DOI: 10.1093/jnci/djq494
Advance Access publication on December 17, 2010

ARTICLE

Genetic Variation at 9p22.2 and Ovarian Cancer Risk for *BRCA1* and *BRCA2* Mutation Carriers

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Manuscript received May 18, 2010; revised October 14, 2010; accepted November 4, 2010.

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Background Germline mutations in the *BRCA1* and *BRCA2* genes are associated with increased risks of breast and ovarian cancers. Although several common variants have been associated with breast cancer susceptibility in mutation carriers, none have been associated with ovarian cancer susceptibility. A genome-wide association study recently identified an association between the rare allele of the single-nucleotide polymorphism (SNP) rs3814113 (ie, the C allele) at 9p22.2 and decreased risk of ovarian cancer for women in the general population. We evaluated the association of this SNP with ovarian cancer risk among *BRCA1* or *BRCA2* mutation carriers by use of data from the Consortium of Investigators of Modifiers of *BRCA1/2*.

Methods We genotyped rs3814113 in 10029 *BRCA1* mutation carriers and 5837 *BRCA2* mutation carriers. Associations with ovarian and breast cancer were assessed with a retrospective likelihood approach. All statistical tests were two-sided.

Results The minor allele of rs3814113 was associated with a reduced risk of ovarian cancer among *BRCA1* mutation carriers (per-allele hazard ratio of ovarian cancer = 0.78, 95% confidence interval = 0.72 to 0.85; $P = 4.8 \times 10^{-9}$) and *BRCA2* mutation carriers (hazard ratio of ovarian cancer = 0.78, 95% confidence interval = 0.67 to 0.90; $P = 5.5 \times 10^{-4}$). This SNP was not associated with breast cancer risk among either *BRCA1* or *BRCA2* mutation carriers. *BRCA1* mutation carriers with the TT genotype at SNP rs3814113 were predicted to have an ovarian cancer risk to age 80 years of 48%, and those with the CC genotype were predicted to have a risk of 33%.

Conclusion Common genetic variation at the 9p22.2 locus was associated with decreased risk of ovarian cancer for carriers of a *BRCA1* or *BRCA2* mutation.

J Natl Cancer Inst 2011;103:105–116

CONTEXT AND CAVEATS

Prior knowledge

Although germline mutations in the *BRCA1* and *BRCA2* genes are associated with increased risks of ovarian cancer, other genetic variants that have not been identified might modify that risk. Such a genetic variant may be located at 9p22.2, as indicated by an association between the rare allele of the single-nucleotide polymorphism (SNP) rs3814113 (ie, the C allele) at this locus and decreased risk of ovarian cancer for women in the general population.

Study design

This SNP was genotyped in *BRCA1* mutation carriers and *BRCA2* mutation carriers. Associations between the SNP and ovarian and breast cancer were assessed.

Contribution

The minor allele of this SNP located at the 9p22.2 locus was associated with decreased risk of ovarian cancer, but not with breast cancer risk, for carriers of a *BRCA1* or *BRCA2* mutation.

Implications

It is likely that there are other genes that also modifying this risk in *BRCA1* or *BRCA2* mutation carriers. Their identification may be useful for genetic testing and risk counseling of such women.

Limitations

Precise family histories for all mutation carriers were not available. Detailed ovarian tumor histology data were not available. The SNP tested is probably located near but is not the genetic variant that is causally related to ovarian cancer.

From the Editors

Pathogenic mutations in the *BRCA1* and *BRCA2* genes confer high risks of ovarian and breast cancers (1,2). Breast cancer risks by age 70 years have been estimated to range between 40% and 87% for *BRCA1* mutation carriers and between 40% and 84% for *BRCA2* mutation carriers (3–13). Ovarian cancer risk estimates by age 70 years range between 16% and 68% for *BRCA1* mutation carriers and between 11% and 27% for *BRCA2* mutation carriers (3–13). Random variation and environmental factors may explain part of the observed variation in risk estimates. There is also considerable evidence for the existence of genetic factors that modify cancer risks for mutation carriers, with the estimated cancer risks varying by family history of the disease (3) and the site of the cancer in the proband for that family's ascertainment (3–5,10). Moreover, the risks of ovarian and/or breast cancers can vary with respect to the location of truncating mutations in both *BRCA1* and *BRCA2* genes, indicating that there may be associations between genotypes and phenotypes (12–16).

Recent genome-wide association studies (GWAS), as reviewed previously (17–19), have identified common alleles associated with risk of breast, ovarian, and/or other cancers. These findings have raised the possibility that common variants are also associated with the risks of disease for carriers of various mutations. The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) has provided evidence that variants near *FGFR2*, *TNRC9/TOX3*, *MAP3K1*, *LSP1*, and 2q35 identified through GWAS of breast cancer patients are also associated with the risk of developing breast cancer for *BRCA1* and/or *BRCA2* mutation carriers (20,21).

To date, a number of studies (22,23) have investigated candidate variants as potential modifiers of ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. However, none of the variants have been validated in independent datasets. At the time of this study, the only confirmed common genetic variants to be identified for ovarian cancer were several in a region on 9p22.2, which was recently reported from a GWAS (19) of patients with invasive ovarian cancer. The most statistically significant association was for the single-nucleotide polymorphism (SNP) rs3814113; the minor allele (ie, the C allele) was associated with a reduced risk of invasive ovarian cancer (odds ratio [OR] = 0.82, 95% confidence interval [CI] = 0.79 to 0.86, GWAS $P_{trend} = 5.1 \times 10^{-19}$); the association with rs3814113 was strongest among patients with the serous histological subtype of ovarian cancer (OR = 0.77, 95% CI = 0.73 to 0.81, GWAS $P_{trend} = 4.1 \times 10^{-21}$). To investigate whether this SNP is associated with the risk of ovarian cancer for *BRCA1* or *BRCA2* mutation carriers, we genotyped rs3814113 in 10029 *BRCA1* mutation carriers and in 5837 *BRCA2* mutation carriers who were recruited by CIMBA through 32 studies (24).

Materials and Methods

Study Subjects

All subjects were women who carried pathogenic mutations in *BRCA1* or *BRCA2* from 32 studies from Europe, North America, and Australia (Supplementary Table 1, available online). Pathogenic mutations were defined as protein-truncating mutations or mutations listed on the Breast Cancer Information Core (http://research.nhgri.nih.gov/bic/), as described previously (25). All subjects were 18 years or older at recruitment. Only self-reported white women were included in the analysis. Subjects were excluded if they were from a country other than that of the study base or if they carried mutations in both *BRCA1* and *BRCA2* genes. If a woman was enrolled in two different studies, her data from only one study were included in the analysis. The data from the study with the most complete information for this individual were included in the analysis. Duplicate mutation carriers were identified by dates of birth and diagnosis and from available genotyping data. Subject information for all studies included year of birth, age at last follow-up, age at breast and/or ovarian cancer diagnosis, and age at bilateral prophylactic mastectomy or oophorectomy. Related subjects were identified through a unique family identifier. *BRCA1* mutations were classified by their predicted functional consequence as follows: class 1 mutations were defined as loss of function mutations, and class 2 mutations were mutations that were expected to generate a stable mutant protein, as described previously (20). *BRCA2* mutations were classified by whether or not they were located in the ovarian cancer cluster region (nucleotides 3059–6629) (12,15). Subjects participated in clinical or research studies at the host institutions under ethically approved protocols and written informed consent was obtained (Supplementary Table 2, available online). Further details about CIMBA were described elsewhere (24).

