Population BRCA1 and BRCA2 Mutation Frequencies and Cancer Penetrances: A Kin–Cohort Study in Ontario, Canada

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Background: **BRCA1 and BRCA2 mutations in general populations and in various types of cancers have not been well characterized. We investigated the presence of these mutations in unselected patients with newly diagnosed incident ovarian cancer in Ontario, Canada, with respect to cancers reported among their relatives.** ***Methods:*** **A population series of 1171 unselected patients with incident ovarian cancer diagnosed between January 1, 1995, and December 31, 1999, in Ontario, Canada, was screened for germline mutations throughout the BRCA1 and BRCA2 genes. Screening involved testing for common variants, then protein truncation testing of long exons, and then denaturing gradient gel electrophoresis or denaturing high-performance liquid chromatography for the remainder of BRCA1 and BRCA2, respectively. Cox regression analysis was used to examine cancer outcomes reported by the case probands for their 8680 first-degree relatives. Population allele frequencies and relative risks (RRs) were derived from the regression results by an extension of Saunders–Begg methods. Age-specific Ontario cancer incidence rates were used to estimate cumulative incidence of cancer to age 80 years by mutation status.** ***Results:*** **Among 977 patients with invasive ovarian cancer, 75 had BRCA1 mutations and 54 had BRCA2 mutations, for a total mutation frequency of 13.2% (95% confidence interval [CI] = 11.2% to 15.5%). Higher risks for various cancer types in the general Ontario population were associated with BRCA1 mutation carriage than with noncarriage, including ovarian (RR = 21, 95% CI = 12 to 36), female breast (RR = 11, 95% CI = 7.5 to 15), and testis (RR = 17, 95% CI = 1.3 to 230) cancers. Higher risks were also associated with BRCA2 mutation carriage than with noncarriage, particularly for ovarian (RR = 7.0, 95% CI = 3.1 to 16), female and male breast (RR = 4.6, 95% CI = 2.7 to 7.8, and RR = 102, 95% CI = 9.9 to 1050, respectively), and pancreatic (RR = 6.6, 95% CI = 1.9 to 23) cancers. Cancer risks differed according to the mutation's position in the gene. Estimated cumulative incidence to age 80 years among women carrying BRCA1 mutations was 24% for ovarian cancer and 90% for breast cancer and among women carrying BRCA2 mutations was 8.4% for ovarian cancer and 41% for breast cancer. For the general Ontario population, estimated carrier frequencies of BRCA1 and BRCA2 mutations, respectively, were 0.32% (95% CI = 0.23% to 0.45%) and 0.69% (95% CI = 0.43% to 1.10%).** ***Conclusions:*** **BRCA1 and BRCA2 mutations may be more frequent in general populations than previously thought and may be associated with various types of cancers. [J Natl Cancer Inst 2006;98:1694–706]**

BRCA1 and BRCA2 mutations in general populations and in various types of cancers have not been well characterized. Germline mutations in these genes account for cancer predisposition in the majority of families with the breast–ovarian cancer syndrome *(1,2)*. In unselected or western populations, estimates of the proportions of ovarian cancer attributable to these mutations range from 1.2% to 13% for BRCA1 mutations *(3–17)* and from 0.0% to 6.0% for BRCA2 mutations *(5,6,8,9,11,15–19)*. The low carriage frequency and high cost of testing for many mutations make it impractical to screen the general population directly. Results of family studies and segregation analyses have indicated that a general or mixed western population frequency for mutations in both genes combined is between 0.06% and 0.26% *(20–23)*, with most estimates toward the lower end of this range.

Information on the proportion of normal individuals and cancer patients carrying mutations in the BRCA1 and BRCA2 genes and on risks for cancer associated with these mutations is important for genetic screening and counseling of patients with cancer and of women with family histories of cancer. Cancer risks associated with carrying a BRCA1 or BRCA2 mutation may extend beyond ovarian and breast cancer, may differ among the various mutations within the genes, and may also apply to males. We investigated these mutations among 1171 unselected patients with newly incident ovarian cancer in Ontario, Canada, with respect to cancers reported among their relatives.

Participants and Methods

Participants

In the Canadian province of Ontario, all patients diagnosed from January 1, 1995, through December 31, 1999, with invasive epithelial ovarian tumors and from January 1, 1995, through

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December 31, 1997, with borderline ovarian tumors were identified by monitoring acquisitions of the Ontario Cancer Registry. For each patient, the investigators reviewed pathology reports to determine eligibility and tumor histologic type. Patients were between 20 and 79 years of age and resident in Ontario at the time of diagnosis of a new primary epithelial ovarian tumor. Of 2338 eligible patients, we were able to obtain and test blood samples from 1171 (50%), of whom 977 had invasive ovarian cancer and 194 had borderline tumors. Reasons for nonparticipation of the other patients included death (696 patients), subject refusal (169 patients), subject too ill (154 patients), physician refusal (40 patients), and inability to locate (108 patients). Family histories were taken from the patients by telephone interview. Styrofoam-packed venipuncture kits with informed consent forms were mailed to subjects, who had blood samples drawn locally and then returned the blood samples and signed consent forms by prepaid courier. All participants were offered the option of receiving their genetic testing results, in the context of a counseling clinic through the study team or through counseling clinics elsewhere in the province. The study was approved by the institutional review boards of the University of Toronto and Yale University. An analysis of the first 649 patients from January 1, 1995, through December 31, 1997, that used somewhat different statistical methodology has been published previously *(9)*.

BRCA1 and BRCA2 Analysis

Lymphocyte DNA was prepared from whole blood. All samples were screened for 11 common mutations (seven in BRCA1 and four in BRCA2), including the three mutations common to Ashkenazi Jews and others of eastern European ancestry and six mutations previously identified in the French Canadian population *(24)*. Nine of these mutations were assayed using a rapid multiplex method *(25)*. We tested separately for the presence of the 6-kilobase (kb) duplication in exon 13 of BRCA1 *(26)* and for the mutation 546G>T in exon 7 of BRCA1.

If no mutations were found, exon 11 of BRCA1 and exons 10 and 11 of BRCA2 were then screened with the protein truncation test. Primer sequences used to amplify overlapping fragments were obtained from the Breast Cancer Information Core (BIC) *(27)*. The protein truncation test, using [^{35}S]methionine and [^{35}S]cysteine (New England Nuclear, Wellesley, MA) for protein detection, was performed with the TNT rabbit reticulocyte lysate system (Promega, Madison, WI).

Patients who did not carry mutations by the preceding methods were then screened for additional BRCA1 and BRCA2 mutations. For other BRCA1 mutations, fluorescent multiplex denaturing gradient gel electrophoresis (DGGE) *(28)* was used. All the remaining coding exons, the exon–intron boundaries, and the beginning and end of exon 11 were included; noncoding exons 1a and 1b and the noncoding part of exon 24 were excluded. For the additional BRCA2 mutations, denaturing high-performance liquid chromatography (DHPLC) was used to screen the remaining coding exons and exon–intron boundaries *(29)*.

All variants identified by protein truncation test, DGGE, and DHPLC were confirmed by direct DNA sequencing (Promega). All the observed mutations included in this report are highly likely to be deleterious. The various founder mutations are deleterious, and the protein truncation test identifies mutations associated with shortened, nonfunctional proteins. The mutations found by DGGE or DHPLC are substitutions producing premature termination codons, which are also associated with nonfunctional truncated proteins, or are mutations that have been reported previously and, as documented in the BIC database *(27)* or elsewhere *(30)*, are deleterious.

