Breast and Ovarian Cancer Risk and Risk Reduction in Jewish *BRCA1/2* Mutation Carriers

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A B S T R A C T

Purpose

Mutations in *BRCA1/2* dramatically increase the risk of both breast and ovarian cancers. Three mutations in these genes (185delAG, 5382insC, and 6174delT) occur at high frequency in Ashkenazi Jews. We evaluated how these common Jewish mutations (CJMs) affect cancer risks and risk reduction.

Methods

Our cohort comprised 4,649 women with disease-associated *BRCA1/2* mutations from 22 centers in the Prevention and Observation of Surgical End Points Consortium. Of these women, 969 were self-identified Jewish women. Cox proportional hazards models were used to estimate breast and ovarian cancer risks, as well as risk reduction from risk-reducing salpingo-oophorectomy (RRSO), by CJM and self-identified Jewish status.

Results

Ninety-one percent of Jewish *BRCA1/2*-positive women carried a CJM. Jewish women were significantly more likely to undergo RRSO than non-Jewish women (54% v 41%, respectively; odds ratio, 1.87; 95% CI, 1.44 to 2.42). Relative risks of cancer varied by CJM, with the relative risk of breast cancer being significantly lower in 6174delT mutation carriers than in non-CJM *BRCA2* carriers (hazard ratio, 0.35; 95% CI, 0.18 to 0.69). No significant difference was seen in cancer risk reduction after RRSO among subgroups.

Conclusion

Consistent with previous results, risks for breast and ovarian cancer varied by CJM in *BRCA1/2* carriers. In particular, 6174delT carriers had a lower risk of breast cancer. This finding requires additional confirmation in larger prospective and population-based cohort studies before being integrated into clinical care.

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INTRODUCTION

Mutations in *BRCA1* and *BRCA2* (*BRCA1/2*) are well-known genetic risk factors for breast and ovarian cancer (BOC). Lifetime breast cancer (BC) risk among *BRCA1/2* carriers has been estimated at 56% to 84%.¹⁻³ Ovarian cancer (OC) risk differs by gene, with *BRCA1* associated with a 36% to 63% lifetime risk and *BRCA2* mutation carriers having a 10% to 27% lifetime risk.³⁻⁶ Cancer risks also vary by mutation location,⁷⁻⁹ by mutations in other genes,^{10,11} and by exposures including oral contraceptive (OCP) use and reproductive history.¹²⁻¹⁸ Risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) significantly

reduce cancer risk^{19,20} and mortality in these women.^{19,21} According to the National Comprehensive Cancer Network guidelines, RRSO is recommended for all *BRCA1/2* mutation carriers by age 35 to 40 or once childbearing is complete.²²

The following three common mutations have been identified in Ashkenazi Jewish (AJ) *BRCA1/2* mutation carriers: c.68_69delAG (185delAG or 187delAG) and c.5266dupC (5382insC or 5385insC) in *BRCA1* and c.5946delT (6174delT) in *BRCA2*.²³⁻²⁵ The prevalence of these mutations is approximately 2.5% in AJs.^{2,26,27} 5382insC is also common in non-Jewish Eastern European populations, as it entered the AJ population in Poland 400 to 500 years ago through population admixture.²⁸ The high

frequency of these mutations has led to the development of panel testing for the three common Jewish mutations (CJMs). Unless their specific mutation is known, AJ women generally undergo an initial round of genetic testing using a CJM panel, which is much less expensive than comprehensive sequencing.²⁹ If the CJM panel is negative, further testing can be considered based on family history and high pretest probability of a *BRCA1/2* mutation.²⁹ However, these specific panels may not be appropriate for all Jewish populations, because different founder mutations have been observed in Jews of Sephardic descent, as well as those who have immigrated to Israel from Iraq, Yemen, Iran, and Afghanistan.³⁰⁻³²

Heterogeneity in cancer risk in women who carry CJMs may exist,^{2,33,34} with BC risk seeming to be lower in 6174delT carriers.³⁴ Additionally, it is unclear whether risk-reduction methods, particularly RRSO, differ in effectiveness by mutation. Therefore, we sought to examine BOC risk and risk reduction in CJM carriers and self-identified Jewish women as a whole using data from the Prevention and Observation of Surgical End Points (PROSE) Consortium.²⁰

METHODS

PROSE Study Cohort

Our study data comprised 4,767 women with disease-associated *BRCA1/2* mutations, ascertained between 1973 and 2010 from 22 international centers in the PROSE Consortium. The PROSE study protocol, which was approved by the institutional review board at each participating institution, has been previously described.^{20,21}

Participants were excluded from all analyses if they did not have a confirmed disease-associated *BRCA1/2* mutation ($n = 101$) or if they had mutations in both *BRCA1* and *BRCA2* ($n = 17$). After these exclusions, there were 4,649 participants available for analysis. Statistical significance was assessed at a two-sided $P < .05$ level. Analyses were performed using STATA version 11.1 (STATA, College Station, TX).

