Published in final edited form as:
*Cancer Res*. 2008 September 1; 68(17): 7006–7014. doi:10.1158/0008-5472.CAN-08-0599.

# The relative contribution of point mutations and genomic rearrangements in *BRCA1* and *BRCA2* in high risk breast cancer families

**Maurizia Dalla Palma**[1], **Susan M. Domchek**[2,3], **Jill Stopfer**[3], **Julie Erlichman**[3], **Jill D. Siegfried**[4], **Jessica Tigges-Cardwell**[3], **Bernard A. Mason**[1,4], **Timothy R. Rebbeck**[2,3], and **Katherine L. Nathanson**[1,3]

[1] Division of Medical Genetics, University of Pennsylvania School of Medicine, Philadelphia, PA

[2] Division of Hematology-Oncology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

[3] Abramson Cancer Center, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA

[4] Joan Karnell Cancer Center at Pennsylvania Hospital, University of Pennsylvania School of Medicine, Philadelphia, PA

## Abstract

Demand for *BRCA1* and *BRCA2* mutation screening is increasing, as their identification will impact medical management. However, both the contribution of different mutation types in *BRCA1* and *BRCA2*, and whom should be offered testing for large genomic rearrangements, have not been well established in the United States high risk population. We define the prevalence and spectrum of point mutations and genomic rearrangements in *BRCA* genes in a large US high-risk clinic population of both non-Ashkenazi and Ashkenazi Jewish descent, using a sample set representative of the US genetic testing population. Two hundred and fifty-one probands ascertained through the University of Pennsylvania high-risk clinic, all with commercial testing for *BRCA1* and *BRCA2*, an estimated prevalence of *BRCA* mutation ≥ 10% using the Myriad II model and a DNA sample available, were studied. Individuals without deleterious point mutations were screened for genomic rearrangements in *BRCA1* and *BRCA2*. In the 136 non-Ashkenazi Jewish probands, 36 (26%) *BRCA* point mutations and 8 (6%) genomic rearrangements, seven in *BRCA1* and one in *BRCA2*, were identified. Forty-seven (40%) of the 115 Ashkenazi Jewish probands had point mutations; no genomic rearrangements were identified the group without mutations. In the non-Ashkenazi Jewish probands, genomic rearrangements constituted 18% of all identified *BRCA* mutations; estimated mutation prevalence (Myriad II model) was not predictive of their presence. While these findings should be confirmed in larger sample sets, our data suggest that genomic rearrangement testing be considered in all non-Ashkenazi Jewish women with an estimated mutation prevalence ≥ 10%.

### Keywords

*BRCA1*; *BRCA2*; point mutations; genomic rearrangements; US clinic population

Corresponding Author: Katherine L. Nathanson, Medicine, Medical Genetics, 351 BRB 2/3, 421 Curie Blvd., Philadelphia, PA 19104, knathans@mail.med.upenn.edu.

## INTRODUCTION

A woman born in the United States has an average lifetime risk of 13% of being diagnosed with breast cancer (1). Family history is associated with 10 to 20% percent of breast cancer cases (2), and within that group approximately one-half (5 to 10% of all cases) are strongly hereditary (3). Germline mutations in *BRCA1* and *BRCA2* are associated with an increased risk of breast and ovarian cancer (4–7). Genetic testing for *BRCA1* and *BRCA2* mutations has been available for more than a decade (8–10). The usefulness of genetic testing as medical management tool has become increasingly recognized (11), as effective risk reduction procedures, such as prophylactic oophorectomy, and screening measures, such as breast MRI, are available (12–17). Our ability to offer effective management for patients with *BRCA1* and *BRCA2* mutations has increased the demand for genetic testing and make it imperative that we detect all mutations.