Statistical Analysis

P values in all results are two-sided. Confidence intervals (CIs) for mutation frequencies were calculated by assuming binomial distributions of the observed numbers of patients. Relative risks (RRs) of cancer in family members by BRCA1 and BRCA2 mutation status of the proband case were determined by Cox proportional hazards regression, with relatives of patients not carrying mutations as baseline. An extended version of the Generalized Linear Interactive Modeling (GLIM) computer program *(31)* that includes Cox regression was used for calculations. Each of the 8680 family members was assumed to be at risk until diagnosis of the cancer of interest, death, or age at the time the family history was reported. Only first-degree relatives were used for the Cox regression analysis, and proband patients were not included as outcomes. Relative risks for cancer in the general population were calculated by the Saunders–Begg method *(32)*. Confidence intervals for the population relative risks were obtained from the Cox regression variance estimates by the delta method *(33)*. For breast, ovarian, colorectal, and prostate cancers, the proportional hazards assumption was examined by plotting the empirical log cumulative hazard versus survival time for relatives of noncarriers, BRCA1 mutation carriers, and BRCA2 mutation carriers. These plots showed the genotype-specific log cumulative hazards to be highly parallel. There were too few other types of cancers among relatives to assess adequately the proportionality assumption for those cancers.

To examine relative risk according to mutation location within the gene coding sequence, we created a series of indicator variables. For each observed mutation location, the indicator variable associated with that index location had value 1 if a subject carried a mutation within 500 nucleotides (for BRCA1) or 1100 nucleotides (for BRCA2) of the location, and 0 otherwise. We carried out a series of Cox regressions, each including one indicator variable adjusted for carriage of the other type of mutation. For example, for BRCA1 location 3053 (corresponding to 3053T>G), the indicator variable was 1 for subjects related to probands carrying mutations between locations 2553 and 3553. This variable was entered into Cox regression, adjusted for the fact of proband carriage of a BRCA2 mutation. Resulting relative risks were transformed by the Saunders–Begg calculation *(32)* and plotted at the index location abscissa. This procedure was repeated for each indicator variable to obtain a series of plotted points for graphical purposes. A smooth line was drawn through the points by use of software that was based on a cubic-spline algorithm (unpublished software).

With knowledge of the frequency of BRCA1 and BRCA2 mutations among ovarian cancer patients and the general population relative risk of ovarian cancer associated with these mutations, the frequency of BRCA1 and BRCA2 mutations in the general population can be estimated. Formulas for these estimates and their derivation are in the Technical Appendix. The delta method was also used to calculate confidence intervals for the general population mutation frequencies.

Cumulative incidence of cancer to age 80 years for all cancer sites was based on Ontario general population age-specific incidence

and mortality data for January 1, 1993, through December 31, 2002 *(34–37)*. The DevCan computer program *(38)*, which takes into account other-cause mortality *(39,40)*, was used to calculate cancer site-specific incidence to age 80 years according to mutation status. For each cancer site, relative risks applicable to noncarriers and to BRCA1 and BRCA2 mutation carriers were multiplied by a common factor so that the sum of incidence to age 80 years for these three classes of individuals totaled the population incidence to age 80 years. Details of this calculation and the determination of variance estimates are in the Technical Appendix.

Results

Among the 977 proband patients in our study with invasive ovarian cancer, 129 mutations were identified (13.2%, 95% CI = 11.2% to 15.5%), 75 in the BRCA1 gene and 54 in the BRCA2 gene (Table 1). No mutations were found in the 194 patients with borderline tumors. Two of the 129 patients were sisters who had the same mutation.

Among the 75 patients carrying BRCA1 mutations, 24 were identified in the screens for individual mutations, 38 by protein truncation test of exon 11, and 13 by DGGE. We observed 40 distinct BRCA1 mutations (Table 1), including 13 identified more than once. Two intronic mutations (IVS4-1 G>T and IVS16+6 T>G) were found. In our proband series, nine women carried the BRCA1 185delAG mutation and eight the 5382insC mutation. One of the nine with the 185delAG mutation was non-Jewish and of Pakistani origin. None of the eight probands with the 5382insC mutation identified herself as Jewish or was known to be Jewish. Three probands of Italian ethnicity carried the 1479delAG mutation. We also identified six probands with the 6-kb duplication mutation in exon 13. The ancestry of all six of these women was from the British Isles in full or in part.

For BRCA2, 41 of the 54 mutations were identified by protein truncation test and five by DHPLC. There were 40 distinct BRCA2 mutations (Table 1). Three French Canadian founder mutations (2816insA, 6085G>T, and 8765delAG) were observed. Three patients of British Isles ancestry carried 6633del5 mutations, as did one woman of Japanese origin. The 6174delT mutation was also seen in four patients, of whom two were Jewish. Only 24–27 of the 54 BRCA2 mutations occurred within the ovarian cancer cluster region (OCCR), depending on the definition of the OCCR (an interval of BRCA2 exon 11 variously defined as starting from nucleotides 3059–4075 and ending at 6503–6629) *(41,42)*.

Frequencies of mutations by age, ethnic group, and tumor histology are shown in Table 2. The age distributions of the case patients with BRCA1 and with BRCA2 mutations were different. The average age of diagnosis of ovarian cancer for patients with BRCA1 mutations was 52.6 years, whereas that of patients without mutations was 57.3 years ($P = .002$), which was similar to the average age of diagnosis of the 54 case patients with BRCA2

Table 1. BRCA1 and BRCA2 mutations detected in 1171 patients with ovarian cancer in Ontario, Canada*

BRCA1				BRCA2			
Age, y	Exon	Mutation	Ethnicity	Age, y	Exon	Mutation	Ethnicity
37	2	185delAG†	Ashkenazi Jewish	45	10	1257delA†	Mixed European
41	2	185delAG†	Ashkenazi Jewish	43	10	1493delA	Mixed European
42	2	185delAG	Ashkenazi Jewish	45	10	1538del4	Mixed European
46	2	185delAG†	Indo-Pakistani	53	10	1538del4	Italian
48	2	185delAG	Ashkenazi Jewish	45	10	2042insA	British Isles
59	2	185delAG†	Ashkenazi Jewish	65	10	2042insA	British Isles
66	2	185delAG†	Ashkenazi Jewish	60	11	2515delC	Mixed European
68	2	185delAG	Ashkenazi Jewish	62	11	2816insA	British Isles
74	2	185delAG	Ashkenazi Jewish	51	11	2814del7†	Mixed European
49	I4‡	IVS4-1 G>T†	British Isles	47	11	3034delAAAC	Mixed European
42	5	297C>T	Mixed European	66	11	3034delAAAC	British Isles
45	5	300T>G†	Slavic	66	11	3036delACAA	Greek
50	5	300T>G†	Mixed European	67	11	3908delTG†	British Isles
54	5	300T>G	Mixed European	50	11	4005delTT	French Canadian
42	11	962del4†	Slavic	72	11	4075delGT†	British Isles
65	11	962del4†	Mixed European	46	11	4206ins4	Mixed European
47	11	1014delGT	Indo-Pakistani	62	11	4510insT†	Italian
59	11	1014delGT	Indo-Pakistani	66	11	4705del4	British Isles
52	11	1048delA	British Isles	59	11	4706del4	British Isles
50	11	1081G>A†	French Canadian	62	11	4706del4†	British Isles
52	11	1081G>A†	Mixed European	49	11	4859delA†	Filipino
54	11	1081G>A	French Canadian	66	11	4866delT	Mixed European
46	11	1294del40	British Isles	71	11	5087T>G†	British Isles
60	11	1294del40†	British Isles	51	11	5102delAA†	Mixed European
43	11	1479delAG†	Italian	73	11	5102delAA†	British Isles
62	11	1479delAG†	Italian	65	11	5302insA†	Italian
67	11	1479delAG	Italian	49	11	5572C>T	Indo-Pakistani
47	11	1510insG	Native Canadian	47	11	5573delAA	French Canadian
49	11	1768delA†	Indo-Pakistani	49	11	5700insA	British Isles
31	11	1959A>T	Mixed European	56	11	5910C>G†	British Isles
49	11	2072del4	Slavic	57	11	5950delCT	Japanese
47	11	2080delA†	Mixed European	67	11	6085G>T	French Canadian
48	11	2190delA†	British Isles	44	11	6174delT†	Mixed European
42	11	2274A>T	Italian	53	11	6174delT†	Ashkenazi Jewish
41	11	2457C>T	Mixed European	58	11	6174delT	Mixed European

(Table continues)

Table 1 (continued).