Genotyping for SNP rs3814113

For 10 studies, the DNA samples were genotyped for SNP rs3814113 at one center by use of the iPLEX Mass Array platform

(Sequenom, Hamburg, Germany) (Supplementary Table 1, available online). The remaining 22 studies (Supplementary Table 1, available online) were genotyped by use of the 5′ endonuclease assay (Taqman), with reagents supplied by Applied Biosystems (Warrington, UK), and tested centrally as described previously (25). All genotyping data were subjected to a standard set of quality control criteria. Samples from subjects with ovarian cancer or those without an ovarian cancer diagnosis (ie, affected and unaffected subjects) were randomly arrayed in the plates within studies. No-template controls were included on every plate, and at least 2% of the samples were tested in duplicate. Samples were excluded if they consistently failed genotyping (defined as a pass rate of <80% for all SNPs in a genotyping round for the iPLEX assay or as the failure of three or more of 10 SNPs for the Taqman assay). For a study to be included in the analysis, the genotype data were required to attain or exceed a call rate threshold of 95% and a concordance between duplicates of 98%. We also evaluated the deviation from Hardy–Weinberg equilibrium for unrelated subjects. For none of these studies was Hardy–Weinberg equilibrium rejected at a predefined threshold of a P value of .001. An additional quality control criterion was consistent results for 95 DNA samples from a standard test plate (Coriell Institute, Camden, NJ) that was genotyped at all centers. If the genotyping was inconsistent for more than one sample in the test plate, the study was excluded. Three additional studies attempted to genotype this SNP, but the SNP failed one or more of the above criteria and, therefore, were not included in this analysis. After these exclusions, a total of 15 866 mutation carriers with genotype data for rs3814113 were eligible for inclusion in the analysis (10 029 with a *BRCA1* mutation and 5837 with a *BRCA2* mutation) (Supplementary Table 1, available online).

Statistical Analysis

The aim of the analysis was to evaluate the association between each genotype and ovarian cancer risk. Phenotype was defined by age at ovarian cancer diagnosis or age at last follow-up. The primary analysis involved censoring of subjects at the age of ovarian cancer diagnosis or bilateral prophylactic oophorectomy, whichever occurred first (irrespective of a breast cancer diagnosis), or the age at last observation. Only subjects with an ovarian cancer diagnosis were assumed to be affected.

BRCA1 and *BRCA2* mutation carriers were not randomly selected with respect to their disease status. Usually mutation carriers are sampled through families who are counseled in genetic clinics, and genetic testing is targeted at those diagnosed with cancer at a relatively young age. Such designs therefore lead to an oversampling of affected subjects. Moreover, affected and unaffected mutation carriers are sampled with different probabilities at different ages. Because the carriers studied do not represent an unselected cohort, standard methods of analysis could give biased estimates of the risk ratios. This is demonstrated by considering an individual affected at age t. In a standard cohort or case–control analysis, the SNP genotype for the individual is compared with the genotypes of those subjects at risk at age t or in a case–control analysis with control subjects randomly sampled from all at-risk subjects. This analysis leads to consistent estimates of the risk ratios. However, in the study design used in this analysis, mutation carriers had been selected previously on the basis of their disease status. Therefore, a standard analysis would lead to case patients being compared with control subjects who were selected on the basis of their future disease status. If a particular genotype is associated with disease, then the risk ratio estimate would be biased toward 1.0 because too many affected subjects (in whom the at-risk genotype would be overrepresented) would be included in the comparison group. A simulation study (26) has shown that this effect can be quite marked. To adjust for this sampling and reduce the potential bias, we conducted the analysis by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes, as described previously (25). The association of each SNP was modeled either as a per-allele hazard ratio (multiplicative model) or as separate hazard ratios for heterozygotes and homozygotes (both parameterized on the log scale). The hazard ratios were assumed to be independent of age (ie, we used a Cox proportional hazards model). The assumption of proportional hazards was tested by adding a "genotype × age" interaction term to the model. Analyses were carried out with the pedigree-analysis software MENDEL (27). Under this approach, the baseline age-specific incidences in the Cox proportional hazards model were chosen so that the overall ovarian cancer incidences, averaged over all genotypic categories, agreed with external estimates of incidence for *BRCA1* and *BRCA2* mutation carriers.

We examined between-study heterogeneity by comparing the models that allowed for study-specific log hazard ratios against models in which the same log hazard ratio was assumed to apply to all studies by use of a robust Wald test statistic. All analyses were stratified by study group and country of residence and used calendar year- and cohort-specific ovarian cancer incidences for *BRCA1* and *BRCA2* mutation carriers (4). For sensitivity analyses with smaller numbers of mutation carriers (see below), small strata were combined on the basis of country of residence. We used a robust variance-estimation approach to allow for the nonindependence of related carriers (28).

To investigate whether our results were influenced by any of our assumptions, we performed additional sensitivity analyses. Breast cancer diagnoses occurring before an ovarian cancer diagnosis were ignored in the primary analysis. Analyses were repeated by also censoring at the age of breast cancer diagnosis and by treating those subjects as unaffected in the analysis of associations with ovarian cancer risk. That is, in this analysis, subjects were followed until one of the following events: age at ovarian cancer diagnosis, age at breast cancer diagnosis or bilateral prophylactic oophorectomy (whichever occurred first), or the age at last observation. Only subjects censored at ovarian cancer were assumed to be affected in this analysis. If the SNP was associated with disease survival, the inclusion of subjects with a prevalent ovarian cancer diagnosis could influence the hazard ratio estimates. We therefore repeated our analysis by excluding mutation carriers who had been diagnosed with ovarian cancer more than 5 years before recruitment into the study.

We also evaluated the associations of this SNP with breast cancer risk for mutation carriers. If the SNP is associated with ovarian cancer risk, analyzing the breast cancer associations by treating women with ovarian cancer as unaffected in the analysis can potentially lead to a spurious association with breast cancer

risk in the opposite direction (to that observed for ovarian cancer). Therefore, to evaluate the associations with breast cancer risk, we performed the analysis within a competing risk framework in which we estimated hazard ratios simultaneously for breast and ovarian cancer. For this purpose, we extended the retrospective likelihood model (25) so that each woman was at risk of developing either breast cancer or ovarian cancer by assuming that the probabilities of developing each disease were independent, conditional on the underlying genotype. A different censoring process was used for this analysis, whereby subjects were followed until the age of their first breast or ovarian cancer diagnosis and were considered to have developed the corresponding disease. No follow-up was considered after the first cancer diagnosis. Subjects were censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of bilateral oophorectomy and were assumed to be unaffected for the corresponding disease. The remaining subjects were censored at the age at last observation and were assumed to be unaffected for both diseases.

