Ovarian Cancer Risk in Ashkenazi Jewish Carriers of *BRCA1* and *BRCA2* Mutations

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ABSTRACT

Purpose: **Several studies to date have reported ovarian cancer risk due to inherited *BRCA1* and *BRCA2* mutations using familial data or population-based series of probands. Familial aggregation associated with both of these methods may result in a substantial ascertainment bias. To address this, we have used a case-control design that does not involve familial aggregation to estimate the lifetime penetrance of ovarian cancer due to *BRCA1* and *BRCA2* mutations.**

Experimental Design: **A total of 382 ovarian cancer cases self-identified as being Jewish with no prior diagnosis of breast cancer were derived from two hospital-based series. In the first series, all 197 invasive epithelial ovarian cancer cases self-identified as Jewish and without a prior history of breast cancer, diagnosed and treated at Memorial Sloan-Kettering Cancer Center between 1986 and 2000, were identified. In the second series, 185 Jewish invasive epithelial ovarian cancer patients without prior breast cancer were identified in a study conducted at 11 centers in North America and Israel from 1995 to 1996. Controls were 3434 Jewish women without any prior history of breast or ovarian cancer from a large study of genotyped volunteers of Jewish origin in the Washington, D. C. area recruited by investigators at the National Cancer Institute. The cases and controls were genotyped for three Ashkenazi Jewish founder mutations, namely 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*. The lifetime penetrances were estimated using the odds ratios, mutation prevalence in the controls, and ovarian cancer incidence rates in the general American population obtained from the Surveillance, Epidemiology and End Results database adjusted for the incidence of ovarian cancer following breast cancer.**

Results: **Mutations were identified in 147 cases and 62 controls. The estimated penetrances at age 70 years were 37% (95% confidence interval, 25–71%) for a *BRCA1* mutation and 21% (95% CI, 13–41%) for a *BRCA2* mutation.**

Conclusions: **The lifetime penetrances of *BRCA1* mutations are lower than estimates obtained using familial data with multiple affected members but larger than estimates from some population-based proband series. The lifetime penetrance estimate of a *BRCA2* mutation is in the range reported by some of the studies based on familial data. These results could have implications for clinical counseling, surgical interventions, and screening recommendations in women carrying these founder mutations.**

INTRODUCTION

Ovarian cancer is a leading cause of cancer-related mortality among women in the United States. The SEER[3] lifetime risk of ovarian cancer is 1.71% (1). It is well known that mutations in the *BRCA1* and *BRCA2* genes account for a large number, but not all, of familial ovarian cancers (2). Inherited mutations commonly found in Ashkenazi Jewish individuals (namely, 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) have been of particular interest. Several studies to date have reported lifetime risk of ovarian cancer due to inherited *BRCA1* and *BRCA2* mutations using familial data and population series of ovarian cancer probands. The lifetime risks are estimated in the range of 28–66% for a *BRCA1* mutation (2–8) and 16–27% for a *BRCA2* mutation (5, 9).

In studies involving family-based ascertainment, families with a high cancer incidence are more likely to be identified than families with no or fewer cancers among the relatives of probands. As a result, this can lead to a substantial positive bias in the risk estimates. Even population-based studies that rely on occurrences of cancer in relatives of probands to estimate penetrance can be biased if incident cases are used as probands (10). We recently used a case-control design to estimate the lifetime risk of breast cancer conferred by inherited *BRCA1* and *BRCA2* mutations among Ashkenazi Jewish women (11). In this design familial aggregation is not used, eliminating ascertainment bias. We showed that the lifetime risk of breast cancer due to an inherited mutation is substantially lower than the estimates reported in family-based studies. The goal of this study is to investigate the lifetime risk of ovarian cancer due to an inherited *BRCA1* or *BRCA2* mutation among Ashkenazi Jewish women ascertained using the same case-control approach and compare the estimates with those obtained by family-based and population-based studies.