CJM and Risk Factor Prevalence in Jewish and Non-Jewish *BRCA1/2* Carriers

We identified all mutations reported in self-identified Jewish women ($n = 969$). Classification of participants as Jewish or non-Jewish was determined entirely by self-report. Furthermore, data were not sufficient to accurately distinguish Ashkenazi or Sephardic ancestry, so the ancestral composition of our cohort was not considered, except as a supplementary analysis. We evaluated mutation prevalence both by individual and by family (ie, counting only one mutation carrier out of multiple carriers in a given family to assess bias from overcounting large families with the same mutation). We compared Jewish with non-Jewish women on several potential BOC risk factors, including birth before 1940, OCP use, parity, age at first live birth, education, first-degree relatives with BOC, RRM, RRSO, and age at surgery. Proportions were compared using the normal approximation to the binomial distribution, and means were compared using the t test. Finally, we explored whether Jewish and non-Jewish women differed in terms of RRM and RRSO uptake using logistic regression to control for the previously mentioned potential confounders as well as *BRCA1/2* mutation. Surgeries were considered prophylactic if they occurred before OC diagnosis for RRSO or before BC diagnosis for RRM.

Relative Hazard of BOC

We used Cox proportional hazards models to determine the relative hazard for developing BOC by CJM and Jewish status. The primary end point was first cancer diagnosis. In models including both *BRCA1* and *BRCA2* carriers, we adjusted for *BRCA1/2* mutation. All models controlled for age at ascertainment, parity ($> \nu \leq$ one pregnancy resulting in live birth), and OCP use (ever ν never use). For all models, we censored participants' follow-up time at death or the date of last contact, and we assumed no competing risks that

would preclude the primary outcome. Proportional hazards assumptions were tested for all covariates, and a robust variance-covariance estimation method was used to account for familial clustering,³⁵ because some families had multiple *BRCA1/2* carriers.

Participants were observed from date of ascertainment until cancer diagnosis or censoring. For BC analyses, RRM, RRSO, and OC were treated as time-dependent covariates to avoid bias from the change in BC risk after mastectomy or oophorectomy.^{19,20,36,37} To perform this analysis, we divided participants' follow-up time into separate exposure windows for each time-dependent covariate that occurred during the study follow-up period. We then conditioned our Cox models on the individual to account for multiple exposure windows per participant. Participants were excluded if they had BC ($n = 2,030$) or were censored ($n = 248$) before ascertainment or if they were missing necessary data to determine follow-up ($n = 9$), leaving 2,362 participants available for analysis. These participants underwent a total of 12,070 years of follow-up, with mean and median follow-up times of 5.1 and 3.7 years, respectively. For OC analyses, RRSO was treated as a time-dependent covariate, and participants were excluded if they had OC ($n = 437$) or were censored ($n = 397$) before ascertainment or if they were missing necessary data to determine follow-up ($n = 28$), leaving 3,787 participants available for analysis. These participants underwent a total of 20,638 years of follow-up, with mean and median follow-up times of 5.4 and 4.2 years, respectively.

Because RRSO was treated as a time-dependent covariate, we could examine its effect on BOC risk. To see whether cancer risk reduction from RRSO varied by specific *BRCA1/2* mutation, we added an interaction term between RRSO and mutation type to the previously mentioned models. The significance of interactions was tested via a joint Wald test for all levels of the interaction terms.