Despite our understanding of the clinical phenotypes most predictive of the presence of *BRCA1* and *BRCA2* mutations (18–22), a significant number of families with both breast and ovarian cancers do not have identifiable mutations (23). An increase in the rate of mutation detection has resulted from the identification of exon duplication(s) or deletion(s), commonly referred to as genomic rearrangements. Genomic rearrangements are not identified using PCR based methods of mutation screening. Initial studies of genomic rearrangements were limited in various ways – they examined only *BRCA1*, included small patient populations, were limited to very high risk breast/ovarian cancer families or to one ethnicity (24–27). More recently, highly sensitive DNA-based quantitative techniques have been developed to analyze both *BRCA1* and *BRCA2* for the presence of genomic rearrangements, and as such are useful in large scale screening. Previous studies, mainly done in homogenous ethnic groups, have suggested that the frequency of genomic rearrangements in *BRCA1* in high risk breast cancer families ranges between 1.3–4.4%, accounting for between 8 –19% of the total mutations, with the number dependant on ethnicity and study eligibility criteria (24,28–35). To date, the prevalence of genomic rearrangements in *BRCA2* results lower than that in *BRCA1* with the frequency in high risk breast/ovarian cancer families ranging from 0–2.4% with contribution of large genomic rearrangements to all the *BRCA2* mutations between 0–11% (29,32,33,36–39). These data have established that genomic rearrangements comprise a significant component of the identifiable mutations in *BRCA1* and *BRCA2*.

While utility of screening for genomic rearrangement in both *BRCA1* and *BRCA2* is clear, there remain several crucial unanswered questions, such as the prevalence of genomic rearrangements in the US high-risk population, their contribution to mutations in populations of mixed ethnic backgrounds and how patients should be selected for screening. Currently, screening for genomic rearrangements is offered only on a standard basis (i.e. incorporated within initial genetic testing, as opposed to being ordered as a separate test) to women with very high risk personal or family histories (approximated to an estimated mutation prevalence > 30%). The goal of our study was to determine the role of testing for *BRCA1* and *BRCA2* genomic rearrangements in a US high-risk clinic, representative of the commercial testing population, including women of both Ashkenazi Jewish and non-Ashkenazi Jewish descent.

## METHODS

### Family Ascertainment

Probands were ascertained from the Cancer Risk Evaluation Program (CREP) at the University of Pennsylvania Health System [Hospital of the University of Pennsylvania (1998–2006) and Pennsylvania Hospital (2001–2006)] (see Eligibility Criteria Flowchart, Supplemental Figure 1). Patients are either self- or physician-referred based on their personal or family history. All participants provided written consent to participate in an institutional review board approved

study of the genetics of hereditary breast cancer. More than 99% of patients seen in CREP participate in a research registry. Only one individual from each family was included in this study. If multiple individuals from the same families were enrolled in our study, the individual affected with breast cancer at the earliest age with commercial screening (Myriad Genetics, Salt Lake City, UT) performed was considered the proband. Pathology reports and/or medical records for confirmation for age and type of cancer diagnosis were collected from probands and affected relatives whenever possible. Ethnicity was self reported. The characteristics of the probands are detailed in Table 1.

## Study Eligibility

Probands were eligible for the current study if they meet all of the following criteria: 1) were affected with breast or ovarian cancer; 2) had full commercial sequencing or Ashkenazi Jewish founder mutation screening (Myriad Genetics, Salt Lake City, UT); 3) had no prior genetic testing of themselves or any family member; 4) had an estimated mutation prevalence of 10% or higher based on the Myriad II model prevalence tables and 5) had a DNA sample available in the laboratory at the University of Pennsylvania.

Probands were excluded if either they or their relatives had previous genetic testing before being evaluated in CREP for two reasons. First, we wanted to exclude mutation positive patients specifically referred for clinical management, so as to limit bias for mutation positivity. Second, we wanted to exclude individuals were referred to us specifically for research participation after uninformative genetic testing, so as to limit bias for mutation negativity.

The estimated prevalence of BRCA mutations was generated using the Myriad II model, which consists of two mutation prevalence tables, stratified by Ashkenazi Jewish ethnicity[3]. The tables were developed following the guidelines initially published by Frank et al. (21) and provide a composite mutation prevalence for *BRCA1* and *BRCA2*. The Myriad II model has been demonstrated to perform similarly to BRCAPRO and BOADICA, and be the most sensitive in predicting mutations in non-Ashkenazi Jewish families (40). All models use only first and second degree relatives. The 507 probands that met above criteria 1–3 were evaluated using the Myriad II model. The predicted prevalence of *BRCA* mutations was calculated for both the maternal and paternal lineages; the lineage with the highest prevalence was used for analytical purposes. Twelve probands had one parent each of Ashkenazi Jewish and non-Ashkenazi Jewish origin. These probands were grouped with the lineage with the highest estimated mutation prevalence – six Ashkenazi Jewish and six non-Ashkenazi Jewish. Sixty-two probands (40 Ashkenazi Jewish and 22 non-Ashkenazi Jewish) had an estimated mutation prevalence over 10%, but did not provide samples. A comparison between the sample and non-sampled groups is included in the Results section. Two hundred and fifty-one probands had both an estimated *BRCA* mutation prevalence of over 10% in either the maternal or paternal lineage and a sample available in the laboratory and thus were included in the study.