Without additional data, such as pedigree data, estimating the absolute risks of ovarian cancer by genotype is difficult in this study due to the retrospective study design. We therefore used the estimated hazard ratios under the primary analysis to predict the age-specific cumulative risks of developing ovarian cancer by age 80 years with respect to rs3814113 genotype in *BRCA1* and *BRCA2* mutation carriers by use of estimates of age-specific ovarian cancer incidences from previous studies (with the implied average cumulative risk of ovarian cancer in *BRCA1* mutation carriers being 44% by age 80 years and in *BRCA2* mutation carriers being 12% by age 80 years) (4).

Results

In total, 10 029 *BRCA1* mutation carriers and 5837 *BRCA2* mutation carriers were eligible for analysis of associations between ovarian cancer risk and SNP rs3814113 at the 9p22.2 locus. The primary analysis (without censoring at breast cancer diagnosis) included 2410 mutation carriers who were censored at diagnosis of invasive ovarian cancer (case subjects) and 13 456 unaffected mutation carriers (including 2959 censored at bilateral prophylactic oophorectomy) (Table 1).

The minor allele of rs3814113 (ie, C allele) was associated with reduced risk of ovarian cancer for both *BRCA1* and *BRCA2* mutation carriers (Table 2). Each copy of the minor allele was estimated to be associated with a reduced risk of ovarian cancer (per-allele hazard ratio [HR] of ovarian cancer = 0.78, 95% CI = 0.72 to 0.85, $P_{trend} = 4.8 \times 10^{-9}$, for *BRCA1* mutation carriers and HR of ovarian cancer = 0.78, 95% CI = 0.67 to 0.90, $P_{trend} = 5.5 \times 10^{-4}$, for *BRCA2* mutation carriers). Results from a combined analysis of *BRCA1* and *BRCA2* mutation carriers were virtually identical (per-allele HR of ovarian cancer = 0.79, 95% CI = 0.73 to 0.84) and the

Table 1. Characteristics of study subjects on the basis of the primary analysis*

Characteristic	Total	*BRCA1* mutation carriers		*BRCA2* mutation carriers	
		Unaffected	Ovarian cancer	Unaffected	Ovarian cancer
No.	15866	8142	1887	5314	523
Person-years of follow-up	730479.8	355745.3	95665.7	249425.7	29643.1
Median age at censure, y (IQR)	45 (37–54)	42 (36–50)	50 (44–56)	46 (38–55)	57 (50–64)
Age group at censure, No. (%)					
0–19 y	79 (0.5)	51 (0.6)	0 (0.0)	27 (0.5)	1 (0.2)
20–29 y	1202 (7.6)	798 (9.8)	12 (0.6)	389 (7.3)	3 (0.6)
30–39 y	3824 (24.1)	2445 (30.0)	187 (9.9)	1178 (22.2)	14 (2.7)
40–49 y	5270 (33.2)	2678 (32.9)	727 (38.5)	1748 (32.9)	117 (22.4)
50–59 y	3326 (21.0)	1366 (16.8)	646 (34.2)	1130 (21.3)	184 (35.2)
60–69 y	1497 (9.4)	533 (6.6)	251 (13.3)	562 (10.6)	15 (28.9)
70–79 y	518 (3.3)	203 (2.5)	59 (3.1)	207 (3.9)	49 (9.4)
≥80 y	150 (1.0)	68 (0.8)	5 (0.3)	73 (1.4)	4 (0.8)
Year of birth, No. (%)					
Before 1920	123 (0.8)	55 (0.7)	8 (0.4)	48 (0.9)	12 (2.3)
1920–1929	574 (3.6)	206 (2.5)	114 (6.0)	185 (3.5)	69 (13.2)
1930–1939	1413 (8.9)	495 (6.1)	336 (17.8)	435 (8.2)	147 (28.1)
1940–1949	3052 (19.2)	1270 (15.6)	641 (34.0)	960 (18.1)	181 (34.6)
1950–1959	4372 (27.6)	2230 (27.4)	568 (30.1)	1480 (27.9)	94 (18.0)
1960 or later	6332 (39.9)	3886 (47.7)	220 (11.7)	2206 (41.5)	20 (3.8)
Mutation class†, No. (%)					
Class 1		5262 (64.6)	1354 (71.8)	4941 (93.0)	498 (95.2)
Class 2		2256 (27.7)	423 (22.4)	137 (2.6)	9 (1.7)
Other		624 (7.7)	110 (5.8)	236 (4.4)	16 (3.1)
Mutation position, No. (%)					
OCCR				1926 (36.2)	251 (48.0)
Non-OCCR				3388 (63.8)	272 (52.0)

* IQR = interquartile range; OCCR = ovarian cancer cluster region.

† Class 1 mutations were defined as loss of function mutations, and class 2 mutations were mutations that were expected to generate a stable mutant protein, as described previously (20).

Table 2. Genotype distribution of the single-nucleotide polymorphism rs3814113 by affection status for ovarian cancer and associations with ovarian cancer risk*

Gene	rs3814113 genotype	Unaffected status, No. (%)	Affected status, No. (%)	HR (95% CI)	*P*†
No censoring at breast cancer					
BRCA1	TT	3526 (43.3)	950 (50.3)	1 (ref)	
	CT	3671 (45.1)	775 (41.1)	0.79 (0.71 to 0.88)	
	CC	945 (11.6)	162 (8.6)	0.61 (0.51 to 0.74)	
	2 *df* test				3.9×10^{-8}
	Per-allele analysis			0.78 (0.72 to 0.85)	4.8×10^{-9}
BRCA2	TT	2436 (45.8)	269 (51.4)	1 (ref)	
	CT	2288 (43.1)	216 (41.3)	0.82 (0.67 to 1.00)	
	CC	590 (11.1)	38 (7.3)	0.56 (0.39 to 0.80)	
	2 *df* test				.0027
	Per-allele analysis			0.78 (0.67 to 0.90)	.00055
BRCA1/2 combined	TT	5962 (44.3)	1219 (50.6)	1 (ref)	
	CT	5959 (44.3)	991 (41.1)	0.80 (0.73 to 0.89)	
	CC	1535 (11.4)	200 (8.3)	0.60 (0.51 to 0.71)	
	2 *df* test				2.2×10^{-10}
	Per-allele analysis			0.79 (0.73 to 0.84)	2.0×10^{-11}
With censoring at breast cancer					
BRCA1	TT	3777 (43.6)	699 (51.3)	1 (ref)	
	CT	3891 (44.9)	555 (40.7)	0.79 (0.68 to 0.92)	
	CC	998 (11.5)	109 (8.0)	0.59 (0.44 to 0.77)	
	2 *df* test				6.7×10^{-5}
	Per-allele analysis			0.77 (0.69 to 0.87)	1.0×10^{-5}
BRCA2	TT	2514 (46.0)	191 (50.4)	1 (ref)	
	CT	2345 (43.0)	159 (42.0)	0.86 (0.65 to 1.12)	
	CC	599 (11.0)	29 (7.6)	0.62 (0.39 to 1.01)	
	2 *df* test				.12
	Per-allele analysis			0.82 (0.67 to 0.99)	.042
BRCA1/2 combined	TT	6291 (44.5)	890 (51.1)	1 (ref)	
	CT	6236 (44.2)	714 (41.0)	0.81 (0.73 to 0.91)	
	CC	1597 (11.3)	138 (7.9)	0.60 (0.49 to 0.73)	
	2 *df* test				1.6×10^{-7}
	Per-allele analysis			0.79 (0.73 to 0.86)	1.9×10^{-8}

* CI = confidence interval; HR = hazard ratio; ref = referent.