Absolute Risk of BOC

We estimated absolute risk as the age-specific cumulative incidence of BC and OC for CJM carriers, adapting the method of Antoniou et al.³⁸ Age-specific cumulative incidence rates were calculated using the following formula:

$$F'(t) = 1 - e^{HR \cdot \ln(1 - F(t))},$$

where $F'(t)$ is the CJM-specific cumulative incidence at age t , $F(t)$ is the baseline cumulative incidence at age t , and HR is the mutation-specific hazard ratio (HR). To estimate a baseline cumulative incidence, we calculated the adjusted Kaplan-Meier failure function in our cohort for BC and OC separately. For BC, we adjusted for RRSO, RRM, and mutation type; for OC, we adjusted for RRSO and mutation type. Thus, the baseline risk assumes that individuals do not have a CJM and have not had prophylactic surgery. We used HR 95% CIs to calculate the absolute risk CIs. If there were no observed events in a particular age interval, upper confidence limits were calculated according to the Wilson's score method.³⁹

RESULTS

We observed 39 unique *BRCA1* mutations and 31 unique *BRCA2* mutations in 969 self-identified Jewish women (Table 1). Ninety-one percent of Jewish women ($n = 885$) and 10% of non-Jewish women ($n = 372$) had a CJM. Among Jewish women, two unique non-CJM *BRCA1* mutations were seen in more than one family (332-11T>G and del exon 1). All other non-CJM *BRCA1/2* mutations among Jewish women were observed in a single family. Data on the usage of various genetic testing procedures to determine mutation status, although incomplete, are summarized in Appendix Table A1 (online only). Data on ethnic background and ancestry were also incomplete; however, Jewish non-CJM carriers did not seem to be substantially different from Jewish CJM carriers in this regard (Appendix Table A2, online only). Mutation prevalence estimates in our cohort were not substantially altered when calculated based on the number of distinct

Table 1. Common *BRCA1/2* Mutations Overall and by Self-Identified Jewish Status (N = 4,649)

Group	Total Mutation Carriers		Mutation Carriers Who Self-Identify As Jewish	
	No.	%	No.	%
<i>BRCA1</i>				
Total sample	2,943		649	
185delAG	599	20	454	70
5382insC	297	10	149	23
332-11T>G	6	0.2	5	0.8
del Exon 1	2	0.07	2	0.3
Any CJM	896	30	603	93
Non-CJM*	2,047	70	46	7.1
<i>BRCA2</i>				
Total sample	1,706		320	
6174delT	361	21	282	88
Any CJM	361	21	282	88
Non-CJM†	1,345	79	38	12

NOTE. Mutations were considered common if they were present in more than one family in our cohort.

Abbreviation: CJM, common Jewish mutation.

*Unique non-CJM *BRCA1* mutations among self-identified Jewish women were 1240delC, 1675delA, 185insA, 187delT, 188del11, 1VS4-1G>T, 2072del4, 2294delG, 2594delC, 2606delT, 2800delAA, 2838del4, 360C>T, 3875del4, 3878delTA, 4184del4, 5055delG, 5060delC, 5221delTG, A1708E, C2457T, C4731T, E1250X (3867G>T), E84X, exon 18 G5255A, IVS12 + 1G>T, IVS23-2A>G, IVS5 + 3A>G, Q541X(174OC>T), R1443X, S713X, S955X, 332-11T>G, Y978X, c.1505_1509delTAAAG, del exon 1, and del exons 3-8.

†Unique non-CJM *BRCA2* mutations among self-identified Jewish women were 1815delTinsCA, 2041insA, 279delAC, 3034del4, 3773delTT, 4075delGT, 5164del4, 5301insA, 5358del4, 5466insT, 6048del14, 6056delC, 6252insG, 6357insA, 6659delA, 6672insT, 8061del10, 8504del4, 9610C>T, C2256X, E2918E, G1639T, I2627F (8107A>T), IVS9 + 1G>T, K944X, Q1994X, Q2042X, R2336P, S1121X, and Y1894X.

families with a given mutation, rather than based on the number of individuals with a given mutation (data not shown).

Jewish women were less likely to have used OCPs, were older at first live birth, were more likely to have higher education, and were older at ascertainment (Table 2). Jewish women, compared with non-Jewish women, were also less likely to have first-degree relatives with either BC (53% v 63%, respectively) or OC (24% v 28%, respectively). However, Jewish women had significantly smaller families on average and were not different in percentage of first-degree relatives with BOC. Among Jewish women, 54% underwent RRSO, whereas 41% of non-Jewish women underwent RRSO (adjusted odds ratio, 1.87; 95% CI, 1.44 to 2.42). However, Jewish women were significantly older when they did undergo RRSO. Jewish women were not more likely to have undergone RRM (adjusted odds ratio, 1.02; 95% CI, 0.69 to 1.52).