[3] The abbreviations used are: SEER, Surveillance, Epidemiology and End Results; CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center; OCCR, ovarian cancer cluster region.

MATERIALS AND METHODS

Cases. Cases were derived from two hospital-based ascertainment series: the first series was from MSKCC, New York (12); and the second series was from 11 centers in North America and Israel (13). The first series comprised of 1150 consecutive ovarian cancer cases diagnosed and treated at MSKCC between 1986 and 2000. A subset of this series has been reported previously (12). Review of patient records identified a total of 228 patients with ovarian cancer who identified themselves as being Ashkenazi Jewish. Of these, 31 patients had a prior history of breast cancer. Archival pathological tissue specimens were obtained from the hospital tissue bank for each of these participants. Once the ethnicity of the participants, overall survival time, and other clinical factors were determined, the samples were anonymized following published guidelines (14). Samples were then analyzed to determine the presence of 185delAG and 5382insC *BRCA1* or 6174delT *BRCA2* mutations using previously published methods (12).

The second series comprised of ovarian cancer cases from 11 centers in North America and Israel, as reported by Moslehi *et al.* (13). Ovarian cancer patients, self-reported as Jewish, were contacted to participate in a study of mutation analysis of *BRCA1* and *BRCA2* genes. A total of 465 ovarian cancer cases of Jewish origin were identified, of whom 208 cases were alive. These 208 individuals were pathologically confirmed to have invasive epithelial ovarian cancer, agreed to participate in the mutation analysis study, and provided blood samples. Twenty-three of these 208 ovarian cancer patients had a prior history of breast cancer.

Aggregating data from these two series gave a total of 436 Ashkenazi Jewish ovarian cancer patients, of whom 382 cases did not have a prior history of breast cancer.

Controls. The controls required for this study were obtained from a study of genotyped volunteers in the Washington, D. C. area (15), providing a large series of Jewish individuals without a history of breast or ovarian cancer at the time of ascertainment. Jewish volunteers, both men and women, were recruited through advertisements. Breast and ovarian cancer history of the volunteers and their families was obtained. Furthermore, blood samples were obtained from all of the volunteers. A total of 3434 women without a personal history of breast or ovarian cancer at the time of data collection were identified for this study. The presence or absence of the three founder mutations was determined for every individual using previously published methods (15). Of these 3434 volunteers, a total of 1606 women (47%) had a first- or second-degree relative affected with breast or ovarian cancer.

Statistical Methods. All analyses were stratified by age. Because breast cancer can be a competing cause of risk for ovarian cancer incidence, inclusion of the 54 ovarian cancer patients with a prior diagnosis of breast cancer may result in biased penetrance estimates. Therefore, penetrance estimates were calculated by restricting the cases to the 382 patients without a prior history of breast cancer. All 3434 controls were included in the analysis. Penetrance estimation calculations are provided in the "Appendix." This approach is similar to the estimation method described in our breast cancer penetrance study (11). Briefly, the lifetime risk in a given age group can be estimated as a function of the following three quantities: (*a*) SEER ovarian cancer incidence rate after adjusting for the SEER incidence of ovarian cancer in patients with a prior diagnosis of breast cancer in that age group, and the SEER breast cancer incidence in that age group; (*b*) the age-specific relative risk of the mutation; and (*c*) the age-specific carrier prevalence of the mutation. This calculation involves the following three assumptions: (*a*) the hospital-based series of Jewish ovarian cancer cases are representative of the general population series of Jewish cases; (*b*) the controls are representative of the general Jewish population; and (*c*) the breast and ovarian cancer incidence rates among the Jewish population without *BRCA* mutation is similar to the SEER breast and ovarian cancer incidence rate. The CIs of the lifetime risk estimates were calculated using the bootstrap method (16). This involves repeatedly calculating penetrance estimates by sampling cases and controls with replacement from the observed data and deriving the CIs from the empirical distribution of the penetrance estimates.