† A robust Wald test statistic was used. All statistical tests were two-sided.

evidence of association was stronger ($P_{trend} = 2.0 \times 10^{-11}$). There was no evidence that the association varied by age among either *BRCA1* ($P = .78$) or *BRCA2* ($P = .17$) mutation carriers. The study-specific hazard ratios are shown in Figure 1. In addition, there was no evidence of heterogeneity in hazard ratios across the studies ($P = .22$ for *BRCA1* mutation carriers and $P = .36$ for *BRCA2* mutation carriers).

We repeated the analysis by censoring at breast cancer diagnosis. This analysis included 1742 case patients with ovarian cancer and 14 124 unaffected mutation carriers (including 8070 censored at breast cancer diagnosis and 1316 censored at bilateral prophylactic oophorectomy). Estimates from this analysis were similar to those from the primary analysis (for *BRCA1* mutation carriers, per-allele HR of ovarian cancer = 0.77, 95% CI = 0.69 to 0.87; and for *BRCA2* mutation carriers, per-allele HR of ovarian cancer = 0.82, 95% CI = 0.67 to 0.99) (Table 2). The *P* values were slightly larger because of the reduced number of ovarian cancer case subjects included in the analysis ($P_{trend} = 1 \times 10^{-5}$ for *BRCA1* mutation carriers and $P_{trend} = .042$ for *BRCA2* mutation carriers).

To investigate the associations between the SNP and ovarian cancer risk after a breast cancer diagnosis, we defined affected subjects as women who were diagnosed with ovarian cancer after a first breast cancer diagnosis (Supplementary Table 3, available online). Although the number of subjects diagnosed with ovarian cancer was greatly reduced in this group (n = 524 for *BRCA1* and n = 144 for *BRCA2*), the associations between the SNP and ovarian cancer risk remained statistically significant (for *BRCA1* mutation carriers, per-allele HR of ovarian cancer = 0.82, 95% CI = 0.72 to 0.93, $P_{trend} = 2.9 \times 10^{-3}$; for *BRCA2* mutation carriers, per-allele HR of ovarian cancer = 0.69, 95% CI = 0.53 to 0.90, $P_{trend} = .006$; and for *BRCA1* and *BRCA2* mutation carriers combined, per-allele HR of ovarian cancer = 0.79, 95% CI = 0.70 to 0.88, $P_{trend} = 5.4 \times 10^{-5}$).

To determine whether any survival bias was introduced by including long-term survivors, we excluded all case subjects with ovarian cancer who were recruited 5 years or more after that diagnosis (Supplementary Table 4, available online). The estimates were unchanged from the primary analysis and remained statistically significant for both *BRCA1* mutation carriers and *BRCA2* mutation carriers, despite the small sample size (for *BRCA1* mutation carriers, per-allele HR of ovarian cancer = 0.78, 95% CI = 0.71 to 0.86, $P_{trend} = 6.0 \times 10^{-7}$; for *BRCA2* mutation carriers, per-allele HR of ovarian cancer = 0.80, 95% CI = 0.68 to 0.94, $P_{trend} = .008$).

