LETTER TO JMG

Incidence of non-founder *BRCA1* and *BRCA2* mutations in high risk Ashkenazi breast and ovarian cancer families

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Inherited predisposition to cancer is a major contributor to the breast and ovarian cancer burden among people of Ashkenazi ancestry. Approximately 2.5% of all people of Ashkenazi Jewish descent carry one of three ancient (founder) mutations in *BRCA1* or *BRCA2* (185delAG or 5382insC in *BRCA1* and 6174delT in *BRCA2)*.[1–3] In a recent population based study, 29% of Jewish women with ovarian cancer were shown to carry one of these three founder mutations.[4] In a series of 220 high risk Ashkenazi breast cancer families, a founder *BRCA* mutation was detected in 44%. If ovarian cancer was present in the kindred, 73% of families segregated a founder *BRCA* mutation.[5]

Despite the high proportion of hereditary breast and ovarian cancer attributed to founder mutations of *BRCA1* or *BRCA2* in this population, some Ashkenazi families with histories highly suggestive of an inherited cancer predisposition have been shown to segregate other (non-founder) mutations of *BRCA1*[6] or *BRCA2*.[7] Counselling of families considering full sequence *BRCA* genotyping is complicated by the limited information available regarding the incidence of these non-founder mutations in the Ashkenazi population.

We present a series of Ashkenazi Jewish kindreds at hereditary risk for breast and ovarian cancer who do not segregate one of the three Ashkenazi founder mutations and who have undergone full sequencing of the coding regions and flanking intronic regions of *BRCA1* and *BRCA2*. Using the BRCAPRO algorithm, we have estimated whether the prevalence of non-founder *BRCA1* and *BRCA2* mutations in a genetic isolate (Ashkenazim) is consistent with the background rate in an admixed population, or if selective or other effects have led to a non-founder mutation rate lower than would be expected.

METHODS

Records of all patients seen by the Clinical Genetics Service at Memorial Sloan-Kettering Cancer Center (MSKCC) from 1.6.95 to 30.6.01, who identified themselves as being of Ashkenazi Jewish descent, and who consented to participate in an ongoing study evaluating the clinical significance of germline *BRCA* mutations, were reviewed. Seventy patients with a personal history of breast or ovarian cancer who underwent full sequence evaluation of *BRCA1* and *BRCA2* after testing negative for the three Ashkenazi founder mutations were identified. Demographic information for these patients is summarised in table 1.

Founder mutation testing was performed in the Diagnostic Molecular Genetics Laboratory at MSKCC using previously published methods.[8–10] In some cases, samples were split and were genotyped a second time at the University of Washington as part of an ongoing cohort study. Sequencing of the coding regions and flanking intronic regions was carried out by Myriad Genetics Laboratories as previously described.[11] All deleterious mutations were confirmed by single amplicon DNA sequencing in the Diagnostic Molecular Genetics Laboratory at MSKCC.

A three generation pedigree for each kindred was entered into the BRCAPRO[12–14] model using CancerGene interface (Version 3.3, University of Texas Southwestern). BRCAPRO is a predictive model using pedigree information of first and second degree relatives and published prevalence[15 16] and penetrance[17 18] estimates of *BRCA1* and *BRCA2* for both Ashkenazi and non-Ashkenazi populations to determine the probability of a deleterious *BRCA* mutation in a person. The model incorporates statistical assumptions for autosomal

Table 1 Proband demographics

Sex	
Female	70 (100%)
Male	0 (0%)
Mean age at time of counselling	51.4 (range 32-84)
Mean age at initial cancer diagnosis	46.8 (range 30-78)
Personal cancer history	
Breast cancer	59 (84.3%)
Bilateral breast cancer	7 (10.0%)
Ovarian cancer	2 (2.9%)
Breast and ovarian cancer	1 (1.4%)
Bilateral breast and ovarian cancer	1 (1.4%)
Mean number of first and second degree relatives with breast cancer (includes proband)	2.41 (range 0-5)
Mean number of first and second degree relatives with ovarian cancer (includes proband)	0.24 (range 0-2)
Mean age of breast cancer diagnosis in first and second degree relatives	51.2 (range 30-95)
Mean age of ovarian cancer diagnosis in first and second degree relatives	60.2 (range 40-81)
Number of site specific breast cancer pedigrees (no ovarian cancer in pedigree)	56 (80%)