BRCA1				BRCA2			
Age, y	Exon	Mutation	Ethnicity	Age, y	Exon	Mutation	Ethnicity
55	11	2524delTG†	Mixed European	66	11	6174delT	Mixed European
63	11	2681insGC	British Isles	66	11	6181delTC†	Mixed European
65	11	2681insGC	British Isles	57	11	6503delTT†	British Isles
52	11	2800delAA†	French Canadian	51	11	6602insA†	Mixed European
58	11	2838del4	Slavic	43	11	6633delCTTAA	British Isles
42	11	2819delTT†	British Isles	50	11	6633delCTTAA	British Isles
37	11	2953delGT	Mixed European	53	11	6633delCTTAA	British Isles
39	11	2953delGTA/insC†	French Canadian	65	11	6633delCTTAA†	Japanese
45	11	2953delGTA/insC	French Canadian	56	11	6819delTG	Italian
78	11	3053T>G†	Mixed European	47	11	6872delACTC	British Isles
52	11	3092del7	Mixed European	60	11	6872delACTC†	Mixed European
48	11	3118delA	British Isles	64	11	6872delACTC	British Isles
54	11	3375insGA†	British Isles	57	19	8568delTAAC	Filipino
53	11	3768insA†	French Canadian	48	20	8765delAG†	French Canadian
42	11	3819delGTAAA†	Slavic	65	20	8765delAG	French Canadian
50	11	3819delGTAAA	Mixed European	71	20	8803delC	British Isles
39	11	3875delGTCT†	Italian	54	23	9345G>A	Mixed European
49	11	3875delGTCT	Italian	71	26	9827C>G	British Isles
57	11	3875delGTCT†	Italian	40	27	9894delT†	Mixed European
46	11	3879insT†	British Isles				
71	12	4236G>T†	Italian				
39	13	6-kb duplication	British Isles				
46	13	6-kb duplication†	British Isles				
46	13	6-kb duplication†	Mixed European				
49	13	6-kb duplication†	British Isles				
56	13	6-kb duplication	Mixed European				
68	13	6-kb duplication	Mixed European				
47	13	4446C>T†	French Canadian				
48	I16‡	IVS16+6 T>G†	Mixed European				
59	18	5225delA	Italian				
53	20	5370C>T†	Mixed European				
31	20	5382insC	Slavic				
40	20	5382insC	British Isles				
46	20	5382insC†	Slavic				
49	20	5382insC	Slavic				
49	20	5382insC	Mixed European				
50	20	5382insC†	Greek				
72	20	5382insC†	Mixed European				
72	20	5382insC	Mixed European				
46	21	5398del55	Mixed European				

*All ethnicities are non-Jewish, except as indicated. kb = kilobase.

†Mutations reported previously *(9)*.

‡Intronic mutation.

mutations (i.e., 58.8 years). Frequency of mutation carriage varied substantially by ethnic group. A high mutation frequency was seen for probands of Jewish (29%), Italian (26%), and Indo-Pakistani (36%) ancestry. Total mutation frequency for probands of British Isles ancestry was 7.4% (3.1% for BRCA1 mutations and 4.3% for BRCA2 mutations). Mutation frequency also differed according to tumor histologic classification. As noted above, no probands with borderline tumors carried BRCA1 or BRCA2 mutations. Moreover, none of the 169 patients with mucinous tumors carried mutations in either gene. One hundred ten (85%) of the 129 probands with mutations had invasive serous ovarian cancers. Such cancers represent 52% of all cancers examined in this study.

Family history also predicted the presence of a mutation (Table 3). The highest mutation frequency (49%, 95% CI = 35% to 68%) was found in probands whose mothers had had ovarian cancer. More generally, 64 (26%, 95% CI = 21% to 32%) of the 247 probands who had first-degree relatives affected by breast or ovarian cancer carried mutations. In contrast, mutations were observed in 65 (7.0%, 95% CI = 5.6% to 8.9%) of the 924 probands who reported no first-degree relatives with breast or ovarian cancer. Defining potential familiality as having a first-degree relative with ovarian cancer or with breast cancer at an age younger than 60 years or as having a combination of two or more first- or second-degree relatives with breast or ovarian cancer, we found 34% (95% CI = 29% to 41%) of such case probands to carry mutations. Probands with both invasive serous cancers and potential familiality had a higher frequency of mutation, 41% (95% CI = 34% to 49%). Forty-nine (65%, 95% CI = 55% to 77%) of 75 case probands with BRCA1 mutations had both invasive serous ovarian tumors and potential familiality, compared with 22 (41%, 95% CI = 30% to 56%) of the 54 with BRCA2 mutations ($P = .006$).

We found increased relative risks of ovarian cancer associated with being a first-degree female relative of a proband carrying a mutation (for BRCA1 mutation carriers, RR = 10.3, 95% CI = 6.01 to 17.6; for BRCA2 mutation carriers, RR = 3.46, 95% CI = 1.55 to 7.72). Using these values and the frequencies of these mutations in our patient series (see Technical Appendix for details), we calculated the frequencies of mutation carriage in

Table 2. Frequency of mutations in patients with ovarian cancer by age, ethnicity, and tumor histology

Category	No. (%*) positive for mutations			Total No. of included patients	Total No. of eligible patients†
	BRCA1	BRCA2	Either		
Age group, y					
≤40	9 (5.7)	1 (0.64)	10 (6.4)	157	227
>40 but ≤50	36 (14)	17 (6.6)	53 (21)	256	466
>50 but ≤60	17 (5.4)	15 (4.8)	32 (10)	316	600
>60	13 (2.9)	21 (4.8)	34 (7.7)	442	1045
All ages	75 (6.4)	54 (4.6)	129 (11)	1171	2338
Selected ethnicities‡					
French Canadian	7 (5.6)	5 (4.0)	12 (9.7)	124	
Ashkenazi Jewish	8 (23)	2 (5.7)	10 (29)	35	
Indo-Pakistani	4 (29)	1 (7.1)	5 (36)	14	
East Asian	0 (0.0)	2 (12)	2 (12)	16	
Italian	9 (18)	4 (8.0)	13 (26)	50	
Slavic	8 (14)	0 (0.0)	8 (14)	57	
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)	15	
British Isles	15 (3.1)	21 (4.3)	36 (7.3)	490	
Mixed European	22 (7.1)	16 (5.2)	38 (12)	309	
Tumor histology					
Invasive	75 (7.7)	54 (5.5)	129 (13)	977	2060
Serous	62 (10)	48 (7.9)	110 (18)	610	1365
Endometrioid/clear cell	13 (4.9)	6 (2.2)	19 (7.1)	268	506
Mucinous	0 (0.0)	0 (0.0)	0 (0.0)	91	164
Other	0 (0.0)	0 (0.0)	0 (0.0)	8	25
Borderline	0 (0.0)	0 (0.0)	0 (0.0)	194	278

*Percentages are according to the total number of included patients in the corresponding category (row).

†As identified.