BC relative hazard was significantly lower in 6174delT carriers than in non-CJM *BRCA2* carriers (Table 3; HR, 0.35; 95% CI, 0.18 to 0.69). Other BOC relative hazards in specific CJMs and in self-identified Jewish women were not significantly different from their respective reference groups (Tables 3 and 4). In a sensitivity analysis, relative hazard estimates were similar when OC and death were treated as competing risks, rather than time-dependent and censoring events, respectively (data not shown). Estimated cumulative incidence of BOC by CJM is shown in Figure 1 and Table 5. Overall, RRSO significantly reduced the relative hazard of BC (HR, 0.62; 95% CI, 0.47 to 0.83) and OC (HR, 0.08; 95% CI, 0.04 to 0.16). No significant differ-

ence in BC hazard reduction from RRSO was observed among specific CJM carriers (joint Wald test, $P = .61$). In addition, no apparent difference in OC hazard reduction from RRSO was observed among specific CJM carriers, although there were not enough events in our cohort to formally conduct a test of interaction.

DISCUSSION

Previous reports in retrospective cohorts and cross-sectional samples have estimated BOC risks conferred by CJMs. Using a cohort with 120 CJM carriers, Struewing et al² estimated that AJ CJM carriers had a 56% risk of BC and a 16% risk of OC by age 70 years. Antoniou et al³⁴ conducted a meta-analysis containing pedigree data from 196 CJM carriers, showing that 185delAG conferred a 64% and 14% risk, 5382insC conferred a 67% and 33% risk, and 6174delT conferred a 43% and 20% risk of BC and OC by age 70 years, respectively. Our cohort was larger than these, comprising 4,649 *BRCA1/2* carriers, of whom 1,257 had a CJM. Additionally, 2,382 participants (including 608 CJM carriers) in our cohort were ascertained prospectively (ie, they did not have BC or OC before ascertainment), which ensures that we were theoretically able to observe cancer cases for all individuals who were at risk for developing cancer in our analyses.

Our finding of heterogeneity in BOC risk among CJM carriers is consistent with previous results.^{2,33,34} Of note, 6174delT conferred a lower risk of BC compared with non-CJM *BRCA2* mutations (Table 3). By contrast, OC risk in this group was not significantly different from the risk in those with non-CJM *BRCA2* mutations. These findings are consistent with the location of 6174delT within the OC cluster region in *BRCA2*, a region in exon 11 of *BRCA2* that has been associated with an increased risk of OC relative to BC.⁴⁰ Notably, the prospectively ascertained 6174delT carriers in our cohort were older at ascertainment than carriers of other mutations (Table 3); however, it is unclear what is causing this discrepancy and whether it could have substantially impacted our results. Conceivably, we may have failed to ascertain certain 6174delT carriers who would have developed BC at a younger age. Alternatively, later ascertainment may simply reflect lower rates of BOC among first-degree relatives of 6174delT carriers than non-CJM *BRCA2* carriers (69% v 78%, respectively; $P = .005$).

Our estimates of absolute risk are consistent with some of the original studies to report BOC risk estimates in *BRCA1/2* carriers overall that were based on multiple-case families (Table 5).^{4,41-43} However, our risk estimates are substantially higher than more recent studies that derived their estimates of BOC risk in CJM carriers and *BRCA1/2* carriers overall from population-based cohorts.^{2,5,44-46}

One possible explanation for the observed elevated BOC risk estimates in our cohort is ascertainment bias, resulting from individuals at a higher risk for cancer being more likely to seek out and enroll onto studies than those at lower risk for cancer. This effect has been documented in several previous studies, especially those that were based on familial aggregation of cancer in high-risk families.⁴⁷ Although our study is a large cohort study rather than a familial aggregation study, it is still quite likely that individuals from high-risk families preferentially enrolled onto our study. In our cohort, 73% of *BRCA1/2* carriers had a known first-degree relative with BOC, making them more likely to be from a high-risk family. However, in a sensitivity analysis, having a first-degree relative with BOC was not significantly associated with an increased hazard of either BC (HR, 0.93; 95%

Table 2. Clinical Characteristics and Surgical Uptake by Self-Identified Jewish Status (N = 4,649)