## Point Mutation Analysis

DNA was extracted from peripheral blood mononuclear cells by using standard procedures. Either blood or DNA samples were provided to Myriad Genetics Laboratory (Salt Lake City, UT) for mutation detection. After analysis, all patients were classified as having a deleterious mutation, a variant of uncertain significance, or no mutation (see Supplemental Tables 1 and 2). The classification of mutations was performed as previously described (21). As detailed in Figure 1, full sequencing in probands with Ashkenazi Jewish ancestry was done in a total of 44 women, either because genetic testing was done prior to the availability of the Ashkenazi

[3]http://www.myriadtests.com/provider/brca-mutation-prevalence.htm

Jewish founder mutation panel, mixed heritage (probands with non-Ashkenazi Jewish ancestors), high prior probability or based on patient request.

## Screening for Genomic Rearrangements

Ninety-four probands (72 non-Ashkenazi Jewish and 22 Ashkenazi Jewish) had testing for the presence of five *BRCA1* genomic rearrangements included in the commercial screening since 2001 at Myriad Genetics Laboratory. The rearrangement panel includes five specific mutations in *BRCA1*: 7.1-kb deletion of exons 8–9, 3.4-kb deletion of exon 13, 6-kb duplication of exon 13, 26-kb deletion of exons 14–20 and 510-bp deletion of exon 22 (24,26,41–43). Multiplex ligation dependent probe amplification (MLPA) was used to screen for genomic rearrangements in *BRCA1* and *BRCA2* in all the mutation negative families. MLPA was performed according to the instructions provided by the manufacturer (MRC-Holland, Amsterdam, Netherlands). The probe mixes MLPA P002 and P087 were used to screen *BRCA1*. The probe mix MLPA P045 kit was used to screen *BRCA2* and for the *CHEK2* 1100delC mutation. The fragments were analyzed on ABI 3100 capillary sequencer (Applied Biosystems Inc., Foster City, CA, USA) using Genescan software. Variation in peak height was evaluated by comparing each test sample to the normal control present in the same experiment and by cumulative comparison of four to six samples always from the same experiment. Any sample with variation in peak height was repeated a total of three times.

## Quantitative Analysis of MLPA

We used GeneMarker, Version 1.4 (Softgenetics LLC) to perform data normalization and analysis. GeneMarker normalizes the peak height (fluorescence intensity) of each MLPA fragment with either the internal control probes or the entire population (all the fragments). Samples for which we obtained a height ratio (normalized fluorescence intensity of each individual probe of a patient sample to a control DNA sample) less than 0.7 (for deletion) and greater than 1.2 (for duplication) had MLPA repeated. Controls with known genomic deletions were studied and had height ratios of ~1.5, 1.0, 0.5, or 0.0 for regions with duplication, the wild-type sequence, a deletion, or absence of the sequence, in that order.

## Identification and Confirmation of Rearrangements

For the rearrangements in *BRCA1* and *BRCA2*, we confirmed the presence of the genomic deletions using both MLPA kits for *BRCA1* and real-time quantitative PCR for the mutations in *BRCA1* and *BRCA2*. Real-time PCR was performed using the LightCycler (Roche Applied Science, V.3.5.3) and SYBR Green I chemistry (LightCycler FastStart DNA Master SYBR Green I). Primers and probes for exons within *BRCA1* and *BRCA2* were designed as described in Barrois et al (44). We selected one test exon within the deleted region of interest. As an endogenous control, we normalized each sample to *ALB* (encoding albumin at 4q11-q13). We determined heterozygosity for a deletion when the ratio of *ALB*:test exon was 2:1. Each assay was run in triplicate; two normal controls (ratio 1:1) and a non-template control were included. PCR reactions were set up in a total volume of 20 μl by distributing aliquots of 18 μl of master mix into the capillaries, followed by 2 μl of DNA adjusted to 10 ng/μl. The reaction mixture contained 0.4 μl of each primer, 2 μl of FastStart DNA kit SYBR Green I and contained 5mM $MgCl_2$. The thermal cycling conditions were: an initial denaturation step at 95°C for 10 min, 45 cycles at 95°C for 10 sec, primer annealing temperature for 5 sec and extension at 72° C for 6 sec. (Primers and annealing temperatures are available on request.) A melting curve was produced after each run for every sample. Quantification data were analyzed using the fit point method of the LightCycler software (Supplemental Figures 2 and 3). In the fit point method for the Lightcycler (Roche, Inc), the relative expression ratio is calculated from the real-time efficiencies and the crossing point (where fluorescence rises above the threshold) deviation of an unknown sample as compared to a control.