The risk conferred by *BRCA1 versus BRCA2* mutations and the risk conferred by 185delAG *versus* 5382insC *BRCA1* mutations were compared using a logistic regression model restricted to mutation carriers (11). The outcome was case-control status. The variables entered into the model were the mutation *BRCA1 versus BRCA2* (or 185delAG *versus* 5382insC) and age. A likelihood ratio test was then used to test the hypothesis of no difference in the risk conferred by the two mutations.

RESULTS

Aggregating the two case series and restricting to only cases without a prior diagnosis of breast cancer provided a total of 382 incident ovarian cancer cases. A *BRCA1* mutation was observed in 103 (27%) cases, and 44 (12%) cases had a *BRCA2* mutation. Table 1 gives the age-specific frequencies of cases and controls and the corresponding mutation rates. The age-specific relative risks of *BRCA1* and *BRCA2* mutations are given in Table 2. The relative risks corresponding to an inherited *BRCA1* mutation were estimated to be 42.4 in the <40 age group, 90.8 in age group 40–49, and 53.0 in the ≥50 age group. The corresponding relative risks due to an inherited *BRCA2* mutation were estimated as 6.5, 14.9, and 29.7, respectively.

Table 3 gives the age-specific SEER ovarian cancer incidence rates in the general population, adjusted for the incidence of breast cancer in the corresponding age groups. These adjusted rates, the age-specific relative risks, and carrier mutation prevalence were used to derive the age-specific lifetime risk estimates given in Table 4. The estimated lifetime risk of ovarian cancer at age 70 was 37% (95% CI, 25–71%) due to an inherited *BRCA1* mutation and 21% (95% CI, 13–41%) due to an inherited *BRCA2* mutation. Based on the likelihood ratio test, the risk conferred by a *BRCA1* mutation is significantly higher than the risk conferred by a *BRCA2* mutation ($P = 0.01$).

These analyses were repeated for 185delAG and 5382insC *BRCA1* mutations (Table 5). However, it must be noted that very few cases and controls carry a 5382insC mutation. The estimated lifetime risks were 66% (95% CI, 37–100%) due to a 185delAG mutation and 29% (95% CI, 16–69%) due to a

Table 1 Mutations in cases and controls

Age (yrs)	Data	No. of positive mutations	BRCA1		BRCA2	No mutation
			185delAG	5382insC	6174delT	
<40	MSKCC[a]	3 (43%)	2	1	0	4
	NA/I[b]	7 (44%)	6	0	1	9
	Control	19 (2.7%)	9	2	8	673
40–49	MSKCC	25 (66%)	15	6	4	13
	NA/I	21 (44%)	13	6	2	27
	Control	23 (2.1%)	9	3	11	1090
≥50	MSKCC	50 (33%)	27	7	16	102
	NA/I	41 (34%)	13	7	21	80
	Control	20 (1.2%)	3	6	11	1609

[a] MSKCC indicates cases ascertained at Memorial Sloan-Kettering Cancer Center, New York, NY.
[b] NA/I indicates case data from 11 centers in North America and Israel (Moslehi *et al.*, Ref. 12).

Table 2 Odds ratios

Age	Mutation	Cases	Controls	Odds ratio[a] (95% CI)
<40	*BRCA1+*	9 (39%)	11 (1.6%)	42.4 (15–119.6)
	BRCA2+	1 (4%)	8 (1.2%)	6.5 (0.8–55.6)
	No mutation	13	673	
40–49	*BRCA1+*	40 (47%)	12 (1.1%)	90.8 (44.3–186.3)
	BRCA2+	6 (7%)	11 (0.9%)	14.9 (5.2–42.2)
	No mutation	40	1090	
≥50	*BRCA1+*	54 (20%)	9 (0.6%)	53.0 (25.8–109.2)
	BRCA2+	37 (14%)	11 (0.7%)	29.7 (14.9–59.3)
	No mutation	182	1609	

[a] Compared with no mutation.