Clinical Characteristic	Overall	Non-Jewish	Jewish	P*
Age at ascertainment, years				< .001
Mean	43.5	42.7	46.6	
SD	12.7	12.6	12.4	
Born before 1940				.11
No.	486	371	115	
%	10.5	10.1	11.9	
Ever used oral contraceptive pills				.02
No.	3,105	2,418	687	
%	77.5	78.3	74.6	
High parity (> 1 term birth)				.31
No.	2,858	2,245	613	
%	63.0	62.6	64.4	
Age at first term birth, years				< .001
Mean	25.9	25.2	28.2	
SD	5.3	5.2	5.0	
More than high school education				< .001
No.	2,049	1,555	494	
%	81.0	77.6	93.9	
No. of first-degree family relatives				< .001
Mean	3.8	4.1	2.6	
SD	2.7	2.9	1.6	
Known first-degree family relative with breast cancer†				< .001
No.	2,845	2,332	513	
%	61.2	63.4	52.9	
No. of first-degree family relatives with breast cancer				< .001
Mean	1.0	1.1	0.7	
SD	1.0	1.1	0.9	
% of first-degree family relatives with breast cancer				.82
Mean	30.6	30.6	30.4	
SD	31.4	30.5	34.5	
Known first-degree family relative with ovarian cancer†				.005
No.	1,269	1,039	230	
%	27.3	28.2	23.7	
No. of first-degree family relatives with ovarian cancer				< .001
Mean	0.4	0.4	0.3	
SD	0.6	0.7	0.6	
% of first-degree family relatives with ovarian cancer				.09
Mean	11.2	10.9	12.4	
SD	22.2	21.3	25.4	
Known first-degree family relative with breast or ovarian cancer				< .001
No.	3,387	2,746	641	
%	72.9	74.6	66.2	
Known first- or second-degree family relative with breast or ovarian cancer				.001
No.	4,025	3,217	808	
%	86.6	87.4	83.4	
RRSO				< .001
No.	2,024	1,502	522	
%	43.5	40.8	53.9	
Age at RRSO, years				< .001
Mean	45.9	45.4	47.3	
SD	8.5	8.4	8.8	
RRM				.48
No.	461	358	103	
%	11.8	11.6	12.5	
Age at RRM, years				.16
Mean	40.9	40.6	42.0	
SD	8.7	8.6	9.0	

Abbreviations: RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; SD, standard deviation.

*P values based on the *t* test for continuous variables and on the normal approximation to the binomial distribution for categorical variables.

†First-degree relatives with cancer were determined by self-report. We were unable to assess whether individuals either chose not to report or were unaware of family cancer history as a result of social, cultural, or other factors, such as a cultural stigma associated with cancer diagnosis or genetic abnormalities.

Table 3. Breast Cancer Hazard Ratios in Specific Groups Among Prospective Study Participants (n = 2,362)

Group	No. of Participants	Age of Ascertainment (years)		Follow-Up (years)		No. of Participants Diagnosed With Cancer	Age at Diagnosis (years)		Hazard Ratio	95% CI
		Mean	Range	Mean	Range		Mean	Range		
BRCA1										
Non-CJM	1,087	37.9	2.2-88.6	5.7	0.0-33.3	171	42.3	22.2-72.7	Ref	
185delAG	312	41.3	10.2-90.4	4.7	0.0-33.1	51	43.5	27.6-73.2	1.23	0.87 to 1.73
5382insC	124	41.4	12.3-87.6	4.6	0.0-18.1	27	43.2	24.9-62.7	1.53	0.96 to 2.45
BRCA2										
Non-CJM	663	40.5	2.0-89.3	4.6	0.0-28.3	134	45.9	19.1-80.1	Ref	
6174delT	176	45.4	17.7-79.1	4.1	0.0-16.2	13	48.1	32.5-70.5	0.35	0.18 to 0.69
Non-Jewish	1,874	39.1	2.0-89.3	5.2	0.0-33.3	334	43.7	19.1-80.1	Ref	
Jewish	488	42.7	10.2-90.4	4.7	0.0-33.1	62	45.2	27.6-73.2	0.76	0.56 to 1.01
RRSO										
No	1,599	38.2	2.0-90.4	4.5	0.0-28.3	317	42.9	19.1-80.1	Ref	
Yes	763	43.2	15.4-83.7	6.5	0.0-33.3	79	47.9	33.3-72.7	0.62	0.47 to 0.83

Abbreviations: CJM, common Jewish mutation; Ref, reference; RRSO, risk-reducing salpingo-oophorectomy.

