* and *BRCA2* mutation carriers combined have, in general, reported a protective effect of parity for ovarian cancer, but the effect was not always significant (14, 15, 17). In the largest study to date, McLaughlin et al. (16) reported a significant 44% reduction in the risk of ovarian cancer risk in parous *BRCA1* mutation carriers, but parity was associated with an increased risk of ovarian cancer in *BRCA2* mutation carriers. The 95% CI of our HR estimate for *BRCA1* mutation carriers does not include the estimate of McLaughlin et al. (16). Our estimated effect among *BRCA2* mutation carriers is consistent with their OR estimate of 2.74 but our analyses were based on a small number of *BRCA2* mutation carriers. However, we saw no evidence to suggest a differential effect of parity in *BRCA1* and *BRCA2* carriers.

Given the results in the general population and the apparently clear association with the number of children, the increased risk in nulliparous women seems likely to be an artifact. This could arise if there was a difference in the HR by attained age as observed in the case of breast cancer (23). In our data set, the ovarian cancer HR for parous *BRCA1* mutation carriers who were less than 45 years of age is estimated to be 2.47 (95% CI, 0.97-6.30), but the HR for those who were 45 years or older was 0.82 (95% CI, 0.36-1.89). However, the difference in the HR between the two groups is not significant ($P = 0.09$) and larger studies will be necessary to investigate this possibility. Another explanation could be selection bias, whereby a woman's decision to test for *BRCA1* and *BRCA2* mutations depends both on the diagnosis (ovarian/breast cancer or unaffected) and on the number of children she has. In particular, the result we observed could be generated if women with ovarian cancer preferentially come forward for testing if they have children.

One previous study found that breast-feeding protects against ovarian cancer in *BRCA1* mutation carriers (16), but others have not found this association (15, 14). Although we found no significant effect for breast-feeding among *BRCA1* mutation carriers, our HR estimate is <1.0 and has a CI that includes the McLaughlin et al. estimate (16). The estimates for *BRCA2* mutation carriers were identical in the two studies (0.72), but were both nonsignificant.

We found no significant evidence that age at menarche was associated with ovarian cancer risk, but the estimates suggest that risk may decrease with increasing age at menarche in both *BRCA1* and *BRCA2* mutation carriers. Two previously published studies in *BRCA1* mutation carriers also found no association between age at menarche and ovarian cancer risk (14, 15).

We found that OC use was associated with a reduction in ovarian cancer risk, and that increasing duration of use was inversely related to ovarian cancer risk in *BRCA1* mutation carriers. These findings are in line with the results in the general population (9, 10) and of several other studies in mutation carriers (14-16, 18, 20), although there have been studies which found no effect (17). In the largest study, McLaughlin et al. (16) found a 61% reduction in ovarian cancer risk in *BRCA1* mutation carriers, slightly higher, but consistent with our estimate (48%). Duration of more than 5 years of OC use was associated with similar risk reduction in both studies (63% versus 66% risk reduction in our study). Therefore, our results provide an independent confirmation of the effect of OCs on ovarian cancer risk for *BRCA1* mutation carriers. We found no such association for *BRCA2* mutation carriers, but the sample size was small and our CI does not exclude the estimate of McLaughlin et al. (16) or the estimate in *BRCA1* carriers in our study. In addition, we found that the protective effect was greater in more recent users of OC, although the protective effect persisted even after 10 years since last use in *BRCA1* mutation carriers. This is in agreement with the recent meta-analysis of studies in the general population (9).

There was no evidence that the risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers varied by HRT use or by whether the carriers had had a hysterectomy. Another small study of incident ovarian cancer cases in *BRCA1* mutation carriers found no effect with HRT use (15). Rutter et al. (19) investigated the effect of a group of gynecological surgeries including hysterectomy, unilateral oophorectomy, and tubal ligation in *BRCA1* and *BRCA2* mutation carriers from Israel and found that they were associated with a reduced risk of ovarian cancer, but results were not presented for hysterectomy alone. Although our estimated HR for the effect of hysterectomy is consistent with estimates from studies in the general population (10, 12, 19), larger studies will be required to clarify the effect in mutation carriers.

Finally, we found that tubal ligation is associated with a reduction in ovarian cancer risk in *BRCA1* mutation carriers. The estimated risk reduction in *BRCA2* mutation carriers (53%), although not significant, was similar to that in *BRCA1* mutation carriers (58%). One previous study reported a significant association with tubal ligation in *BRCA1* mutation carriers (30), although the

more recent re-analysis by the same group using additional subjects found no significant effect (16). Our estimated risk reduction is similar to that reported in the general population.