All genomic rearrangements identified by MLPA, a sub-set of which were confirmed by real-time PCR, were sent for the BRAC*Analysis*® Rearrangement Test (BART) (Myriad Genetics, Salt Lake City, UT). All mutations confirmed by real-time PCR also were identified by BART. No mutations unconfirmed by real-time PCR were identified by BART. In three families, additional affected family members were available and co-segregation of the mutation with disease was observed.

### Statistical Methods

Comparisons of discrete and quantitative variables were made by using Fisher's exact tests and Kruskal-Wallis chi-square tests, respectively (STATA v. 9, StataCorp, Texas). The latter was used to to test the null hypothesis that there was no difference in the median ages of cancer diagnosis in the mutation and non-mutation carrying groups and between the estimated mutation prevalences (Myriad II model) in the sampled and non-sampled groups. Chi-square tests comparing observed vs. expected mutation distributions also were computed. Logistic regression was used to evaluate whether the estimated Myriad prevalences predicted the presence of genomic rearrangement. Null hypotheses were rejected at a p-value of $p<0.05$, and all comparisons were made using two-sided tests.

## RESULTS

### Family Characteristics

Probands from 251 families met the eligibility criteria for inclusion, 244 females and 7 males (Table 1). Of the 251 high risk families, 115 (46%) were of Ashkenazi Jewish descent and 136 (54%) were of non-Ashkenazi Jewish descent. The proband characteristics of the non-Ashkenazi Jewish and Ashkenazi Jewish families were not significantly different. The range of estimated prevalence of point mutations in *BRCA1* and *BRCA2* was from 11.2 to 79.3% with a median of 17.6%; in the non-Ashkenazi Jewish probands, from 11.2 to 79.3%, with a median of 22.9%; and in the Ashkenazi Jewish probands from 11.6 to 75%, with a median of 16%. The characteristics of the non-Ashkenazi Jewish (Table 2) and Ashkenazi Jewish families were very similar: over 95% of families contained women with unilateral breast cancers, 45% at least one woman with ovarian cancer, 15% at least one woman with breast and ovarian cancers, 5–7% at least one male breast cancer case and 20% at least one man with prostate cancer. The familial characteristics differed significantly between non-Ashkenazi Jewish and Ashkenazi Jewish probands only in the percentage of families with women with breast cancer diagnosed under age 50, 96% and 86%, respectively (p=0.01). We identified 62 probands who met the study eligibility requirements but did not provide samples; of these 40 were Ashkenazi Jewish and 22 were non-Ashkenazi Jewish.

### Point mutations and variants of uncertain significance in BRCA1 and BRCA2

In total, 83 (33%) of the 251 total probands studied were found to have deleterious point mutations, 49 (59%) in *BRCA1* and 34 (41%) in *BRCA2*, respectively (Figure 1). The 83 mutations are comprised of 22 and 15 distinct mutations in *BRCA1* and *BRCA2*, respectively. All mutations are listed in Supplementary Data Table 1. The three Ashkenazi Jewish founder mutations accounted for 47 (56%) of the mutations detected. While a higher rate of point mutations was found in the Ashkenazi Jewish group (40%) than in the non-Ashkenazi Jewish group (26%) (p=0.02), the proportion of mutations identified in *BRCA1* (60%) and *BRCA2* (40%) was identical in both groups.

In the 115 Ashkenazi Jewish probands, 47 mutations (40% of families) were identified, 28 (24%) in *BRCA1* and 19 (16%) in *BRCA2*, respectively. Of the identified mutations, forty-five were Ashkenazi Jewish founder mutations (*BRCA1* 185delAG - 22, 5382insC – 5; *BRCA2* – 6174delT – 18) and two were non-founder mutations (1135insA in *BRCA1* and 5466insT in

*BRCA2*). *BRCA1* 1135insA, has been described as an ancient founder mutation in the Norwegian population and previously has been reported in an Ashkenazi Jewish family of Norwegian descent, as our family is (45,46).