Table 2 Deleterious non-founder mutations detected

Kindred	Gene	Mutation	Type	Citations in BIC[22] database
1	*BRCA2*	9325insA	Frameshift: T3033, 3043X	Novel
2	*BRCA2*	2082insA	Frameshift: A618, 621X	2
3	*BRCA2*	1982delA	Frameshift: K585, 613X	2

Table 3 Non-founder missense mutations of uncertain clinical significance

Kindred	Gene	Exon	Nucleotide change	Amino acid change	Citations in BIC[22] database	Results of segregation analysis
4	*BRCA1*	11	3832C>T	P1238L	15	Segregation analysis uninformative*
5	*BRCA2*	10	2117C>T	T630I	6	Family structure not amenable to analysis
6	*BRCA2*	11	6566A>G	N2113S	1	Mutation did not cosegregate with disease
7	*BRCA2*	11	2192C>T	P655R	23	Segregation analysis not done†
8	*BRCA2*	11	2192C>T	P655R	23	Segregation analysis not done†
9	*BRCA2*	11	5298A>C	K1690N	6	Family structure not amenable to analysis
	BRCA2	15	7772C>T	T2525I	14	
10	BRCA2	11	5540G>A	G1771D	6	No segregation analysis attempted
	BRCA2	23	9304C>G	Q3026E	1	

*Segregation analysis attempted on archival tissue. PCR amplification was unsuccessful.
†This mutation has not cosegregated with disease in at least four other families (personal communication, Myriad Genetic Laboratories).

dominant transmission and performs Bayesian risk calculations. The model has been validated in several previous studies in both the Ashkenazi and non-Ashkenazi populations.[19 20] For kindreds in which a *BRCA* founder mutation was not present, carrier probability for non-founder alleles was calculated using non-Ashkenazi prevalence and penetrance functions.[14] The expected number of mutation carriers and 95% confidence intervals were estimated using a bootstrap analysis.[21]

RESULTS

Three (4.3%) of the 70 kindreds were found to segregate protein truncating *BRCA* mutations (table 2). In kindred 1, the proband was diagnosed with breast cancer at the age of 30, her mother with ovarian cancer at the age of 48, and her maternal grandfather's sister with breast cancer in her 40s. A frameshift mutation in *BRCA2*, 9325insA, resulting in a stop codon at amino acid position 3043 was found. In kindred 2, the proband was diagnosed with breast cancer at the age of 68, her mother with breast cancer at the age of 82, and her maternal grandmother, two maternal aunts, and two maternal first cousins were diagnosed with breast cancer in their 40s to 80s. An additional maternal aunt was diagnosed with breast cancer in her 40s and ovarian cancer in her 80s. A frameshift mutation in *BRCA2*, 2082insA, resulting in a stop codon at amino acid 621 was present. In kindred 3, the proband was diagnosed with breast cancer at the age of 42, and a paternal aunt and paternal grandfather's sister were diagnosed with breast cancer in their 50s. A frameshift mutation in *BRCA2*, 1982delA, was present resulting in a stop codon at amino acid 613.

Seven patients were shown to have a total of nine missense mutations of uncertain clinical significance (table 3). The P655R variant in *BRCA2* was seen in two kindreds. This variant has been reported 23 times in the Breast Cancer Information Core (BIC)[22] database and has failed to cosegregate with disease in at least four families (personal communication, Myriad Genetic Laboratories). Analysis of a novel mutation in *BRCA2*, N2113S, failed to show cosegregation of this variant allele with disease in kindred 6. Segregation analysis was attempted on kindred 4 using archival tissue without success. In the remaining cases, family structures were either not amenable to segregation analysis (two kindreds) or segregation analysis was not attempted (one kindred).