Table 3 SEER incidence rates

SEER ovarian (I_a*) and breast (F_a*) cancer incidence rates expressed as the probability of developing ovarian or breast cancer over the corresponding 10-year range. For example, the SEER rate of ovarian cancer for women in the age group 20–29 is 4 per 10,000 person-years or 0.0004 when expressed as a probability and similarly for breast cancer. The standardized incidence ratio (SIR) SIR_a is the incidence of a primary ovarian cancer in breast cancer patients in a given age group, relative to the general population incidence of ovarian cancer for the same age group. This is calculated using the SEER database. For example, the incidence of ovarian cancer among breast cancer patients in the age group 20–29 is 11.42 times higher than the incidence of ovarian cancer in the general population for the same age group. The adjusted incidence is given by $R_a* = (I_a* - SIR_a \times I_a* \times F_a*)/(1 - F_a*)$.

Age (yrs)	Ovarian cancer incidence (I_a*)	Ovarian cancer SIR (SIR_a)	Breast cancer incidence (F_a*)	Adjusted incidence (R_a*)
20–29	0.0004	11.42	0.0004	0.0004
30–39	0.0008	8.37	0.0040	0.0008
40–49	0.0018	3.73	0.0138	0.0017
50–59	0.0033	2.29	0.0212	0.0032
60–69	0.0046	1.67	0.0292	0.0045
70–79	0.0059	1.32	0.0342	0.0058
80+	0.0057	1.16	0.0349	0.0057

5382insC mutation. There was no significant difference between the risks conferred by these *BRCA1* mutations ($P = 0.38$).

DISCUSSION

The lifetime risk estimate for *BRCA1* was lower than estimates from familial studies (3, 4) but larger than estimates from some of the population-based studies (6, 9). The lifetime risk of *BRCA2* mutation was in the range of 16–27% reported in two family studies (4, 5). The penetrance estimates reported here represent the risk of ovarian cancer in the absence of any risk of prior breast cancer. A total of 54 ovarian cancer cases

with a prior diagnosis of breast cancer were excluded from our analysis. Of the 54 cases, 25 had a 185delAG mutation, 5 had a 5382insC mutation, and 9 had a 6174delT BRCA2 mutation. The remaining 15 cases did not carry any of these three mutations.

The lifetime risks were estimated based on three major assumptions: (*a*) the hospital-based cases are representative of the population of ovarian cancer cases; (*b*) the volunteer controls are representative of the general Ashkenazi Jewish population; and (*c*) the cancer incidence in the general Ashkenazi Jewish population without BRCA mutations is similar to the

Table 4 Age-stratified analysis of lifetime risk of ovarian cancer

	SEER adjusted incidence rate[a]	Carrier prevalence	Relative risk	Carrier incidence rate	Penetrance[b] (95% CI)
BRCA1					
20–29 yrs	0.0004	0.016	42.4	0.010	1% (0–2%)
30–39 yrs	0.0008	0.016	42.4	0.020	3% (1–7%)
40–49 yrs	0.0017	0.019	90.8	0.080	11% (7–21%)
50–59 yrs	0.0032	0.006	53.0	0.132	23% (16–44%)
60–69 yrs	0.0045	0.006	53.0	0.185	37% (25–71%)
70–79 yrs	0.0058	0.006	53.0	0.240	52% (35–90%)
80+ yrs	0.0057	0.006	53.0	0.233	63% (44–96%)
BRCA2					
20–29 yrs	0.0004	0.012	6.5	0.002	0.2% (0–1%)
30–39 yrs	0.0008	0.012	6.5	0.005	0.7% (0–3%)
40–49 yrs	0.0017	0.010	14.9	0.023	3% (1–8%)
50–59 yrs	0.0032	0.007	29.7	0.080	11% (7–21%)
60–69 yrs	0.0045	0.007	29.7	0.112	21% (13–41%)
70–79 yrs	0.0058	0.007	29.7	0.145	32% (20–60%)
80+ yrs	0.0057	0.007	29.7	0.141	42% (26–73%)

[a] The adjusted incidence rates (R_a*) from Table 3.
[b] Penetrance is the probability of a mutation carrier developing ovarian cancer by the end of the age interval.