‡Ethnicity information was unavailable for nonparticipant patients.

the general Ontario population (Table 4). The estimated carrier frequencies of BRCA1 and BRCA2 mutations, respectively, were 0.32% (95% CI = 0.23% to 0.45%) and 0.69% (95% CI = 0.43% to 1.10%), for a total carriage frequency of 1.01%, approximately 1 in 99 persons. To validate our methods, we calculated the carriage frequency for Ashkenazi Jews, based on the small numbers of them included in our sample (see Table 2). The frequencies of mutation carriage, 1.27% (95% CI = 0.61% to 2.64%) for BRCA1 and 0.86% (95% CI = 0.20% to 3.63%) for BRCA2 (Table 4), were consistent with published population values for Ashkenazim, averaging 1.22% for BRCA1 and 1.23% for BRCA2 *(43–46)*. Finally, we again calculated the frequencies

Table 3. Frequency of mutations in patients with ovarian cancer by personal or family history of breast or ovarian cancer

Category	No. (%*) positive for mutations			Total No. of patients
	BRCA1	BRCA2	Either	
Mother with†				
Breast cancer	14 (14)	9 (8.8)	23 (23)	102
Ovarian cancer	13 (37)	4 (11)	17 (49)	35
Neither cancer	48 (4.6)	41 (4.0)	89 (8.6)	1035
Sister with				
Breast cancer	22 (21)	8 (7.5)	30 (28)	106
Ovarian cancer	8 (26)	3 (9.7)	11 (35)	31
Neither cancer‡	33 (4.3)	28 (3.7)	61 (8.0)	762
Any first-degree female relative with				
Breast cancer	31 (15)	14 (6.9)	45 (22)	203
Ovarian cancer	21 (31)	7 (10)	28 (42)	67
Neither cancer§	30 (3.2)	35 (3.8)	65 (7.0)	924
Proband case with				
Previous breast cancer	16 (32)	5 (10)	21 (42)	50
No previous breast cancer	59 (5.3)	49 (4.4)	108 (9.6)	1121
Potential familiality‖				
All histologic types	56 (24)	25 (11)	81 (34)	238
Invasive serous only	49 (28)	22 (13)	71 (41)	175
No potential familiality	19 (2.0)	29 (3.1)	48 (5.1)	933

*Percentages are according to the total number of patients in the corresponding category (row).

†One mother was reported to have had both breast and ovarian cancers.

‡Among the 76% of patients having at least one sister.

§No first-degree female relative with breast or ovarian cancer.

‖Potential familiality defined as having a first-degree relative with breast cancer who was diagnosed at an age of younger than 60 years or ovarian cancer at any age or as having a combination of two or more first- or second-degree relatives with breast or ovarian cancer.

Table 4. Calculated frequency of BRCA1 and BRCA2 mutation carriage in various populations

Population and gene	Frequency, % (95% confidence interval)	No. of subjects positive/total No. tested
General population of Ontario, Canada		
BRCA1	0.32 (0.23 to 0.45)	75/1171
BRCA2	0.69 (0.43 to 1.10)	54/1171
Total	1.01 (0.64 to 1.59)	
Ashkenazi Jews (this study)*		
BRCA1	1.27 (0.61 to 2.64)	8/35
BRCA2	0.86 (0.20 to 3.63)	2/35
Total	2.12 (0.98 to 4.60)	
Ashkenazi Jews†		
BRCA1	1.17 (0.90 to 1.51)	367/1510
BRCA2	1.29 (0.85 to 1.95)	138/1444
Total	2.45 (1.70 to 3.54)	

*The Ashkenazi Jewish subjects in this study as shown above and in Table 2.

†The Ashkenazi Jewish subjects from published studies of mutation frequencies among such patients with ovarian cancer *(43–46)*.

of mutation carriage for Ashkenazi Jews by use of Ashkenazi Jewish BRCA1 and BRCA2 mutation frequencies in ovarian cancer from published studies *(9,47–54)*. We found the frequencies, 1.17% (95% CI = 0.90% to 1.51%) for BRCA1 and 1.29% (95% CI = 0.85% to 1.95%) for BRCA2 (Table 4), again to be close to the published population estimates for this ethnic group.

General population relative risks for ovarian and other cancers are given in Table 5. Statistically significant higher risks associated with BRCA1 mutation carriage than with noncarriage were seen for ovarian cancer (RR = 21, 95% CI = 12 to 36), female breast cancer (RR = 11, 95% CI = 7.5 to 15), and testis cancer (RR = 17, 95% CI = 1.3 to 230). Aside from these types, statistically significantly elevated risks were observed for cancers of the stomach, kidney and bladder, and hepatobiliary tract; for leukemias and lymphomas; and for all cancer sites combined among females.

Statistically significant increased risks were also associated with carriage of BRCA2 mutations (Table 5), particularly for ovarian cancer (RR = 7.0, 95% CI = 3.1 to 16), female and male breast cancer (RR = 4.6, 95% CI = 2.7 to 7.8, and RR = 102, 95% CI = 9.9 to 1050, respectively), and pancreatic cancer (RR = 6.6, 95% CI = 1.9 to 23). Statistically significantly increased risk was seen for prostate cancer and for all cancer sites combined among women. Among men, increased risk for all cancer sites combined was associated with BRCA1 or BRCA2 mutation (RR = 1.6, 95% CI = 1.1 to 2.5). The population attributable risks for ovarian and breast cancer associated with BRCA1 and BRCA2 mutations combined were 9.6% (95% CI = 4.0% to 15%) and 5.3% (95% CI = 2.8% to 7.7%), respectively.

Table 6 presents population cumulative incidence to age 80 years for the various types of cancers, according to carriage of BRCA1 or BRCA2 mutation. We estimated that 24% of BRCA1 mutation carriers and 8.4% of BRCA2 mutation carriers would be diagnosed with ovarian cancer by age 80 years. The corresponding estimates for female breast cancer were 90% and 41%, respectively. The remaining individual cancer sites had cumulative incidence to age 80 years of less than 10%, except for leukemias, male breast cancer, and prostate cancer. The estimated cumulative incidence to age 80 years of cancer of any type was approximately 100% among female BRCA1 mutation carriers and 73% for female BRCA2 mutation carriers. Cumulative incidence of any cancer type for male mutation carriers was almost 60%.

Finally, we examined population relative risks of breast and ovarian cancers according to position of the BRCA1 or BRCA2 mutation in the coding sequence of the gene (Figs. 1 and 2). For this analysis, we assumed that the position of the 6-kb duplication in exon 13 of BRCA1 was at nucleotide 4497 because it results in an abnormal ter1460 (stop codon) in the mRNA *(26)*. For breast cancer in women, we observed a trend of increasing risk associated with increasing downstream location of BRCA1 mutation (continuous linear $P_{trend} = .15 \times 10^{-19}$; a 32% increase in risk associated with each additional 10%, or 559 nucleotides, of downstream distance). For BRCA2, compared with no mutation, we found increased risk associated with mutations outside of the OCCR (defined as nucleotides 3035–6629; RR = 9.2, 95% CI = 5.4 to 16) but not with mutations in the OCCR (RR = 1.0, 95% CI = 0.18 to 5.9). These results were similar regardless of which published endpoints of the OCCR were used *(41,42)*, and the increase was more strongly associated with mutations located distal to the OCCR (Fig. 2).

For ovarian cancer, we observed the greatest increased risks associated with BRCA1 mutations located in the central portion of the coding sequence and smaller increased risks associated with mutations on the 3′ side of that region (Fig. 1). This observation was opposite to the pattern of breast cancer risks associated with BRCA1 mutations. In BRCA2, ovarian cancer risks were fairly constant across the coding sequence, with a mild excess observed in the OCCR and toward the 3′ end.

Most other cancer sites were not differentially affected by BRCA2 mutations located inside or outside of the OCCR.

Table 5. Population relative risks and 95% confidence intervals of cancer by mutation status and cancer site*

Cancer site	BRCA1	BRCA2
Ovary	21 (12 to 36)	7.0 (3.1 to 16)
Breast		
Females	11 (7.5 to 15)	4.6 (2.7 to 7.8)
Males	–†	102 (9.9 to 1050)
Colorectum	–†	1.3 (.35 to 5.1)
Stomach	4.8 (1.5 to 15)	3.4 (.87 to 13)
Lung	1.3 (.30 to 5.6)	.46 (.020 to 11)
Kidney, bladder	4.4 (1.5 to 13)	–†
Leukemias, lymphomas, etc	3.7 (1.5 to 9.5)	–†
Liver, gallbladder, bile duct	8.1 (2.0 to 33)	4.6 (.73 to 28)
Prostate	.65 (.051 to 8.3)	2.7 (1.1 to 7.1)
Pancreas	3.1 (.45 to 21)	6.6 (1.9 to 23)
Uterus	1.7 (.17 to 17)	1.6 (.15 to 16)
Testis	17 (1.3 to 230)	–†
All cancers		
Females	6.7 (5.0 to 8.8)	3.0 (2.0 to 4.5)
Males	1.6 (.87 to 2.9)	1.6 (.85 to 2.9)

*Cancers analyzed from among 534 first-degree relatives of patients with BRCA1 mutations, 446 first-degree relatives of patients with BRCA2 mutations, and 7700 first-degree relatives of patients with no mutations. Ovarian and uterine cancers were analyzed from female relatives only, prostate and testis cancers were analyzed from male relatives only, and other cancers were analyzed from relatives of both sexes as indicated. Relative risks and 95% confidence intervals were obtained from extended proportional hazards regression models, as described by Saunders and Begg *(32)* and as described in Technical Appendix, with subjects not carrying mutations as baseline.