Using the BRCAPRO model and prevalence and penetrance functions for non-Ashkenazi populations, the probands of families 1, 2, and 3 had a predicted probability of carrying a deleterious *BRCA* mutation of 25%, 63%, and 4%, respectively. The range of predicted mutation probabilities obtained for the entire cohort was 0-99%. When the entire cohort was analysed using a bootstrap analysis, 13.82 (95% CI 8.89 to 18.74) patients in this cohort would be expected to have a deleterious mutation assuming that the incidence of non-founder mutations in the Ashkenazi population is the same as in the non-Ashkenazi population.

DISCUSSION

Our results show a significantly lower incidence of non-founder *BRCA* mutations in the Ashkenazi Jewish population than would be expected if the underlying rate of these mutations were similar to the general population. In two series published to date, two deleterious non-founder mutations and seven missense mutations of uncertain clinical significance have been identified in 69 high risk Ashkenazi Jewish families (table 4).[23 24] Our results are consistent with these findings.

Some of the discrepancy between the observed and expected number of mutations may be accounted for by limitations of the BRCAPRO model. Some authors have suggested that the BRCAPRO model may overestimate the probability of carrying a deleterious *BRCA* mutation.[25] Part of this discrepancy occurs because BRCAPRO predicts the probability that a *BRCA* mutation is present even if it is not detectable by PCR based mutation assays. In an analysis by the Breast Cancer Linkage Consortium of 237 families with more than four cases of breast cancer, only 63% of families with disease linked to *BRCA1* had a detectable mutation.[18] Recent data from a multicentre validation study of BRCAPRO showed that 79% of probands with a mean BRCAPRO probability of greater than 95% had a demonstrable mutation.[20] Part of the difference between mutations observed and mutations predicted was probably the result of limitations in the sensitivity of sequencing based approaches.

Several other models predicting *BRCA* testing results have been published. Couch *et al*[26] published a logistic regression model for estimating *BRCA1* mutation status based on data from 169 families who presented to a referral cancer genetics clinic.[26] The model incorporates average age of cancer diagnosis, the presence or absence of ovarian cancer in the family, the

Table 4 Non-founder mutations in *BRCA1* and *BRCA2* detected in series of Ashkenazi patients

Study	No of patients	Inclusion criteria	Method of mutation detection	Mutations identified
Ganguly *et al*[23]	43	Proband Affected with breast or ovarian cancer Wild type for *BRCA1* Negative for 6174delT mutation in *BRCA2* Family 3 or more cases of breast and ovarian cancer at any age on one side of the family	*BRCA1* CSGE *BRCA2* CSGE	2 protein truncating 0 missense
Shiri-Sverdlov *et al*[24]	26	Proband Affected with breast or ovarian cancer Family 2 additional 1st or 2nd degree relatives with one of the following: Breast cancer diagnosed under age 40 Bilateral breast cancer Breast or ovarian cancer in the same person	*BRCA1* DHPLC, PTT *BRCA2* DGGE	0 protein truncating 12 missense (5 did not cosegregate with disease)

CSGE, conformation sensitive gel electrophoresis.
DHPLC, denaturing high performance liquid chromatography.
PTT, protein truncation test.
DGGE, denaturing gradient gel electrophoresis

presence of persons with both breast and ovarian cancer, and ethnicity. When family information from our cohort and non-Ashkenazi status was entered into the Couch model, 7.7 (95% CI 5.6 to 10.6) non-founder *BRCA1* mutations would be expected versus none observed. Shattuck-Eidens *et al*[27] also published a logistic regression model predicting *BRCA1* test results based on data from 798 families not involved in previous linkage studies for *BRCA1*. This model incorporates number of family members affected with breast or ovarian cancer, youngest age of diagnosis of cancer in the family, and ethnicity. When family data from our cohort were entered into this model, 6.5 (95% CI 4.3 to 8.9) non-founder *BRCA1* mutation carriers would be expected versus none observed.