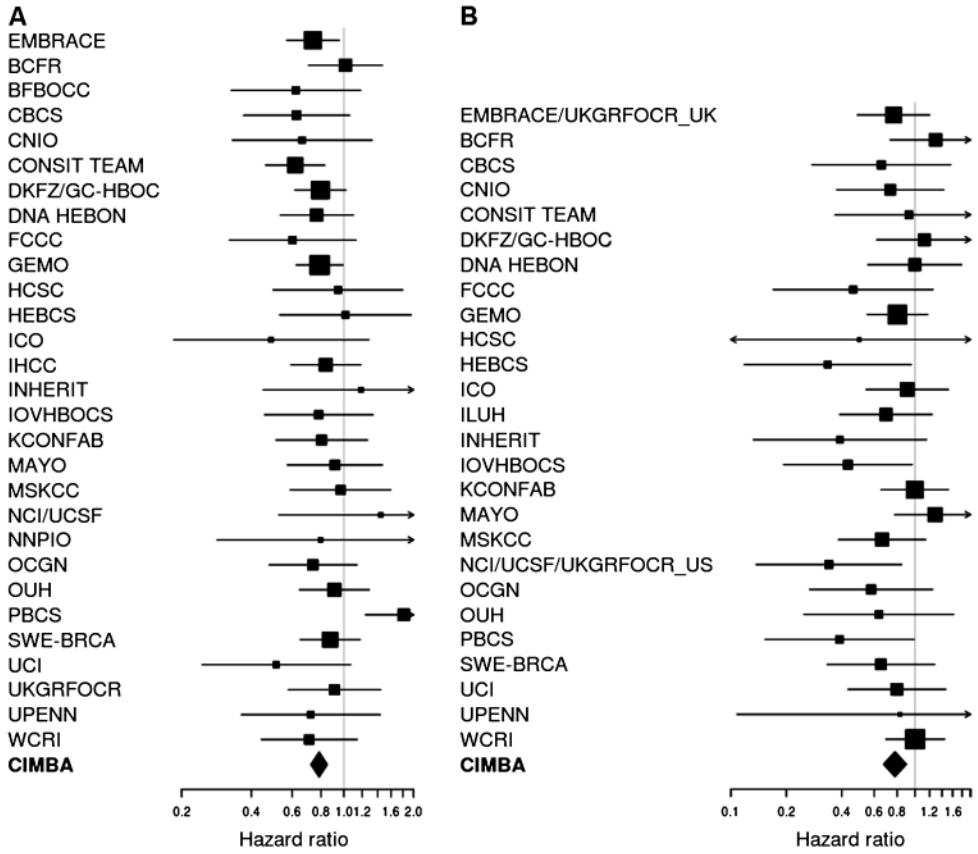

Figure 1. Forest plots of study-specific associations between the single-nucleotide polymorphism (SNP) rs3814113 and ovarian cancer risk among *BRCA1* or *BRCA2* mutation carriers. Study-specific per-allele hazard ratio estimates are presented. **A**) *BRCA1* mutation carriers. **B**) *BRCA2* mutation carriers. The **area of the square** is proportional to the inverse of the variance of the estimate. **Horizontal lines** = 95% confidence intervals; **diamonds** = the summary for all of Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). Some of the smaller studies of *BRCA2* mutation carriers have been combined with other studies from the same country. Study names are as follows: BCFR = Breast Cancer Family Registry; BFBOCC = Baltic Familial Breast and Ovarian Cancer Consortium; CBCS = Copenhagen Breast Cancer Study; CNIO = Spanish National Cancer Centre; CONSIT TEAM = CONsorzio Studi ITaliani sui Tumori Ereditari Alla Mammella; DKFZ = Deutsches Krebsforschungszentrum; DNA HEBON = HEreditary Breast and Ovarian study Netherlands; EMBRACE = Epidemiological Study of BRCA1 and BRCA2 Mutation Carriers; FCCC = Fox Chase Cancer Center; GC-HBCO = German Consortium of Hereditary Breast and Ovarian Cancer; GEMO = Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers; HCSC = Hospital Clinico San Carlos; HEBCS = Helsinki Breast Cancer Study; ICO = Institut Català d'Oncologia; IHCC = International Hereditary Cancer Centre; ILUH = Iceland Landspitali—University Hospital; INHERIT = Interdisciplinary Health Research International Team Breast Cancer Susceptibility; IOVHBOCS = Istituto Oncologico Veneto Hereditary Breast and Ovarian Cancer Study; KCONFAB = Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; MAYO = Mayo Clinic; MSKCC = Memorial Sloane Kettering Cancer Center; NCI = National Cancer Institute; NNPIO = N. N. Petrov Institute of Oncology; OCGN = Ontario Cancer Genetics Network; OUH = Odense University Hospital; PBCS = Pisa Breast Cancer Study; SWE-BRCA = Swedish Breast Cancer Study; UCI = University of California Irvine; UCSF = University of California San Francisco; UKGRFOCR = UK and Gilda Radner Familial Ovarian Cancer Registries; UPENN = University of Pennsylvania; WCRI = Women's Cancer Research Institute.

We examined the associations between ovarian cancer risk and rs3814113 by the *BRCA1* mutation class (which was based on the predicted functional consequence) and also with respect to the ovarian cancer cluster region in *BRCA2*. We found no evidence of a difference in the hazard ratio estimate by *BRCA1* mutation type (for class 1, per-allele HR of ovarian cancer = 0.78, 95% CI = 0.71 to 0.86, $P_{trend} = 6.0 \times 10^{-7}$; for class 2, per-allele HR of ovarian cancer = 0.82, 95% CI = 0.70 to 0.96, $P_{trend} = .016$ and P for difference in HRs = .87). Similarly, there was no evidence for a difference in the association between the SNP and ovarian cancer risk by mutation position in *BRCA2* (for a mutation in ovarian cancer cluster region, per-allele HR of ovarian cancer = 0.77, 95% CI = 0.62 to 0.95, $P = .015$; for a mutation not in ovarian cancer cluster region, per-allele HR of ovarian cancer = 0.77, 95% CI = 0.63 to 0.93, $P = .007$).

To determine whether SNP rs13814113 is also associated with breast cancer risk for *BRCA1* mutation carriers and *BRCA2* mutation carriers, we performed a competing risk analysis in which we estimated hazard ratios for breast and ovarian cancer simultaneously (Table 3). There was no evidence of association between this SNP and breast cancer risk for mutation carriers (for *BRCA1* mutation carriers, per-allele HR of breast cancer = 1.03, 95% CI = 0.98 to 1.10, $P_{trend} = .24$; and for *BRCA2* mutation carriers, per-allele HR of breast cancer = 0.97, 95% CI = 0.90 to 1.05, $P_{trend} = .45$). The estimates for ovarian cancer risk under this analysis were similar to those estimated in the primary analysis.

We used the rs13814113 minor allele frequency of 0.28 in the general population (23) to determine that 52% of *BRCA1* or *BRCA2* mutation carriers were expected to have the TT genotype, which is associated with the highest risk of ovarian cancer. *BRCA1*

Table 3. Competing risk analysis: genotype distribution of single-nucleotide polymorphism rs3814113 by affection status and associations with ovarian and breast cancer risk*

Gene	rs3814113 genotype	Unaffected subjects, No. (%)	Ovarian cancer patients, No. (%)	Ovarian cancer		Breast cancer patients, No. (%)	Breast cancer	
				HR (95% CI)	P†		HR (95% CI)	P†
BRCA1	TT	1569 (44.4)	699 (51.3)	1 (ref)		2208 (43.0)	1 (ref)	
	CT	1562 (44.2)	555 (40.7)	0.82 (0.71 to 0.94)		2329 (45.4)	1.07 (0.98 to 1.15)	
	CC	403 (11.4)	109 (8.0)	0.60 (0.47 to 0.76)		595 (11.6)	1.04 (0.91 to 1.18)	
	2 *df* test				2.8×10^{-5}			.28
	Per-allele analysis			0.79 (0.71 to 0.87)	4.4×10^{-6}		1.03 (0.98 to 1.10)	.24
BRCA2	TT	1012 (45.4)	191 (50.4)	1 (ref)		1502 (46.5)	1 (ref)	
	CT	969 (43.5)	159 (42.0)	0.82 (0.65 to 1.04)		1376 (42.6)	0.95 (0.85 to 1.06)	
	CC	247 (11.1)	29 (7.6)	0.61 (0.40 to 0.93)		352 (10.9)	0.96 (0.81 to 1.15)	
	2 *df* test				.042			.63
	Per-allele analysis			0.80 (0.67 to 0.95)	.012		0.97 (0.90 to 1.05)	.45
BRCA1/2 combined	TT	2581 (44.8)	890 (51.1)	1 (ref)		3710 (44.4)	1 (ref)	
	CT	2531 (43.9)	714 (41.0)	0.82 (0.73 to 0.92)		3705 (44.3)	1.02 (0.95 to 1.08)	
	CC	650 (11.3)	138 (7.9)	0.60 (0.49 to 0.74)		947 (11.3)	1.01 (0.91 to 1.12)	
	2 *df* test				1.1×10^{-6}			.89
	Per-allele analysis			0.79 (0.73 to 0.86)	1.6×10^{-7}		1.01 (0.96 to 1.06)	.73

* CI = confidence interval; HR = hazard ratio; ref = referent.

† A robust Wald test statistic was used. All statistical tests were two-sided.

mutation carriers with the TT genotype were predicted to have a risk to age 80 years of 48%, those with the TC genotype were predicted to have a risk of 40%, and those with the CC genotype were predicted to have a risk of 33%. *BRCA2* mutation carriers with the TT genotype were predicted to have a risk to age 80 years of 14%, those with the TC genotype were predicted to have a risk of 11%, and those with the CC genotype were predicted to have a risk of 9%.