†Too few cancers among family members of patients with these mutations to obtain proportional hazards or population results (*see* Table 6).

Table 6. Population cumulative incidence of cancer to age 80 years, by mutation status and cancer site*

Cancer site	No mutation		BRCA1		BRCA2		
	No. of relatives with cancer	Cumulative incidence, % (95% CI)†	No. of relatives with cancer	Cumulative incidence, % (95% CI)†	No. of relatives with cancer	Cumulative incidence, % (95% CI)†	*m*†
Ovary	42	1.2 (1.1 to 1.3)	20	24 (15 to 38)	7	8.4 (3.9 to 17)	.907
Breast among							
Females	176	9.3 (9.1 to 9.6)	47	90 (77 to 97)	24	41 (26 to 60)	.951
Males	1	0.13 (0.05 to 0.34)	1	–‡	4	11 (2.8 to 37)	.635
Colorectum	121	4.7 (4.7 to 4.8)	3	–‡	7	6.3 (1.7 to 22)	.998
Stomach	37	0.74 (0.71 to 0.77)	5	3.5 (1.1 to 10)	4	2.5 (0.66 to 9.0)	.973
Lung	108	5.5 (5.5 to 5.6)	6	7.2 (1.7 to 27)	4	2.6 (0.12 to 45)	1.00
Kidney, bladder	46	2.1 (2.0 to 2.1)	6	9.1 (3.3 to 24)	1	–‡	.989
Leukemias, lymphomas, etc	68	2.9 (2.9 to 3.0)	8	11 (4.4 to 25)	2	–‡	.991
Liver, gallbladder, bile duct	15	0.05 (0.04 to 0.06)	3	0.40 (0.10 to 1.6)	2	0.22 (0.04 to 1.3)	.955
Prostate	89	11 (11 to 12)	4	7.4 (0.59 to 63)	9	31 (13 to 62)	.990
Pancreas	22	0.77 (0.72 to 0.82)	2	2.3 (0.35 to 15)	4	4.9 (1.5 to 16)	.957
Uterus	32	2.0 (2.0 to 2.1)	2	3.4 (0.36 to 29)	2	3.2 (0.31 to 28)	.994
Testis	2	0.23 (0.20 to 0.27)	1	4.0 (0.34 to 39)	0	–‡	.952
All cancers among							
Females	491	32 (32 to 33)	80	98 (92 to 100)	47	73 (56 to 87)	.983
Males	423	40 (39 to 40)	31	59 (37 to 82)	30	58 (36 to 82)	.994

*Population cumulative incidence was based on site- and age-specific incidence and mortality rates for the general population of Ontario, Canada.

†*See* Technical Appendix for discussion of the parameter *m* and for how the cumulative incidences for the three mutation classes were constrained to sum to the population cumulative incidence according to class frequency as given in Table 4. The quantity $(1 - m)$ is approximately the population attributable risk fraction for the two genetic exposures combined. CI = confidence interval.

‡There were too few cancers among family members of patients carrying these mutations to obtain proportional hazards or population results.

However, an increased risk of prostate cancer was associated with mutations outside of the OCCR (RR = 3.5, 95% CI = 1.1 to 11), and an increased risk of pancreas cancer was associated with mutations within the OCCR (RR = 10, 95% CI = 2.6 to 38). These risks did not change appreciably with choice of OCCR endpoints.

Discussion

In this study, we were able to calculate the relative risks and penetrances of BRCA1 and BRCA2 mutations associated with a number of types of cancers, as well as the prevalences of these mutations in the general population of Ontario. Nevertheless, our study has several limitations. Our overall case participation fraction (50%) was lower than desired, and by midstudy the 30% nonparticipation resulting from mortality before subject contact had increased the proportion of case patients with borderline histology relative to that of patients with invasive histology. Because we found no mutations in the 194 patients with borderline tumors sampled during the first 3 years of the study and because of their relatively excess numbers (compared with what would have been sampled had mortality issues not been appreciable in our study sample), we stopped enrolling such patients after the first 3 years. In our patient sample, probands with borderline tumors accounted

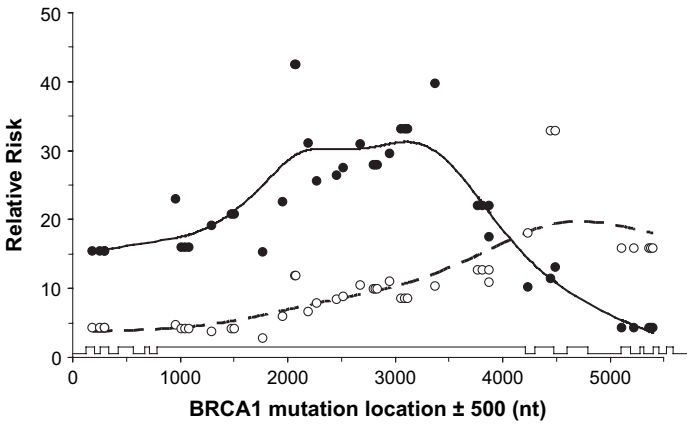

Fig. 1. Relative risks of ovarian and breast cancers in the general Ontario population for BRCA1 mutations within 500 nucleotides of the position plotted. Ovary = **solid circles** and **solid line** (smoothed); breast = **open circles** and **dashed line** (smoothed). The **thin line** at the bottom indicates locations of the 5′-untranslated region and exons 2, 3, and 5–24 according to positions in the cDNA. The **long middle span** in this line is exon 11.

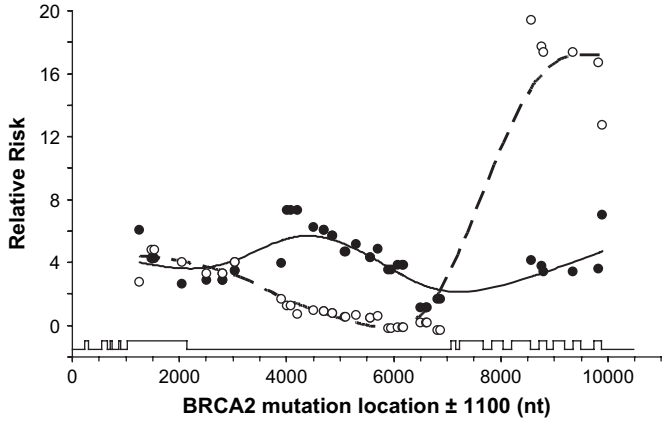

Fig. 2. Relative risks of ovarian and breast cancers in the general Ontario population for BRCA2 mutations within 1100 nucleotides of the position plotted. Ovary = **solid circles** and **solid line** (smoothed); breast = **open circles** and **dashed line** (smoothed). The **thin line** at the bottom indicates the locations of the 5′-untranslated region and exons 2–27 in the cDNA. The **long middle span** in this line is exon 11.

for 16.6% of the total of 1171 patients, a fraction that is comparable to the 17.8% observed for all ovarian cancers in the Surveillance, Epidemiology, and End Results database from January 1, 1992, through December 31, 1998 *(55)*.