Table 5 Age-stratified analysis of lifetime risk of ovarian cancer associated with *BRCA1* mutations

	SEER adjusted incidence rate[a]	Carrier prevalence	Relative risk	Carrier incidence rate	Penetrance[b] (95% CI)
185delAG					
20–29 yrs	0.0004	0.013	46.0	0.011	1% (0.4–3%)
30–39 yrs	0.0008	0.013	46.0	0.022	3% (1–8%)
40–49 yrs	0.0017	0.008	84.8	0.087	12% (7–25%)
50–59 yrs	0.0032	0.002	117.9	0.311	39% (23–100%)
60–69 yrs	0.0045	0.002	117.9	0.436	66% (37–100%)
70–79 yrs	0.0058	0.002	117.9	0.565	85% (53–100%)
80+ yrs	0.0057	0.002	117.9	0.549	93% (63–100%)
5382insC					
20–29 yrs	0.0004	0.003	25.9	0.010	1% (0–5%)
30–39 yrs	0.0008	0.003	25.9	0.019	3% (0–14%)
40–49 yrs	0.0017	0.003	109.0	0.146	17% (6–55%)
50–59 yrs	0.0032	0.004	20.6	0.062	22% (11–60%)
60–69 yrs	0.0045	0.004	20.6	0.087	29% (16–69%)
70–79 yrs	0.0058	0.004	20.6	0.112	37% (22–78%)
80+ yrs	0.0057	0.004	20.6	0.109	44% (29–86%)

[a] The adjusted incidence rates (R_a*) from Table 3.
[b] Penetrance is the probability of a mutation carrier developing ovarian cancer by the end of the age interval.

SEER rate. The cases were derived from a hospital-based series of ovarian cancer patients. Because initial management of ovarian cancer in the United States is predominantly surgical, cases from the MSKCC series are likely to be similar to the general ovarian cancer case population in the United States. Furthermore, previous analysis showed that the clinicopathological features of high-risk (*i.e., BRCA*-linked) cancer patients diagnosed and treated at MSKCC were similar to those of sporadic ovarian cancer cases (12). The controls were derived from a series of volunteers recruited via both general and Jewish-targeted media outlets. It is likely that individuals with a strong family history were more likely to participate in a study analyzing genetic influence on cancer risk. If the control group contained an enriched proportion of mutation carriers, then the odds ratios derived in our analysis would be underestimates, and the true penetrance figures would actually be higher. A total of 62 (1.8%) controls had a *BRCA1* or *BRCA2* mutation. This

mutation frequency is similar to the 2.2% reported in the study of general Ashkenazi Jewish population (17), suggesting that the mutation prevalence is not inflated among these controls. The SEER ovarian cancer incidence rates were assumed to the represent ovarian cancer incidence among the general Jewish population and the incidence of second primary ovarian cancer following a first primary breast cancer. Violation of this assumption would lead to biased risk estimates. Therefore, a sensitivity analysis was performed to determine lifetime risk when the Jewish population had 10% higher risk than the SEER population. The lifetime risk at age 70 years increased to 40% for a *BRCA1* mutation and to 23% for a *BRCA2* mutation.

Gayther *et al.* (18) reported a correlation between the location of a truncating mutation in the *BRCA1* coding region and the chances of developing breast or ovarian cancer using data from 60 families. Mutations near the 5′ end of the coding region are thought to confer a higher risk than mutations near

the 3′ end. The 185delAG mutation is located near the 5′ end, and the 5382insC mutation is located near the 3′ end of the *BRCA1* coding region. Our estimate of a higher penetrance associated with a 185delAG mutation than a 5382insC mutation, although not statistically significant, is consistent with these findings.