After full sequencing in the probands from the 136 non-Ashkenazi Jewish families, 36 point mutations (26% of families) were identified. Twenty-one mutations (15%) and 15 (11%) were identified in *BRCA1* and in *BRCA2*, respectively. The only mutations identified more than once were both in *BRCA1*, 5832insC in two probands of Polish descent and IVS16+6T>6 in two African American probands. Five of 16 (31%) African Americans had identified mutations as compared to 31/120 (25.8%) European Americans. The estimated mutation prevalence for the African American probands ranged from 16.3 to 73.7% with a median of 26.3%. Twenty variants of uncertain significance (VUS) were identified in the 251 probands (see Supplementary Data Table 2). Four VUS were found in patients who also had deleterious mutations. Eight of the VUS were identified in *BRCA1* and 12 in *BRCA2*. Of these, *BRCA1* V1688del may be deleterious, but it is not yet formally classified as such (47). Eight of the 20 (40%) VUS were found in probands of African American ancestry.

## Comparison of sampled and non-sampled probands

In order to assess any bias based on sample collection, we evaluated in 62 probands who met eligibility criteria but did not provide a sample. Comparing the sampled (251) and non-sampled (62) probands, there was no significant difference in the estimated mutation prevalence (p=0.4, Ashkenazi Jewish and p=0.12, non-Ashkenazi Jewish). In the 40 Ashkenazi Jewish probands, 12 (29%) had mutations, not significantly different from the 115 Ashkenazi Jewish probands with samples (p=0.12). None of the 22 non-Ashkenazi Jewish probands carried mutations, significantly different than the sampled group (p=0.002). However, the inclusion of the non-sampled probands did not significantly changed the rate of point mutations, which decreased from 26 to 23% (p=0.49). Eighty-six percent of the potential non-Ashkenazi Jewish probands were included in the study.

## Comparison of Testing Population with Myriad Genetics Testing Population

In order to determine whether we could extrapolate our findings to the larger commercial testing population, we compared the expected number to the observed number of point mutations based on the Myriad II model. The majority of probands had an estimated mutation prevalence between 10 and 20%, comprising 49% and 55% of those studied in the non-Ashkenazi Jewish and Ashkenazi Jewish groups, respectively. In the non-Ashkenazi Jewish group, there was no significant difference between the number of observed and expected mutations (Figure 2a). In the entire Ashkenazi Jewish group, we found a significant difference between the number of observed and expected point mutations (p=0.008); this result was entirely due to the considerable difference between number of observed (20) and expected (9) mutations in the group with the estimated mutation prevalence between 11.2–16.7% (Figure 2b). In the 52 Ashkenazi Jewish probands with an estimated mutation prevalence over 20%, there was no significant difference between the number of observed and expected point mutations.

## Prevalence of Genomic Rearrangements in BRCA1 and BRCA2

In total, we screened 167 probands for genomic rearrangements in *BRCA1* and *BRCA2* using MLPA. Probands were included if they had negative result after full sequencing, the Ashkenazi Jewish founder mutation screen (if Ashkenazi Jewish) or a variant of uncertain significance. Using MLPA in the 68 Ashkenazi Jewish probands, four samples with decreases in peak height as compared to controls were identified, all of *BRCA2* exons 1–2. None of the peak height decreases were confirmed as true deletions by real time PCR of exon 2 of *BRCA2* or by BART. In summary, no genomic rearrangements were identified in the 68 Ashkenazi Jewish probands

studied. Twenty-five (37%) had an estimated mutation prevalence over 10%, which is the cutoff used for non-Ashkenazi Jewish women.

In the 100 non-Ashkenazi Jewish probands without deleterious point mutations, eight genomic rearrangements were detected - seven in *BRCA1* and one in *BRCA2*, all deletions (Table 3). One large genomic rearrangement (deletion of *BRCA1* exons 14–20) was identified by the 5-site rearrangement panel (Myriad Genetics, Salt Lake City, UT). The additional five in *BRCA1* and one in *BRCA2* were identified by MLPA and confirmed by real-time PCR of one or more of the relevant exon(s) of *BRCA1* or *BRCA2* (Supplemental Figures 2 and 3) and BART. A benign polymorphism, *BRCA2* 2192C→ G (P655R), known to be found in African Americans, within the MLPA *BRCA2* exon 11 probe binding site (probe 2279-L1770) created a false positive in two samples, which was not confirmed by real time PCR or BART. Five of these genomic rearrangements previously have been reported (33,43,48,49). We identified two novel large genomic deletions - the deletion of exons 11–12 in *BRCA1* and of exons 1–13 in *BRCA2*. We identified a deletion of *BRCA1* exons 21, 22, 23 and 24 in two independent families. The deletion of exons 8–9 in the African American family presumably is different than the previously reported deletion in women of European origin, (42) as it was not detected by the commercially available 5-site genomic rearrangement panel. Walsh and colleagues also detected a deletion of exons 8 and 9 in an African American family so it is possible that it is a founder mutation in this population (48). In our family, the deletion was in linkage disequilibrium with *BRCA1* A102G.