It is possible that our enrolled patients with invasive ovarian cancers could overrepresent those of better prognoses. Whether patients carrying BRCA1 or BRCA2 mutations have appreciably better prognoses than noncarriers is unclear *(56–62)*. If they do have better prognoses, then the frequency of mutations among our patients could be slightly high. However, such an excess of mutations would have essentially no effect on the relative risks or cumulative risks of cancer to age 80 years that we calculated. Because of the validation of our results for Ashkenazi Jews, we believe that possible differential survival for carriers and noncarriers is unlikely to have affected our estimates of general population mutation frequencies. Additionally, our ovarian cancer mutation frequencies are reasonably similar to those observed in other studies of patients with invasive cancers *(43–46)*. Our patient sample thus appears to be adequately representative of patients with ovarian cancer in North America.

A second possible limitation of this study is that family history information was obtained by personal interview but was not confirmed by pathology report or other medical records. Although such information may be less valid, errors are generally nondifferential between mutation carriers and noncarriers and among carriers of the various types of mutations—tending, if anything, to shift associations toward the null. Except for tabulated results concerning potential familiality, our analyses used only information on first-degree relatives, for whom the reported cancer histories are likely to be accurate *(63,64)*.

A third consideration is that our patient series was derived from the general population of Ontario, Canada. This population is multiethnic, with a preponderance of individuals with ancestry from the British Isles or other European countries. The applicability of our results to other general populations is, therefore, limited to those of similar ethnic compositions.

Finally, even though we tested 1171 patients, only 129 of them had mutations, which limited the statistical power for examining certain associations. In most instances, no more than one cancer of a specific type occurred in any given family, and few families had multiple first-degree relatives with breast cancer. The one family with proband sisters with ovarian cancer was included only once in the regression models. Thus, the standard Cox regression models that we used for obtaining estimates of confidence intervals and statistical significance are likely to be reasonably accurate.

A strength of this study is its population-based case sampling and thus its representativeness of all incident ovarian cancers arising in a defined geographic area of North America (i.e., Ontario, Canada). Probands were not restricted to having early-onset disease or to coming from families that were selected for a high occurrence of cancer, as in studies based in genetic testing clinics. Our study obtained detailed family histories on all probands, and this information was provided blindly with respect to knowledge about mutation status. Although this study is an extension of our earlier work *(9)*, it was almost twice the size and included screening for all BRCA2 mutations, rather than just exons 10 and 11 as was done previously. This study of 1171 unselected patients is the largest population-based ovarian cancer series to date screened for BRCA1 and BRCA2 mutations.

Aside from our population-based sample of patients, a strength of this study is the use of Ontario population cancer incidence and mortality rates to estimate cumulative incidence of cancer to age 80 years. Ontario incidence and mortality rates are calculated from data from many more cancer patients than would be found in any kin–cohort study, and thus, the cumulative incidence estimates are more precise. Begg *(65)* suggested that penetrance estimates derived from studies of patient probands can be inflated because of possible overrepresentation of risk factors in the patients. We have noted previously *(66)* that this potential problem does not apply to the relative risks or penetrances estimated in kin–cohort studies, when applicable general population vital rates are used instead of the cumulative incidence in first-degree relatives and when any such heritable risk factor overrepresentation applies equally to noncarriers and carriers. In a study of Ashkenazi Jews in Washington, DC *(45,67)*, having a first-degree relative with a history of breast cancer was associated with an approximately 50% increase in risk of breast cancer among BRCA1 and BRCA2 mutation noncarriers. That study, however, had too few carrier patients to determine whether or not having an affected relative similarly increased the risk of breast cancer among mutation carriers. In our analyses, we have assumed that heritable risk factors other than BRCA1 and BRCA2 mutation status are equally prevalent among noncarrier and carrier patient probands. The fact that our estimated mutation prevalences among Ashkenazi Jews are similar to the known prevalences indicates that the relative risks for ovarian cancer that we observed are likely to be accurate and thus that our assumption is probably valid.

In examining mutations, our hierarchical testing strategy was designed to be reasonably rapid and inexpensive and also comprehensive. Nevertheless, some mutations could have been missed with this screen. The testing methods that we used, as does sequencing, miss genomic rearrangements, which are thought to account for fewer than 10% of BRCA1 mutations and even fewer BRCA2 mutations *(68)*. For this reason, we included specific testing for the 6-kb duplication variant in exon 13 of BRCA1, which is observed in British and British-derived populations *(69,70)*.

In testing of the 1171 Ontario patients with ovarian cancer, we found that the hereditary proportion of invasive ovarian tumors was approximately 13%. For the large subgroup of serous ovarian cancers, the frequency reached 18%. Previous estimates of the fraction of ovarian cancer in general or western populations associated with BRCA1 or BRCA2 mutation have typically been less than these estimates. In a multi-institutional US hospital-based pathology series, germline BRCA1 mutations were identified in 7 (6.1%) of 115 patients diagnosed with invasive cancer *(3)*. Stratton et al. *(4)* found BRCA1 mutations in 13 (3.5%) of 374 patients diagnosed with ovarian tumors, both borderline and invasive, in a single hospital in England. Ten (8.8%) germline BRCA1 mutations were found in a Philadelphia hospital series of 113 patients with ovarian cancer *(5)*. In a hospital-based series in Hungary, 10 (11%) of 90 patients with ovarian cancer carried BRCA1 mutations *(8)*, and in a population-based series in Poland, 49 (13%) of 364 patients carried BRCA1 mutations *(14)*. Anton-Culver et al. *(7)* found BRCA1 mutations in only 4 (1.9%) of 120 patients in a population-based study in southern California, although another population series in Florida observed mutations in 20 (9.6%) of 209 patients *(17)*. A clinic-based series of patients with invasive cancers from across the United States found mutations in 4.7% *(10)*. Studies of population series in Finland, Sweden, and Norway found germline BRCA1 mutations

in approximately 4.9% of patients *(11–13,15)*, but a study in Iceland *(16)* found germline BRCA1 mutations in 1.2% of patients. Overall, germline BRCA1 mutations have thus been observed in approximately 6.4% of patients with ovarian cancer.

For BRCA2 mutations, two (4%) patients with germline mutations were found among 50 patients with ovarian cancer in a combined sample from Australia, the United Kingdom, and the United States *(18)*. Takahashi et al. *(19)* identified four (3.1%) BRCA2 mutation carriers among 130 patients in a pathology series, although none were observed in the hospital series in Hungary *(8)* and only one patient carried a BRCA2 mutation among 113 patients in a Philadelphia study *(5)*. The Florida series found that 12 (5.7%) of 209 patients with ovarian cancer carried BRCA2 mutations *(17)*. In Finland, only two (0.9%) of 233 patients with ovarian cancer carried BRCA2 mutations *(11)*, although 10 (6.1%) of 165 patients with invasive cancer carried BRCA2 mutations in a population series in Iceland, where the 999del5 variant is a founder mutation *(16)*. The Swedish study observed that one (0.6%) patient carried a mutation among 161 patients examined *(15)*. Thus, in western populations, approximately 4.0% of patients with ovarian cancer appear to carry germline BRCA2 mutations, or more than 10% of such patients appear to carry mutations in either BRCA1 or BRCA2.

Because of the population-based sampling of our case series and the complete reporting of cancer histories among first-degree relatives, we could estimate the cumulative risk of breast, ovarian, and other cancers associated with carriage of germline mutations. The cumulative risk of breast cancer among BRCA1 mutation carriers to age 80 years that we observed (90%) was somewhat greater than the previously reported values of 45%–87% *(12,21,71–77)*, whereas that of ovarian cancer (24%) was slightly below the previously reported values of 28%–66% *(12,21,71–73,75–78)*. For BRCA2 mutation carriers, the cumulative risk of breast cancer to age 80 years that we observed (41%) was in the range of previously reported values (36%–75%) *(72,74–77,79)*, whereas that of ovarian cancer (8.4%) was lower than previously reported values (11%–32%) *(72,75–78,80)*. The ranges of these reported cumulative risks are wide. Some of the estimates were made from population-based case–control studies that had no mutation testing and that, therefore, required assumptions to be made about the carriage of mutations from the family history of cancer or from modeling of both an unselected patient series and a set of highly affected families. Our estimated cumulative risks were based on a large population series of unselected patients with ovarian cancer and on general population age-specific incidence rates and not on families selected for cancer occurrence. The validation of our mutation carriage frequencies for Ashkenazi Jews indicates that our population relative risks are likely to be accurate. For relatively infrequent outcomes, such as breast or particularly ovarian cancer, given that the cumulative incidence among mutation carriers is approximately the cumulative incidence among non-carriers multiplied by the population relative risk (*see* Tables 5 and 6), the cumulative risks that we calculated for BRCA1 and BRCA2 carriers should be close to the correct values for the population of Ontario, Canada.