Discussion

Recent studies have shown that common genetic variants associated with small increments in susceptibility to breast cancer can also modify breast cancer risks for *BRCA1* and/or *BRCA2* mutation carriers (20,21). This study demonstrated that common genetic variants modify the ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. We genotyped a 9p22.2 SNP, rs3814113, that was recently found (19) to be associated with ovarian cancer in the general population, in a cohort of 10 029 *BRCA1* mutation carriers and 5837 *BRCA2* mutation carriers. For both *BRCA1* and *BRCA2* mutation carriers, a similar reduced risk of ovarian cancer was associated with the rare allele (ie, C allele) of rs3814113 (HR of ovarian cancer = 0.78, for each group). The level of statistical significance for *BRCA1* carriers ($P = 4.8 \times 10^{-9}$) would be regarded as "genome-wide" significant in a GWAS. Although the *BRCA2* sample size was smaller, the *BRCA2* association was also clear, given that it is such a strong candidate. To our knowledge, this is the first confirmed report of a common genetic variant modifying ovarian cancer risk for either *BRCA1* or *BRCA2* mutation carriers.

When the data were analyzed within a competing risks framework, we observed no association between the SNP rs3814113 and breast cancer risk among *BRCA1* or *BRCA2* mutation carriers. None of the published breast cancer GWAS (29–33) of women from the general population have reported associations for this SNP at strict genome-wide levels of statistical significance [eg, in the largest study (34), per-allele OR = 1.06, $P = .09$]. These results indicate that, for both groups of mutation carriers and for the general population, the predominant association is with ovarian cancer risk and that the association with breast cancer risk, if any, is very weak.

This study had several limitations. It was not possible to take the precise family histories of carriers into account. Although this did not invalidate the statistical tests of association, it may have affected the hazard ratio estimates and will need to be taken into consideration if these associations are to be used in counseling. Another limitation was that at the time of analysis, we did not have detailed ovarian tumor histology data available. Future CIMBA studies will aim to assess the associations in mutation carriers by different histological subtypes. A final uncertainty was that the SNP tested is probably not the variant at this locus that is causally related to ovarian cancer, but it is correlated with the causal SNP. This did not invalidate the associations but may indicate that the association with the causal variant, when it is identified by fine mapping, will prove to be somewhat stronger.

The gene basonuclin 2 (*BNC2*), located on chromosome 9p22.2, may be a good candidate in this region that is associated

with risk of ovarian cancer. *BNC2* is the closest gene to the SNP rs3814113, which is located approximately 44 kilobases upstream of the gene. The *BNC2* gene is highly conserved across vertebrates, encodes a DNA-binding zinc-finger protein, and is proposed to have a function in nuclear processing of mRNA (35,36). This gene may potentially generate more than 2000 different proteins from 90 000 mRNA isoforms (37). *BNC2* has recently been reported (38) to be a tumor suppressor gene in esophageal adenocarcinoma. The highest level of expression of *BNC2* is in the ovary (39), indicating that *BNC2* may potentially be the relevant causal gene at the 9p22.2 locus. In addition, the high level of expression in the ovary is consistent with the observation that the association appears, to date, to be restricted to this cancer type. This locus may also be involved in oocyte development (39). Although it is not possible to assess this hypothesis directly, parity may be related to oocyte development and so may be a surrogate for oocyte development. Unfortunately, data on parity for the study subjects were not available at the time of analysis. When these data become available, further analysis stratified by parity is warranted.

The ovarian cancer hazard ratios associated with the minor allele of rs3814113 and ovarian cancer were modest and of similar magnitude for women from the general population, for *BRCA1* mutation carriers, and for *BRCA2* mutation carriers. Although these hazard ratios for ovarian cancer translated to small differences in absolute risk between different genotypes for the vast majority of women at low risk of this disease, the absolute risk differences for mutation carriers were much greater. Several additional ovarian cancer susceptibility alleles have recently been identified by GWAS (40,41) at 19p13.11, 8q24, 2q31, 3q25, and 17q21; these alleles could be strong candidates as risk modifiers for carriers. If these and other variants also prove to be associated with ovarian cancer risk for mutation carriers, such information in combination with other risk factors, such as parity and oral contraceptive use, should contribute toward the stratification of mutation carriers by ovarian cancer risk and could eventually provide information for the clinical management of *BRCA1* and *BRCA2* mutation carriers (42,43).

In conclusion, we have identified the first common allele that modifies ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. It is likely that other such modifying risk variants exist and their identification could have future implications for genetic testing and risk counseling of women with *BRCA1* and *BRCA2* mutations.

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Funding

The CIMBA data management and data analysis was supported by Cancer Research UK grants (to D.F.E. and A.C.A.). G.C.-T. founded CIMBA to provide the infrastructure to study genetic modifiers of cancer risk for *BRCA1* and *BRCA2* mutation carriers.

Breast Cancer Family Registry (BCFR): Supported by the National Cancer Institute (NCI), National Institutes of Health under RFA-CA-06-503 and through cooperative agreements with members of the BCFR and Principal Investigators (PIs), including Cancer Care Ontario (U01 CA69467), Columbia University (U01 CA69398), Fox Chase Cancer Center (U01 CA69631), Huntsman Cancer Institute (U01 CA69446), Northern California Cancer Center (U01 CA69417), University of Melbourne (U01 CA69638), and Research Triangle Institute Informatics Support Center (RFP No. N02PC45022-46). The content of this article does not necessarily reflect the views or policies of the NCI or any of the collaborating centers in the BCFR nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR.

Copenhagen Breast Cancer Study (CBCS): Supported by the Neye Foundation.

Spanish National Cancer Center (CNIO) and the Spanish Consortium: Partially supported by Fundación Mutua Madrileña, Asociación Española Contra el Cáncer, and the Spanish Ministry of Science and Innovation (FIS PI08 1120). Funded in part by the Basque Foundation for Health Innovation and Research (BIOEF) (BIO07/CA/006).

CONsorzio Studi Italiani Tumori Ereditari Alla Mammella (CONSIT TEAM): Supported by grants from Associazione Italiana per la Ricerca sul Cancro (4017) and by funds from Italian citizens who allocated the 5×1000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects "5×1000") to P.P. Supported by grants from Ministero della Salute ("Progetto Tevere"—Linea 1 RC D/08/02B—"Progetto Tumori Femminili"—F/08/0PZ—Linea1 RC CORR/08) to S.M. Supported by grants from Associazione Italiana per la Ricerca sul Cancro (8713) to L.O. Supported by grants from Ministero della Salute (Extraordinary National Cancer Program 2006, "Alleanza contro il Cancro" and Integrated Program N.5) to V.G. Supported by grants from Fondazione Italiana per la Ricerca sul Cancro (Special Project "Hereditary tumors"), Ministero della Salute (RFPS-2006-3-340203, Extraordinary National Cancer Program 2006 "Alleanza contro il Cancro," and "Progetto Tumori Femminili") and Ministero dell'Universita' e Ricerca (RBLAO3-BETH) to P.R.