The frequency of genomic rearrangements in all non-Ashkenazi Jewish probands from our clinic based population was 6% (8/136), increasing to 8% (8/100) in those without identified point mutations. Together the genomic rearrangements constituted 18% (8/44) of all mutations identified in the non-Ashkenazi Jewish group; 29% (8/28) and 6% (1/16) of those in *BRCA1* and *BRCA2*, respectively. One of the genomic rearrangements was found in an African American individual; in this population, it constituted 1/6 (16%) of all mutations identified. The estimated mutation prevalences using the Myriad Genetics tables were not predictive of identifying genomic rearrangements in *BRCA1* or *BRCA2* in the non-Ashkenazi Jewish group (p=0.27). The median estimated mutation prevalence in the non-Ashkenazi Jewish probands was 22.9%.

In families without identified point mutations in *BRCA1* or *BRCA2*, the median estimated mutation prevalence was 17.9%; in the eight of these families subsequently identified with a genomic rearrangement the median estimated mutation prevalence was 17.6%, supporting a family history comparable to those families that did not have identified mutations. While the number of individuals identified with genomic rearrangements was small, those with rearrangements in *BRCA1* were more likely to have bilateral breast cancer (37.5% vs. 8%, p=0.03) than the mutation negative probands. There were no other significant differences between the personal or family history of the probands with genomic rearrangements as compared to the mutation negative probands.

## DISCUSSION

While the presence of genomic rearrangements in addition to point mutations in both *BRCA1* and *BRCA2* has been well established, the proportion of women carrying mutations and their relative contribution to the total mutations in a United States based high risk clinic representative of the commercial testing population has not been determined. In our study, 6% of non-Ashkenazi Jewish women with an estimated mutation prevalence over 10% had a genomic rearrangement, comprising 8% of those without an identified point mutation. Of importance, genomic rearrangements accounted for 18% of the mutations identified and their presence did not correlate with the estimated prevalence of *BRCA* mutation. Specifically, six

of the eight women with genomic rearrangements had an estimated mutation prevalence under 30%, and thus would not have been eligible for standard screening for genomic rearrangements, which is offered only to women with an estimated mutation prevalence over 30% (approximated from the Myriad Genetics criteria). While it is likely that the phenotypic predictors for genomic rearrangements in *BRCA1* and *BRCA2* are the same as those for point mutations, we did not identify enough rearrangements to fully evaluate mutation predictors. Our data support the consideration of genomic rearrangement screening in *BRCA1* and *BRCA2* for all non-Ashkenazi Jewish women with an estimated mutation prevalence over 10%.

The non-Ashkenazi Jewish group included sixteen (16/136, 12%) probands of African American ethnicity. Among the African American families with a negative sequencing result, we detected one family with a genomic rearrangement (deletion of exons 8–9) in *BRCA1*, representing 6% of all African American families and 16% of all mutations identified in this group (1/6). Our data underline the need for larger studies to explore the contribution of genomic rearrangements to the *BRCA1* and *BRCA2* mutation spectra among minority populations in the United States. The rate of genomic rearrangements identified in this series is consistent with previous series from Europe and Australia, but lower than a previous United States based series, in which 12% of probands without point mutations were found to have a rearrangement in *BRCA1* and *BRCA2* (48). The discrepancy likely is due to differences in the study eligibility criteria. The previous study included families with at least four cases of female breast cancer, ovarian cancer and/or male breast cancer, whereas the current study included patients with an estimated prevalence of over 10%, which encompasses families with as few as two case of female breast cancer. Nonetheless, the conclusion of both studies is the same – that non-Ashkenazi Jewish women without point mutations in *BRCA1* and *BRCA2* should be offered screening for genomic rearrangements in the clinical setting.