Myriad Genetic Laboratories (Salt Lake City, UT) publishes *BRCA1* and *BRCA2* mutation prevalence tables based on data from over 6700 patients who have undergone commercial *BRCA* mutation testing.[28] Using the tables for non-Ashkenazi probands, 11.4 (95% CI 9.5 to 13.6) non-founder *BRCA1* and *BRCA2* mutations would have been expected versus the three observed. Similar results to ours have also been noted in preliminary data from an ongoing study of over 1800 women with both a personal and family history of breast cancer diagnosed before the age of 50 and/or ovarian cancer at any age. In that study, 4.7% of Ashkenazi Jewish subjects possessed a deleterious *BRCA* mutation other than one of the three Ashkenazi founder mutations versus 31.3% of non-Ashkenazi subjects with comparable personal and family histories.[29]

Several explanations are possible for the lower than expected frequency of clearly deleterious "private" mutations in this group. It has been speculated that the reproductive isolation of the Ashkenazi population has led to genetic drift, resulting in relative under-representation of mutations seen in other populations.[24] While this can explain some of the apparent discrepancy, a significant de novo mutation rate would tend to minimise this effect. Though documented de novo mutations of *BRCA1* and *BRCA2* are rare,[29 30] there is a presumed new mutation rate for these large genes that is reflected by the relatively high proportion (63%) of unique mutations documented in the BIC.[22] For at least three other common syndromes with distinct founder alleles in the Ashkenazim, cystic fibrosis, Tay-Sachs disease, and Canavan disease, approximately 1-5% of disease causing alleles are the result of non-founder mutations.[31–33] Another possible explanation for the apparent under-representation of non-founder deleterious mutations in the Ashkenazim is that there may be both founder alleles as well as sporadic mutations that are large deletions, inversions, and other structural alterations of *BRCA1* or *BRCA2* that have not been detected by PCR based sequencing.[34 35] This effect has been seen in other populations in which large structural alterations in *BRCA1* and *BRCA2* have been shown to be founder mutations.[36 37] Also, it is possible there are other as yet undiscovered genes that confer susceptibility to breast and ovarian cancer in the Ashkenazi Jewish population. Linkage analysis has shown that 16% of families with at least four cases of breast cancer do not show linkage to *BRCA1* or *BRCA2*.[18] It is speculated that other, as yet unidentified, genes can explain some of the apparent cancer predisposition in these families.

Because of the clinic based ascertainment, it is not possible to estimate from this study the population frequency of non-founder mutations in the Ashkenazim. Another limitation is that some of the identified missense mutations of undetermined significance may, in fact, represent deleterious mutations. Other validation studies of the BRCAPRO model have generally not included such variants in their analysis. Even if one assumes that all four kindreds where segregation analysis was either uninformative or unavailable segregated a deleterious mutation, the number of deleterious mutations would still be lower than would be expected in a comparable non-Ashkenazi population. A third limitation of our study is that 80% of the kindreds in our cohort did not have any affected relatives with ovarian cancer. Only 58% of site specific breast cancer families with four or more affected relatives show linkage to *BRCA1* or *BRCA2* compared to 95% of similar families with both breast and ovarian cancer.[18] Lastly, in the majority of kindreds only one affected person was sequenced. It is possible that this person was a phenocopy and that a deleterious mutation was present in other members of the family.

This is one of the largest studies to date looking at the incidence of non-founder *BRCA* mutations in a cohort of Ashkenazi Jewish ancestry. Consistent with previous smaller studies, we did not observe as many non-founder mutations as would have been expected in the general population. In order to confirm this result, population based series in the Ashkenazim looking at the entire coding sequence of *BRCA1* and *BRCA2* are needed. Genetic studies including linkage and association approaches will be necessary to establish whether other inherited cancer predisposing genes exist in this population. In addition, novel genotyping strategies are needed to exclude the presence of large structural alterations in already known genes that may be undetected by current sequence based analysis.

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These results have been confirmed in a recent series reported by Frank *et al*[29] published after this manuscript was accepted. Included in that report is kindred 3 from this report and 13 of the 67 kindreds in this report without a deleterious non-founder mutation.

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