The penetrance of *BRCA2* mutation has not been widely reported. Our results show that a *BRCA2* mutation is not a significant risk factor in younger women (age <40 years; odds ratio, 6.5; 95% CI, 0.8–55.6). The odds ratio increases as the population ages, suggesting *BRCA2* to be a risk factor only in older women. The 6174delT mutation is located in the OCCR (19), in the region of exon 11 extending from nucleotide 3035 to 6629. Truncating mutations in OCCR are known to be associated with an increased risk of breast and ovarian cancer (5, 19). Furthermore, founder mutations in *BRCA1* are believed to have a significantly higher penetrance than a founder mutation in *BRCA2* (20). Our results are consistent with the findings of these published studies. Recent studies have reported associations between other cancers such as colorectal, stomach, pancreatic, and prostate cancers and mutations in *BRCA1* and OCCR *BRCA2* mutations (2, 5, 9, 13, 21, 22).

Our penetrance estimates can have implications for the management of ovarian cancer in germ-line mutation carriers. Prophylactic mastectomy and oophorectomy may be reasonable options for germ-line *BRCA1* and *BRCA2* mutation carriers. Their advantages have been reported in recent literature (23–26). The penetrance estimates derived in this study can be used in decisions regarding such preventive measures (*i.e.,* risk-reducing oophorectomy might safely be delayed until after menopause in carriers of the 6174delT *BRCA2* mutation). Surgical removal of the ovaries is increasingly offered to *BRCA* mutation carriers, given the variable sensitivity of ovarian cancer screening strategies and the finding of early stage tumors in "prophylactic" oophorectomy specimens (27). In the absence of more sensitive means of detecting ovarian cancer, penetrance estimates such as those provided here will continue to be used to inform surgical as well as medical interventions in populations at greatest hereditary risk for ovarian cancer.

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Appendix

Penetrance Estimate. The penetrance of ovarian cancer in mutation carriers at a given age is the probability of developing ovarian cancer by that age in a randomly selected individual, assuming that the individual does not die of competing causes of risk before that age. Denote $I_{10}, I_{20}, \ldots$ as the age-specific incidence of ovarian cancer among carriers without a prior history of breast cancer in age groups 1, 2, ... The penetrance (P_a) at the end of the ath age interval can be written as shown below.

$$P_a = 1 - [(1-I_{10})(1-I_{20})\ldots(1-I_{a0})]$$

The age-specific carrier incidence in the ath age group, I_{a0}, can be calculated as a function of the following three quantities:

(*a*) the general population incidence rate of ovarian cancer without a prior history of breast cancer in the ath age group, denoted R_a* (referred to as the age-specific adjusted ovarian cancer incidence rate); (*b*) the age-specific mutation prevalence, denoted π_a; and (*c*) the age-specific relative risk of the mutation, denoted ϕ_a.

The overall incidence of ovarian cancer for a given age group in the general population is the weighted average of ovarian cancer incidence with and without a prior history of breast cancer, weighted by the (competing risk of) breast cancer incidence in the general population in that age group. Furthermore, the ovarian cancer incidence among those without a prior history of breast cancer in the general population is a weighted average of the incidence among carriers and noncarriers without breast cancer, weighted by the mutation prevalence. For the ath age group, denote I_a* as the general population incidence of ovarian cancer, S_a* as the incidence of (second primary) ovarian cancer among (first primary) breast cancer cases, and F_a* as the incidence of breast cancer in the general population. Then, the age-specific adjusted ovarian cancer incidence rate is given by:

$$R_a* = (I_a* - S_a* F_a*)/(1-F_a*)$$

The age-specific carrier incidence rate I_{a0} can then be written as:

$$I_{a0} = R_a* \phi_a / (\pi_a \phi_a + 1 - \pi_a)$$

In practice, the quantity S_a* can be obtained as a product of the age-specific standardized incidence ratio of ovarian cancer in breast cancer cases and the age-specific incidence of ovarian cancer in the general population.

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