While genomic rearrangements significantly contribute to the total number of mutations in *BRCA1* and *BRCA2*, we did not identify any large genomic rearrangements in the Ashkenazi Jewish probands negative for point mutations. Within the Ashkenazi Jewish group, 45 of 47 (96%) point mutations were founder mutations. Our data are consistent with previous studies, demonstrating that the founder mutations account for more than 90% of mutations in Ashkenazi Jewish women (50,51). In total, reported in the literature and including our study, 99 Ashkenazi Jewish probands from high risk families have been negatively screened for genomic rearrangements (48). Thus, founder mutations continue to account for the vast majority of all mutations in this population. Even if 18% of all detectable non-founder mutations in our Ashkenazi Jewish cohort were genomic rearrangements, they nevertheless would represent very rare events, accounting for 0.72% of mutations based on the prevalence of non-founder mutations in the Ashkenazi Jewish population. These data suggest that routine screening for large genomic rearrangements does not appear warranted in Ashkenazi Jewish women. However, larger studies of this population need to be done.

Empiric predictive models, such as Myriad II, Couch and Manchester Scoring System are intended to estimate the possibility of a *BRCA1* or *BRCA2* mutation in a woman based on her family history and are used widely in clinical practice (5,21,52,53). Currently these models do not account for genomic rearrangements and as such underestimate the number of women with identifiable mutations, particularly in *BRCA1*. In addition, understanding the proportion of mutation that are missed using current methods to identify *BRCA1* or *BRCA2* is useful when counseling patients about their chances of being undetected mutation carriers. Previous studies from the Breast Cancer Linkage Consortium have suggested that the percentage of linked families with a detectable point mutation may be as low as 65% (23). However, the study was limited as various mutation detection techniques were used, some of which only detect 60–65% of mutations as compared to sequencing as a gold standard (54). Nonetheless, these studies did not include genomic rearrangements and thought should be given to repeating them with

improved mutation detection techniques and the larger spectrum of mutations now identified, so that women can be accurately counseled about their chances to carry an undetected mutation. We attempted to limit bias for and against mutations in our population by only including probands with a sample available in the laboratory and excluding any probands who themselves or any family member had prior genetic testing before being seen in CREP and having commercial testing. Due to our strict eligibility criteria, the number of probands available for study was restricted; as such, these findings will need to be replicated in a larger population. However, any such study will need to include systematic screening of a clearly defined population, so that the findings can be generally applied. While our study is based on a single high risk clinic population and thus limited, we have demonstrated that the number of observed mutations does not significantly different than those expected in the commercial testing population based on the Myriad II model. The Myriad II model has been demonstrated to perform similarly to BOADICEA and BRCAPRO; all of the models are limited in that they generally under predict mutations at the lower end of prediction probability and overestimate the upper ends (40,55). In the Ashkenazi Jewish population, the models did under predict the number of mutations at the lower end the mutation prevalence spectrum. Most models are limited to first- and second- degree relatives; however, in clinical practice family history characteristics of more distant relatives are important in evaluating a family. Overall, 80% of potentially eligible probands provided a sample; 86% of the non-Ashkenazi Jewish probands. The sampled Ashkenazi Jewish probands were representative of the entire potentially eligible Ashkenazi Jewish group. The non-sampled non-Ashkenazi Jewish probands did not differ in their estimated mutation prevalence, but did have fewer point mutations than the sampled group. However, including the non-sampled probands in the overall total did not significantly affect the rate of point mutations. As such, our clinic and the data presented herein are representative of patients seen at high risk clinics across the United States.

## Acknowledgments

We thank the families for participating in this study. We would like to acknowledge Dr. Barbara Weber who started the Cancer Risk Evaluation Program at the University of Pennsylvania.

Grant support: Breast Cancer Research Foundation (KLN), Associazione Italiana Ricerca sul Cancro (MDP), QVC Network and the Fashion Footwear Association of New York, Marjorie B. Cohen Foundation, National Cancer Institute Cancer Genetics Network [HHSN216200744000C] (SMD).