CI, 0.70 to 1.23) or OC (HR, 1.21; 95% CI, 0.78 to 1.89). As a result, it is difficult to determine from our own data the extent to which ascertainment bias may be impacting our results.

Additionally, our risk estimates were based only on prospectively ascertained participants, and these individuals, in theory, may have systematically higher baseline cancer risk than retrospectively ascertained individuals for reasons similar to those described earlier. In a sensitivity analysis, however, prospectively ascertained individuals in our cohort had a significantly lower hazard of both BC (HR, 0.76; 95% CI, 0.68 to 0.85) and OC (HR, 0.79; 95% CI, 0.64 to 0.98). Thus, the exclusion of retrospectively ascertained individuals seems unlikely to account for the elevated BOC risks observed in our study.

Furthermore, as has been previously argued,³⁸ the vast majority of individuals who seek *BRCA1/2* genetic testing come from high-risk families with multiple cases, the same types of individuals who would be most likely to enroll onto our study. As a result, our estimates may not be especially high in this target population, as opposed to the general population of CJM carriers. However, because of uncertainty

in the accuracy of our estimates, more studies involving prospective and population-based cohorts will be essential before mutation-specific BOC risk estimates can be used as a basis for clinical risk management decisions. Our results should prompt others to update and re-evaluate their data, so the most accurate possible penetrance estimates can be made available to women with *BRCA1/2* mutations.

In our cohort, Jewish women were significantly more likely than non-Jewish women to undergo RRSO (54% v 41%, respectively). This discrepancy may indicate increased awareness, acceptance, or access to RRSO among Jewish women or their physicians. There was no difference between Jewish and non-Jewish women in use of RRM.

Overall, RRSO significantly reduced the hazard of BOC (Tables 3 and 4), consistent with previous studies in *BRCA1/2* mutation carriers.^{19,20} HRs were not significantly different for each of the specific CJMs, suggesting that RRSO is equally effective regardless of *BRCA1/2* mutation. The efficacy of RRSO is especially impressive given that 35% of CJM carriers and 33% of non-CJM *BRCA1/2* carriers receiving RRSO were postmenopausal at the time of surgery in our cohort. In a

Table 4. Ovarian Cancer Hazard Ratios in Specific Groups Among Prospective Study Participants (n = 3,787)

Group	No. of Participants	Age of Ascertainment (years)		Follow-Up (years)		No. of Participants Diagnosed With Cancer	Age at Diagnosis (years)		Hazard Ratio	95% CI
		Mean	Range	Mean	Range		Mean	Range		
BRCA1										
Non-CJM	1,668	40.2	2.2-88.6	6.0	0.0-33.3	96	50.6	30.1-89.3	Ref	
185delAG	472	43.5	10.2-90.4	5.1	0.0-33.1	20	53.2	36.8-74.0	0.97	0.58 to 1.63
5382insC	228	43.4	12.3-87.6	5.6	0.0-25.4	6	53.6	44.8-63.3	0.61	0.27 to 1.38
BRCA2										
Non-CJM	1,132	43.1	2.0-89.3	5.1	0.0-28.3	24	55.8	44.0-74.9	Ref	
6174delT	287	47.5	17.7-76.6	4.1	0.0-16.2	5	59.8	49.4-76.4	1.34	0.48 to 3.73
Non-Jewish	3,034	41.5	2.0-89.3	5.6	0.0-33.3	127	51.7	30.1-89.3	Ref	
Jewish	753	45.1	10.2-90.4	5.0	0.0-33.1	24	54.4	36.8-76.4	0.93	0.59 to 1.46
RRSO										
No	2,086	39.7	2.0-90.4	4.5	0.0-28.3	139	52.4	30.1-89.3	Ref	
Yes	1,701	45.3	15.4-83.7	6.6	0.0-33.3	12	49.7	37.8-61.6	0.08	0.04 to 0.16

Abbreviations: CJM, common Jewish mutation; Ref, reference; RRSO, risk-reducing salpingo-oophorectomy.