We found a trend of increasing risk of breast cancer associated with increasingly downstream location of mutations in the BRCA1 coding sequence and a peak in ovarian cancer risk associated with mutations in the middle of the coding sequence. We previously noted this finding for breast cancer *(9)*, and similar results for both breast and ovarian cancers have been reported in a meta-analysis of 22 studies *(75)*. An analysis of BRCA1 mutations in 356 families of the Breast Cancer Linkage Consortium also confirmed that ovarian cancer risk may peak in the central section of the gene *(81)*.

In contrast to our previous report *(9)*, in this study, we found overall an increased risk of breast cancer associated with carriage of BRCA2 mutations. This association appeared to be restricted to non-OCCR mutations, particularly those in the region 3′ of the OCCR (Fig. 2). Mutations in the OCCR were apparently not associated with risk of breast cancer. A similar pattern of lower risks for breast cancer associated with BRCA2 mutations in the OCCR than with those outside of the OCCR was noted in the 22-study meta-analysis *(75)* and in a study of 164 families of the Breast Cancer Linkage Consortium *(41)*.

A previous study *(81)* also found a lower risk of ovarian cancer associated with 3′ BRCA1 mutations than with 5′ and central BRCA1 mutations. For BRCA2, Lubinski et al. *(42)* found a mildly increased number of ovarian cancers associated with mutations in nucleotides 3500–7400 and beyond nucleotide 9300, compared with a uniform mutation location distribution. Their graph appears similar to Fig. 2, in which we plotted the population relative risk of ovarian cancer by mutation position.

As we previously reported *(9)*, we again found that elevated risks of stomach cancer and of leukemias and lymphomas were associated with BRCA1 mutations. Indeed, in this larger study, we observed that increased risks of hepatobiliary and testicular cancers were associated with BRCA1 mutations. Increased risks of liver and gallbladder cancer associated with both BRCA1 and BRCA2 mutations have also been reported by the Breast Cancer Linkage Consortium *(71,80)*. Testicular cancers have been reported in families of BRCA1 mutation carriers *(24)*. The increased risk of male breast cancer associated with BRCA2 mutations has also been reported *(82,83)*, as has the lack of association between BRCA2 mutation and increased risk of prostate cancer *(7,84,85)*, although positive prostate cancer associations for non-OCCR mutations were found in the Breast Cancer Linkage Consortium analysis of 173 BRCA2 mutation–positive families *(80)* and in a study in Iceland, in which the founder mutation 999del5 is located on the 5′ side of the OCCR *(86)*. We also found the increased risk of prostate cancer associated only with non-OCCR BRCA2 mutations.

To date, general population frequencies of BRCA1 and BRCA2 mutations have been estimated only by indirect calculations. Studies of families, segregation analyses, and other indirect analytic methods have produced estimates for general or western populations of 0.056% for BRCA1 *(22)*, 0.072% for BRCA2 *(22)*, 0.24% for BRCA1 *(23)*, and 0.06% *(20)* and 0.14% *(21)* for the two genes combined. Our estimates of 0.32% and 0.69% for the two genes are greater than these values, and because they are based on empirical ovarian cancer mutation frequencies and relative risks that lie within the ranges of published values, they are likely to be substantially correct.

We have found that BRCA1 and BRCA2 mutations may be more frequent in general populations than previously thought and may be associated with various types of cancers. In addition, our finding of little increased risk of breast cancer associated with BRCA2 OCCR mutations, if confirmed, indicates that patients carrying such mutations may be able to avoid disfiguring

prophylactic mastectomy. Our lifetime ovarian cancer penetrance estimate for BRCA2 mutations is also low and indicates that women with BRCA2 mutations may be able to delay prophylactic oophorectomy until menopause. However, increased risks associated with distal BRCA2 mutations and all BRCA1 mutations appear to merit serious consideration of prevention methods for breast and ovarian cancers. BRCA1 or BRCA2 mutations should be suspected in families with breast, ovarian, and various other cancers, involving male relatives as well as female relatives.

Technical Appendix

For an infrequent autosomal dominant allele, Saunders and Begg *(32)* have shown that the phenotype relative risk estimated in a kin-cohort study of first-degree relatives (denoted by ψ) is related to the phenotype odds ratio as would be seen in a population-based case–control study (denoted by φ) as follows:

$$\psi - 1 = \frac{1-f}{2-f}[(\varphi-1)^{-1} + f]^{-1},$$

for parents and offspring in the cohort, and

$$\psi - 1 = \frac{1-3f/4}{2-f}[(\varphi-1)^{-1} + f - f^2/4]^{-1},$$

for siblings in the cohort, where f is the allele frequency in the general population. If the allele frequency is low, as for BRCA1 and BRCA2 mutations ($f < 1\%$), then the factors $(1-f)/(2-f)$ and $(1-3f/4)/(2-f)$ can be replaced by 1/2, the term $f^2/4$ can be ignored, and

$$\psi - 1 = \tfrac{1}{2}[(\varphi-1)^{-1} + f]^{-1} \quad [1]$$

for the entire cohort. When φ is moderate in size, f is small compared with $(\varphi-1)^{-1}$ and can be ignored as well, leading to the relation that the excess odds ratio in the population is approximately twice the excess relative risk in the kin–cohort study. However, for BRCA1 and BRCA2 mutations and certain cancer outcomes, φ can be 10 or larger, thus f is retained in Equation 1.

In a population-based case–control study using incidence-density sampling of control subjects, under the rare disease assumption, the fraction of control subjects that carry mutations will approximate the general population frequency of mutations, $2f(1-f)$, or $2f$ because f is small and because homozygotes are rare. If a is the fraction of observed patients that carry the mutation of interest, then

$$\varphi = \frac{a(1-2f)}{(1-a)2f}$$

or

$$2f = \frac{1}{1+\varphi(a^{-1}-1)}. \quad [2]$$

Substituting f from Equation 2 into Equation 1 and rearranging gives

$$\varphi^2(1-a) + \varphi(2a + \psi a - 2\psi) - 2a = 0$$

or

$$\varphi = \frac{\psi - (1+\psi/2)a + \sqrt{[(1+\psi/2)a-\psi]^2 + 2a(1-a)}}{1-a} \quad [3]$$

and

$$2f = \frac{a}{\psi(1-a/2) + \sqrt{[(1+\psi/2)a-\psi]^2 + 2a(1-a)}}. \quad [4]$$

Because a is a binomial proportion, log a and its standard error can be estimated by relative risk regression *(87)*, for example, by the computer program GLIM *(31)*. Then, log ψ and its standard error were estimated from the kin-cohort Cox regression of ovarian cancer patients among first-degree relatives. The delta method *(33)* was used to estimate Var(log φ), as follows:

$$\begin{aligned}\mathrm{Var}(\log\varphi) = {} & \left[\frac{\partial\log\varphi}{\partial\log\psi}(\log\hat{\psi},\log\hat{a})\right]^2 \mathrm{Var}(\log\psi) \\ & + \left[\frac{\partial\log\varphi}{\partial\log a}(\log\hat{\psi},\log\hat{a})\right]^2 \mathrm{Var}(\log a) \\ & + 2\left[\frac{\partial\log\varphi}{\partial\log\psi}(\log\hat{\psi},\log\hat{a})\right] \\ & \left[\frac{\partial\log\varphi}{\partial\log a}(\log\hat{\psi},\log\hat{a})\right]\mathrm{Cov}(\log\psi,\log a). \quad [5]\end{aligned}$$

We note that Cov(log ψ, log a) = 0 because in Cox regression, the distribution of the outcome variable is conditional on the realized values of the covariates. The partial derivatives in Equation 5 can easily be obtained from Equation 3. Var[log($2f$)] was estimated similarly by the delta method applied to Equation 4. Confidence intervals for φ and $2f$ were calculated on the log scale and exponentiated.