Deutsches Krebsforschungszentrum (DKFZ) study: Supported by the DKFZ.

Epidemiological study of *BRCA1* and *BRCA2* mutation carriers (EMBRACE): Cancer Research UK grants (C1287/A10118 and C1287/A8874 to D.F.E., S.P., M.C., D.F., and C.O., and C8197/A10123 and C8197/A10865 to A.M.D.). National Institute for Health Research grant to the Biomedical Research Centre, Manchester (D.G.E.). The Investigators at the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust are supported by a National Institute of Health Research grant to the Biomedical Research Centre at the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust. Cancer Research UK grant (C5047/A8385 to R.E., E.B., and L.D'M.).

Fox Chase Cancer Center (FCCC): National Institutes of Health (P50 CA83638, U01 CA69631, and 5U01 CA113916 to A.K.G.); Eileen Stein Jacoby Fund.

The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC): German Cancer Aid (107054).

Genetic Modifiers of cancer risk in *BRCA1/2* mutation carriers (GEMO): Cancer Genetics Network "Groupe Génétique et Cancer," Fédération Nationale des Centres de Lutte Contre le Cancer, France, is supported by the Ligue National Contre le Cancer; Association for International Cancer Research grant (AICR-07-0454); Association "Le cancer du sein, parlons-en!" Award.

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON): Dutch Cancer Society (NKI 1998-1854, NKI 2004-3088 and NKI 2007-3756).

Hospital Clinico San Carlos: National Institute of Health Carlos III (RTICC 06/0020/0021, FIS 070359, and FIS 0900850).

Helsinki Breast Cancer Study (HEBCS): Helsinki University Central Hospital Research Fund, Academy of Finland (132473), the Finnish Cancer Society, and the Sigrid Juselius Foundation.

International Hereditary Cancer Center: State Committee for Scientific Research (PBZ_KBN_122/P05/2004).

Interdisciplinary Health Research International Team Breast Cancer Susceptibility (INHERIT BRCAs): Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program (CRN_87521); Canadian Breast Cancer Research Alliance (019511).

Istituto Oncologico Veneto—Hereditary Breast Ovarian Cancer Study: "Ministero della Salute" (RFPS 2006-5-341353, ACC2/R6.9).

KCONFAB: National Breast Cancer Foundation, the National Health and Medical Research Council (NHMRC), and the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. A.B.S. and G.C.-T. are Senior and Senior Principal Research Fellows of the NHMRC, respectively.

Mayo Clinic Study: National Institutes of Health (R01 CA128978 and P50 CA116201); Komen race for the cure (KG081527); Breast Cancer Research Foundation.

Memorial Sloane Kettering Cancer Center: Breast Cancer Research Foundation and the Lomangino Family Research Fund.

NCI: Intramural Research Program of the US NCI at the National Institutes of Health; support services contracts (NO2-CP-11019-50 and N02-CP-65504 to P.L.M. and M.H.G.) with Westat, Inc, Rockville, MD.

N.N. Petrov Institute of Oncology: Russian Foundation for Basic Research (08-04-00369-a, 10-04-92110 and 10-04-92110-a); Federal Agency for Science

and Innovations (contract 02.740.11.0780); Commission of the European Communities (PITN-GA-2009-238132); Royal Society International Joint (JP090615).

Ontario Cancer Genetics Network (OCGN): Supported by Cancer Care Ontario, Canada (I.L.A.); and the NCI, National Institutes of Health under RFA-CA-06-503 and through cooperative agreements with members of the BCFR and PIs. The content of this article does not necessarily reflect the views or policies of the NCI or any of the collaborating centers in the Cancer Family Registry (CFR) nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the CFR.

Pisa Breast Cancer Study: Fondazione Cassa di Risparmio di Pisa (122/07) and grant 2010 from Istituto Toscano Tumori.

Swedish Breast Cancer Study (SWE-BRCA): Supported by the Swedish Cancer Society.

University of California Irvine: National Institutes of Health (R01 CA74415 to SLN and Y.C.D.).

University of California San Francisco (UCSF): Clinical and Translational Science Institute at the University of California, San Francisco (to M.S.B.).

UK and Gilda Radner Familial Ovarian Cancer Registries (UKGRFOCR): UKFOCR was supported by a project grant from CRUK to P.P. Some of this work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre funding scheme.

University of Pennsylvania: Breast Cancer Research Foundation (K.L.N.); Cancer Genetics Network (HHSN21620074400C to S.M.D.).

Women's Cancer Research Institute: Supported in part by the American Cancer Society Early Detection Professorship, L & S Milken Family Foundation, and Entertainment Industry Foundation.

Notes

The authors had full responsibility in the design of the study; collection of the data, analysis, and interpretation of the data; decision to submit the article for publication; and the writing of the article.

A. C. Antoniou is a Cancer Research UK Senior Cancer Research Fellow. D. F. Easton is Cancer Research UK Principal Research Fellow.

BCFR: Samples from the FCCC, Huntsman Cancer Institute, and Cancer Prevention Institute of California were processed and distributed by the Coriell Institute for Medical Research.

Baltic Familial Breast Ovarian Cancer Consortium (BFBOCC): A special acknowledgment for Laima Tihomirova (Latvian Biomedical Research and Study Center, Riga, Latvia) for providing samples and data for joint Lithuanian-Latvian BFBOCC study.

CBCS: We thank Mette K. Andersen and Susanne Kjaergaard for clinical data.

Spanish National Cancer Center (CNIO) and the Spanish Consortium: We thank R. M. Alonso, G. Pita, and R. M. Milne for their assistance. We thank the Molecular Genetics Laboratory from Hospital de Cruces for the samples and data provided. We thank Instituto de Biología y Genética Molecular-Consejo Superior Investigaciones Científicas, Universidad de Valladolid and Junta de Castilla y León.

CONSIT TEAM: We thank Carla B. Ripamonti and Marco A. Pierotti of the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, and Bernardo Bonanni of the Istituto Europeo di Oncologia, Milan, Italy, and Laura Tizzoni and Loris Bernard of the Cogentech, Consortium for Genomic Technologies, Milan, Italy.

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FCCC We thank Ms JoEllen Weaver and Dr Betsy Bove for their technical support.

GC-HBOC: We thank Christoph Engel (GC-HBOC National Databank, Institute for Medical Genetics, Statistics and Epidemiology, University of Leipzig, Germany) for providing clinical data, Sabine Preisler-Adams (Center Münster), Ines Schönbuchner (Center Würzburg), Ursula Froster (Center Leipzig), and Dieter Schäfer (Center Frankfurt) for providing samples, and Juliane Köhler for her excellent technical assistance.