Fig 1. Estimated age-specific cumulative risk of (A) breast and (B) ovarian cancers by common Jewish mutations (CJMs). The average proportion of specific CJM carriers developing cancer by a given age was calculated based on the hazard ratios shown in Table 3, with baseline cancer risks adjusted for no CJM and no prophylactic surgery. Error bars represent 95% CIs. Numerical values for these risks are listed in Table 4.

sensitivity analysis, however, RRSO was not found to be significantly less effective at reducing BC risk if performed after menopause (test for interaction, $P = .70$), although we were likely underpowered for such an analysis. We did not have enough events to determine whether RRSO was less effective at reducing OC risk if performed after menopause.

Our data indicate the potential for using mutation-specific information to determine individual cancer risk, although additional validation may be required before counseling based on mutation-specific risks is ready for clinical practice. BOC risks seem to vary by CJM, with 6174delT conferring a lower risk of BC than other mutations. However, our data are limited to average cancer risks among a population.

Individual cancer risk may still vary substantially around this average, with some individuals having a low risk and some having a high risk of BOC. Until accurate individualized risk prediction can be accomplished, perhaps including knowledge of genetic and environmental risk modifiers, we do not suggest any alteration from current management approaches in *BRCA1/2* mutation carriers as a whole.

In our cohort, 72% of Jewish *BRCA1/2* carriers with no first- or second-degree relatives with BOC were ascertained after being diagnosed with cancer themselves. Furthermore, among these women, 84% were CJM carriers. Because effective interventions exist that reduce mortality in *BRCA1/2* carriers,¹⁹ there may be a benefit to case-based screening and, possibly, to wider, population-based

Table 5. Estimated Cumulative Incidence of Breast and Ovarian Cancer by CJM

Cancer	Estimated Mutation-Specific Cumulative Incidence of Cancer by Age									
	30 Years		40 Years		50 Years		60 Years		70 Years	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Breast cancer										
<i>BRCA1</i> , no CJM*	7.0		36		61		72		76	
185delAG	8.5	6.1 to 12	42	32 to 54	69	56 to 80	79	68 to 89	83	72 to 92
5382insC	11	6.7 to 16	49	35 to 66	76	59 to 90	86	71 to 96	89	75 to 97
<i>BRCA2</i> , no CJM*	12		48		73		85		90	
6174delT	4.3	2.2 to 8.4	20	11 to 36	37	21 to 59	48	28 to 73	55	33 to 79
Ovarian cancer										
<i>BRCA1</i> , no CJM*	0.0		4.4		24		47		60	
185delAG	0.0	0.0 to 1.0†	4.2	2.5 to 7.0	23	15 to 36	46	30 to 64	58	41 to 77
5382insC	0.0	0.0 to 1.0†	2.7	1.2 to 6.0	16	7.2 to 32	32	16 to 58	42	22 to 71
<i>BRCA2</i> , no CJM*	0.0		0.0		5.3		23		29	
6174delT	0.0	0.0 to 2.2†	0.0	0.0 to 0.7†	7.0	2.6 to 18	30	12 to 63	37	15 to 73

Abbreviation: CJM, common Jewish mutation.

*Because baseline risks were adjusted for no CJM or prophylactic surgery, we could not estimate 95% CIs.

†Upper confidence limits for cells with no observed events were calculated according to Wilson's score method.

screening for CJs. Furthermore, cost-utility analyses have predicted that implementing a CJM screening program in the US Jewish population would lead to 2,800 fewer cases of OC and cost about \$8,300 per quality-adjusted life-year gained,⁴⁸ compared with \$10,000 to \$25,000 per quality-adjusted life-year gained for mammographic screening in the general population.⁴⁹ Thus, a discussion among key constituencies on wider screening for CJs in the AJ population seems warranted. Such a screening program would have complex social, cultural, and policy implications,^{48,50} and clinicians and genetic counselors would need to be alert to the many unique aspects of genetic testing in the Jewish population.⁵¹⁻⁵⁵

Our findings help fill a gap in knowledge of BOC risk and risk reduction in Jewish women who carry *BRCA1/2* mutations. There seems to be variability in BOC risks conferred by the different CJs, with 6174delT carriers in particular seeming to have a lower BC risk. Thus, a patient's specific mutation could one day provide clinically relevant information about individual cancer risk. RRSO seemed equally effective at reducing both BC and OC risks in all subgroups, suggesting that this is an appropriate risk-reduction strategy regardless of specific mutation. These results may ultimately help improve individualized risk assessment and management strategies in the Jewish population.

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