In a kin–cohort study of ovarian cancer probands, after $2f$ has been estimated from the number of ovarian cancers occurring among the female first-degree relatives, population odds ratios of other cancer types according to mutation status can be estimated from the Cox regression of those cancers and from Equation 1, which may be rearranged as follows:

$$\varphi = 1 + 2[(\psi-1)^{-1} - 2f]^{-1}. \quad [6]$$

Var(log φ) was again estimated by the delta method applied to Equation 6, and confidence intervals for φ were calculated as above on the log scale and exponentiated.

We calculated the cumulative incidence of cancer to age 80 years for individual cancer sites with the DevCan computer program *(38)*. For a given cancer site, the DevCan program uses age-specific incidence rates (denoted by vector **ρ**), mortality rates (denoted by vector **μ**), and total other-cause mortality rates (denoted by vector **ξ**). The cumulative population incidence to age 80 years can be thought of as arising from three subpopulations: individuals carrying no mutations plus those carrying mutations in BRCA1 or BRCA2. We use subscripts 1 and 2 to denote quantities associated with carriage of BRCA1 or BRCA2 mutation, respectively. The total population incidence to age 80 years from DevCan (denoted by D) satisfies

$$\begin{aligned}D(\boldsymbol{\rho},\boldsymbol{\mu},\boldsymbol{\xi}) = {} & (1-2f_1-2f_2)D(m\boldsymbol{\rho},m\boldsymbol{\mu},\boldsymbol{\xi}) \\ & + 2f_1D(m\varphi_1\boldsymbol{\rho},m\varphi_1\boldsymbol{\mu},\boldsymbol{\xi}) + 2f_2D(m\varphi_2\boldsymbol{\rho},m\varphi_2\boldsymbol{\mu},\boldsymbol{\xi}), \quad [7]\end{aligned}$$

where m, the relative rate for noncarriers compared with the average of the whole population, maintained the relative rates according to the three classes of mutation carriage. All the mutation frequencies and arguments in Equation 7 except m were obtained from population rates or calculated from our regression results as described above. For each cancer site of interest, we estimated m numerically to satisfy Equation 7, by use of Ontario general population sex- and age-specific incidence and mortality data for the years from 1993 through 2002 for the quantities **ρ**, **μ**, and **ξ** *(34–37)*. The calculation of $D(m\boldsymbol{\rho},m\boldsymbol{\mu},\boldsymbol{\xi})$ and $D(m\varphi_i\boldsymbol{\rho},m\varphi_i\boldsymbol{\mu},\boldsymbol{\xi})$ occurred as part of calculating m.

Without its consideration of mortality, the DevCan calculation would yield an approximate survival function,

$$1 - D(m\varphi\boldsymbol{\rho},m\varphi\boldsymbol{\mu},\boldsymbol{\xi}) \doteq [1 - D(\boldsymbol{\rho},\boldsymbol{\mu},\boldsymbol{\xi})]^{m\varphi}, \quad [8]$$

for φ = 1, φ_1, or φ_2. With the mortality component, the survival function is tempered approximately by

$$1 - D(m\varphi\boldsymbol{\rho}, m\varphi\boldsymbol{\mu}, \xi) \doteq [1 - D(\boldsymbol{\rho}, \boldsymbol{\mu}, \xi)]^{m\varphi[1-D(m\varphi\boldsymbol{\rho}, m\varphi\boldsymbol{\mu}, \xi)]^{-0.1}},$$

or on the scale of complementary log-log,

$$\begin{aligned}&\log[-\log(1 - D(m\varphi\boldsymbol{\rho}, m\varphi\boldsymbol{\mu}, \boldsymbol{\xi}))]\\ &\quad\doteq \log[-\log(1 - D(\boldsymbol{\rho}, \boldsymbol{\mu}, \boldsymbol{\xi}))] + \log m\\ &\qquad + \log\varphi - 0.1\log(1 - D(m\varphi\boldsymbol{\rho}, m\varphi\boldsymbol{\mu}, \boldsymbol{\xi})),\end{aligned} \quad [9]$$

where the exponent, −0.1, was estimated by linear regression from the total data of all cancer sites and all three subpopulations and had a very small variance. This adjustment factor for the $m\varphi$ exponent provided only a very minor correction for almost all the cancer sites. For ease of notation, if we let

$$C(m\varphi) = \log[-\log(1 - D(m\varphi\boldsymbol{\rho}, m\varphi\boldsymbol{\mu}, \boldsymbol{\xi}))],$$

then Equation 9 can be rearranged as

$$C(m\varphi) - 0.1e^{C(m\varphi)} \doteq C(1) + \log m + \log\varphi. \quad [10]$$

Equation 10 can be used to obtain an approximate variance for $C(m\varphi)$ by the delta method and by noting that

$$\mathrm{Var}\left(C(m\varphi) - 0.1e^{C(m\varphi)}\right) = \left(1 - 0.1e^{C(m\varphi)}\right)^2 \mathrm{Var}\, C(m\varphi).$$

Thus,

$$\mathrm{Var}\, C(m\varphi) \doteq \frac{\mathrm{Var}(C(1) + \log m + \log\varphi)}{\left(1 - 0.1e^{C(m\varphi)}\right)^2}. \quad [11]$$

As long as $m\varphi D(\boldsymbol{\rho},\boldsymbol{\mu},\xi)$ is smaller than unity, from Equation 8 (or 9), we can approximate $D(m\varphi\boldsymbol{\rho},m\varphi\boldsymbol{\mu},\xi) = m\varphi D(\boldsymbol{\rho},\boldsymbol{\mu},\xi)$. Inserting this expression in Equation 7, canceling the factor $D(\boldsymbol{\rho},\boldsymbol{\mu},\xi)$, and solving for m gives

$$m \doteq [1 + 2f_1(\varphi_1 - 1) + 2f_2(\varphi_2 - 1)]^{-1}. \quad [12]$$

For each cancer site, we used the value of m from Equation 12 as the initial value for solving Equation 7 by numerical methods. It should be noted that $(1 - m)$ is the population attributable risk fraction for the two genetic exposures. In our analyses, Equation 12 approximated m exceedingly well, within 1.0%, when $D(m\varphi\boldsymbol{\rho},m\varphi\boldsymbol{\mu},\xi) < 0.1$, and within 3.5%, for $0.1 \le D(m\varphi\boldsymbol{\rho},m\varphi\boldsymbol{\mu},\xi) < 0.8$. For values greater than 0.8, we included the correction factor for the $m\varphi$ exponent in our initial value for m. This procedure was necessary only for female breast cancer and BRCA1 mutations and for both mutations for all cancers combined in women. Nevertheless, for estimating cumulative incidence of cancer to age 80 years, the approximations for m were used only for starting values, and full numerical solutions of Equation 7 were obtained for all our results. Finally, to calculate an approximate Var $C(m\varphi)$, we used Equation 12 to substitute for m in the numerator of Equation 11. Because m and φ in the variance expression are calculated from a and ψ, there are no covariance terms in the Equation 11 numerator involving $C(1)$. The delta method was used to obtain the variance, and confidence intervals for $D(m\varphi\boldsymbol{\rho},m\varphi\boldsymbol{\mu},\xi)$ were calculated by taking confidence intervals for $C(m\varphi)$ and inverting from the complementary log–log scale. It should be noted that because we used population incidence and mortality data for the entire province of Ontario, the variances of $C(1)$ and m were in all instances quite small, and for all cancer sites, almost all the variance in Equation 11 was due to the log φ term. Thus, the approximations that we used had little consequence for most of our results.

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NOTES

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