GEMO: We thank all the GEMO collaborating groups for their contribution to this study. GEMO Collaborating Centers are Coordinating Centres, Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Centre Hospitalier Universitaire de Lyon/Centre Léon Bérard, UMR5201 CNRS, Université de Lyon, Lyon: O. M. Sinilnikova, L. Barjhoux, Sophie Giraud, Mélanie Léone, S. Mazoyer; and INSERM U509, Service de Génétique Oncologique, Institut Curie, Paris: D. Stoppa-Lyonnet, Marion Gauthier-Villars, Claude Houdayer, V. Moncoutier, Muriel Belotti, Antoine de Pauw. Institut Gustave Roussy, Villejuif: Brigitte Bressac-de-Paillerets, Audrey Remenieras, Véronique Byrde, Olivier Caron, Gilbert Lenoir. Centre Jean Perrin, Clermont–Ferrand: Y.-J. Bignon, Nancy Uhrhammer. Centre Léon Bérard, Lyon: Christine Lasset, V. Bonadona. Centre François Baclesse, Caen: Agnès Hardouin, Pascaline Berthet. Institut Paoli Calmettes, Marseille: Hagay Sobol, Violaine Bourdon, Tetsuro Noguchi, François Eisinger. Groupe Hospitalier Pitié-Salpétrière, Paris: Florence Coulet, Chrystelle Colas, Florent Soubrier. CHU de Arnaud-de-Villeneuve, Montpellier: Isabelle Coupier. Centre Oscar Lambret, Lille: Jean-Philippe Peyrat, Joëlle Fournier, Françoise Révillion, Philippe Vennin, Claude Adenis. Centre René Huguenin, St Cloud: Etienne Rouleau, R. Lidereau, Liliane Demange, C. Nogues. Centre Paul Strauss, Strasbourg: Danièle Muller, Jean-Pierre Fricker. Institut Bergonié, Bordeaux: Michel Longy, Nicolas Sevenet. Institut Claudius Regaud, Toulouse: Christine Toulas, Rosine Guimbaud, Laurence Gladieff, Viviane Feillel. CHU de Grenoble: D. Leroux, Hélène Dreyfus, Christine Rebischung. CHU de Dijon: Cécile Cassini, L. Faivre. CHU de St-Etienne: F. Prieur. Hôtel Dieu Centre Hospitalier, Chambéry: S. Fert Ferrer. Centre Antoine Lacassagne, Nice: Marc Frénay. CHU de Limoges: Laurence Vénat-Bouvet. Creighton University, Omaha, NE: Henry T. Lynch.

HEBCS: We thank Dr Carl Blomqvist and Tuomas Heikkinen for their help with the patient data and samples.

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INHERIT BRCAs: J. Simard, Francine Durocher, Rachel Laframboise, Marie Plante, Centre Hospitalier Universitaire de Quebec and Laval University, Quebec, Canada; Peter Bridge, Jilian Parboosingh, Molecular Diagnostic Laboratory, Alberta Children's Hospital, Calgary, Canada; Jocelyne Chiquette, Hôpital du Saint-Sacrement, Quebec, Canada; Bernard Lesperance, Hôpital du Sacré-Cœur de Montréal, Montréal, Canada. J. Simard is Chairholder of the Canada Research Chair in Oncogenetics.

KCONFAB: We thank Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow-Up Study (funded by NHMRC 145684, 288704 and 454508) for their contributions to this resource, and the many families who contribute to kConFab.

OCGN: We thank Mona Gill, Lucine Collins, Nalan Gokgoz, Teresa Selander, Nayana Weerasooriya and members of the Ontario Cancer Genetics Network for their contributions to the study.

SWE-BRCA: P. Karlsson, Margareta Nordling, Annika Bergman, and Zakaria Einbeigi, Gothenburg, Sahlgrenska University Hospital; M. Stenmark-Askmalm and Sigrun Liedgren, Linköping University Hospital; Å. Borg, Niklas Loman, H. Olsson, U. Kristoffersson, Helena Jernström, Katja Harbst, and Karin Henriksson, Lund University Hospital; A. Lindblom, B. Arver, Anna von Wachenfeldt, Annelie Liljegren, Gisela Barbany-Bustinza, and Johanna Rantala, Stockholm, Karolinska University Hospital; Beatrice Melin, Henrik Grönberg, Eva-Lena Stattin, and Monica Emanuelsson, Umeå University Hospital; Hans Ehrencrona, Richard Rosenquist Brandell, and Niklas Dahl, Uppsala University Hospital.

UCSF: We thank Ms Salina Chan for her database support and management and to Ms Beth Crawford for her genetic counseling services.

UKGRFOCR: UKFOCR thank Carole Pye, Patricia Harrington, and Eva Wozniak for family recruitment and technical support. GRFOCR would like to acknowledge Lara Sucheston (Department of Cancer Prevention and Control) and Kunle Odunsi (Departments Gynecologic Oncology and Immunology). We would like to acknowledge the Roswell Park Alliance Foundation for their continued support of the Gilda Radner Ovarian Family Cancer Registry.

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Petrov Institute of Oncology, St-Petersburg, Russia (ENI); Vilnius University Hospital Santariskiu Clinics, Hematology, Oncology and Transfusion Medicine Center, Vilnius, Lithuania (RJ); Hereditary Cancer Program, Catalan Institute of Oncology, Barcelona, Spain (IB, CL); Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY (KBM); Women's Cancer Research Institute at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, CA (BYK, JG); University of California, San Francisco (UCSF) Cancer Risk Program and Department of Medicine, Department of Epidemiology, and Department of Biostatistics, UCSF, San Francisco, CA (MSB); Centre of Familial Breast and Ovarian Cancer, Department of Gynaecology and Obstetrics and Centre for Integrated Oncology (CIO), University hospital of Cologne, Germany (RS, BW); Department of Gynaecology and Obstetrics, Division of Tumor Genetics, Klinikum rechts der Isar, Technical University Munich, Germany (AM); Department of Gynaecology and Obstetrics, Ludwig- Maximillians University Munich, Germany (IR); Institute of Human Genetics, University of Regensburg, Regensburg, Germany (BF); Institute of Human Genetics, Department of Human Genetics, Laboratory of Molecular Genetics, University of Heidelberg, Heidelberg, Germany (CS); Department of Gynaecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Germany (NA); Department of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany (HD); Institute of Human Genetics, Campus Virchov Klinikum, Charite Berlin, Germany (RV-M); Department of Gynaecology and Obstetrics, University Hospital Carl Gustav Carus, Technical University Dresden, Germany (KK); Department of Gynaecology and Obstetrics, University Hospital Düsseldorf, Heinrich-Heine University Düsseldorf, Germany (DN); Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover, Germany (DG); Molecular Oncology Laboratory, Hospital San Carlos, Madrid, Spain (TC, MdlH); Helsinki University Central Hospital, Department of Obstetrics and Gynecology, Helsinki, Finland (HN); Helsinki University Central Hospital, Department of Clinical Genetics, Helsinki, Finland (KA); Cancer Genomics Laboratory, Centre Hospitalier Universitaire de Québec and Laval University, Quebec, Canada (JS, PS); Cancer Research United Kingdom Genetic Epidemiology Unit, University of Cambridge, Strangeways Research Laboratory, Cambridge, United Kingdom (DFE).