Our results provide further confirmation that OC use and tubal ligation are associated with ovarian cancer risk in carriers, to a similar relative extent as in the general population. The absolute difference associated with these risk factors is, however, much greater in carriers. For example, according to published *BRCA1* ovarian cancer risks (31), the average cumulative risk of developing the disease by age 70 for an unaffected 40-year-old *BRCA1* mutation carrier would be 32%. If we assume that our HR estimate of 0.52 for ever OC use applies from the point of first OC use for the remaining lifetime, then the corresponding risk for a *BRCA1* carrier who has never used OC would be 41%, but for someone who had used OC in the past, the corresponding risk would be 24%. However, OC use has been associated with an increased risk of breast cancer in the general population (21). Estimates for the associations of OC use and the risk of breast cancer risk for *BRCA1* mutation carriers are conflicting and therefore the precise effect of OC use on breast cancer risk remains unresolved. Two studies reported that OCs may increase the risk of breast cancer in *BRCA1* mutation carriers (22, 32), and one study reported no association (33), whereas another study reported that OC use may reduce the risk of breast cancer for BRCA1 (34). Therefore, although OCs provide an attractive approach to ovarian cancer risk reduction, their use as chemoprevention for ovarian cancer risk needs to take into account the precise effect on breast cancer risk. Longer-term prospective studies will be needed to establish definitively the balance between benefit and risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix A. Extending the Weighted Cohort Approach To Account for Oversampling With Respect To Both Breast And Ovarian Cancer

Our analyses are complicated by the fact that *BRCA1* and *BRCA2* mutation carriers are not randomly sampled with respect to their disease status. Many carriers are sampled through families seen in genetic clinics. The first tested individual in a family is usually someone diagnosed with cancer at a relatively young age. Such study designs therefore tend to lead to an oversampling of affected individuals, and standard analytical methods such as Cox regression might lead to estimates of the risk ratios which are biased towards the null (27). The weighted cohort approach for analyzing modifying risk factors assigns relative weights to all study subjects to reflect the probabilities with which they were sampled (27). We have previously shown that this approach leads to estimates which are close to unbiased at the expense of some loss in power (27). Here, we extend this approach to reflect the fact that *BRCA1* and *BRCA2* mutation carriers are oversampled with respect to both breast and ovarian cancer. The aim is to correct the bias by differential weighting of unaffected carriers, carriers who are censored at breast cancer, and those censored at ovarian cancer such that the breast and ovarian cancer incidence rates implied by the weighted cohort agree with incidence rates for *BRCA1* and *BRCA2* mutation carriers derived from a separate study.

We assume that our study includes n subjects in which individual i is followed up to age t_i (either at breast cancer, ovarian cancer, or censored as unaffected). Age is divided into a number of intervals (in our case, at 5-year intervals) such that in the k^{th} age group, there are r_k breast cancer cases, d_k ovarian cancer cases, and s_k censored individuals. We also assume that in age group k, the breast cancer cases accumulate p_k person years, the ovarian cancer cases accumulate x_k person years, and the censored individuals accumulate q_k person years. We further assume that our study subjects are sampled from a population with true breast cancer incidence rate μ_k in age group k, and ovarian cancer incidence rate λ_k in age group k. We then assign weights w_k to the breast cancer cases, z_k to the ovarian cancer cases, and v_k to the censored subjects such that the observed incidence rates agree with true incidence rates:

$$\mu_k = \frac{w_k r_k}{w_k p_k + v_k q_k + z_k x_k + t_k \sum_{l>k} (w_l r_l + v_l s_l + z_l d_l)}$$

$$\lambda_k = \frac{z_k d_k}{w_k p_k + v_k q_k + z_k x_k + t_k \sum_{l>k} (w_l r_l + v_l s_l + z_l d_l)}$$

where t_k is the number of years in age interval k. The numerators in these expressions represent the weighted number of cases occurring in the interval and the denominators the total weighted person years accumulated in age group k by all the individuals at risk. As in Antoniou et al. (27), to obtain a unique solution, we impose further constraints such that the average contribution of breast and ovarian cancer cases and censored individuals in each age group is equal to 1, that is,

$$\frac{w_k r_k + v_k s_k + z_k d_k}{r_k + s_k + d_k} = 1.$$

Although other constraints are possible, this provides a solution in which the variances of the estimates are not seriously compromised, as compared with the unweighted estimates. It is then possible to iteratively solve the three sets of equations above for w_k, z_k, and v_k, for each age group k.

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