## References

1. Ries, LAG.; Harkins, D.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2003. 2006. [cited; Available from: http://seer.cancer.gov/csr/1975_2003/
2. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst 1995;87:1681–5. [PubMed: 7473816]
3. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer 1996;77:2318–24. [PubMed: 8635102]
4. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401–8. [PubMed: 9145676]
5. Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997;336:1409–15. [PubMed: 9145677]
6. Easton D. Breast cancer genes--what are the real risks? [news] Nat Genet 1997;16:210–1. [PubMed: 9207777]
7. Antoniou A, Pharoah PD, Narod S, et al. Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. Am J Hum Genet 2003;72:1117–30. [PubMed: 12677558]

8. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71. [PubMed: 7545954]
9. Tavtigian SV, Simard J, Rommens J, et al. The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds [see comments]. Nat Genet 1996;12:333–7. [PubMed: 8589730]
10. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2 [see comments] [published erratum appears in Nature 1996 Feb 22;379(6567):749]. Nature 1995;378:789–92. [PubMed: 8524414]
11. Nelson HD, Huffman LH, Fu R, Harris EL. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2005;143:362–79. [PubMed: 16144895]
12. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol 2006;24:2437–43. [PubMed: 16636335]
13. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group [see comment]. J Clin Oncol 2004;22:1055–62. [PubMed: 14981104]
14. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23:7804–10. [PubMed: 16219936]
15. Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol 2006;7:223–9. [PubMed: 16510331]
16. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365:1769–78. [PubMed: 15910949]
17. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609–15. [PubMed: 12023992]
18. Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer [see comments]. N Engl J Med 1997;336:1409–15. [PubMed: 9145677]
19. Thompson D, Easton D. Breast Cancer Linkage C. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 2001;68:410–9. [PubMed: 11170890]
20. Thompson D, Easton D. Breast Cancer Linkage C. Variation in BRCA1 cancer risks by mutation position. Cancer Epidemiol Biomarkers Prev 2002;11:329–36. [PubMed: 11927492]
21. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol 2002;20:1480–90. [PubMed: 11896095]
22. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. JAMA 2005;294:1925–33. [PubMed: 16234499]
23. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676–89. [PubMed: 9497246]
24. Petrij-Bosch A, Peelen T, van Vliet M, et al. BRCA1 genomic deletions are major founder mutations in Dutch breast cancer patients [published erratum appears in Nat Genet 1997 Dec;17(4):503]. Nat Genet 1997;17:341–5. [PubMed: 9354803]
25. Puget N, Torchard D, Serova-Sinilnikova OM, et al. A 1-kb Alu-mediated germ-line deletion removing BRCA1 exon 17. Cancer Res 1997;57:828–31. [PubMed: 9041180]
26. Puget N, Sinilnikova OM, Stoppa-Lyonnet D, et al. An Alu-mediated 6-kb duplication in the BRCA1 gene: a new founder mutation? Am J Hum Genet 1999;64:300–2. [PubMed: 9915971]
27. Unger MA, Nathanson KL, Calzone K, et al. Screening for genomic rearrangements in families with breast and ovarian cancer identifies BRCA1 mutations previously missed by conformation-sensitive gel electrophoresis or sequencing. Am J Hum Genet 2000;67:841–50. [PubMed: 10978226]

28. Agata S, Viel A, Della Puppa L, et al. Prevalence of BRCA1 genomic rearrangements in a large cohort of Italian breast and breast/ovarian cancer families without detectable BRCA1 and BRCA2 point mutations. Genes Chromosomes Cancer 2006;45:791–7. [PubMed: 16715518]
29. Preisler-Adams S, Schonbuchner I, Fiebig B, Welling B, Dworniczak B, Weber BH. Gross rearrangements in BRCA1 but not BRCA2 play a notable role in predisposition to breast and ovarian cancer in high-risk families of German origin. Cancer Genet Cytogenet 2006;168:44–9. [PubMed: 16772120]
30. Gad S, Caux-Moncoutier V, Pages-Berhouet S, et al. Significant contribution of large BRCA1 gene rearrangements in 120 French breast and ovarian cancer families. Oncogene 2002;21:6841–7. [PubMed: 12360411]
31. de la Hoya M, Gutierrez-Enriquez S, Velasco E, et al. Genomic rearrangements at the BRCA1 locus in Spanish families with breast/ovarian cancer. Clin Chem 2006;52:1480–5. [PubMed: 16793929]
32. Thomassen M, Gerdes AM, Cruger D, Jensen PK, Kruse TA. Low frequency of large genomic rearrangements of BRCA1 and BRCA2 in western Denmark. Cancer Genet Cytogenet 2006;168:168–71. [PubMed: 16843109]
33. Woodward AM, Davis TA, Silva AG, Kirk JA, Leary JA. Large genomic rearrangements of both BRCA2 and BRCA1 are a feature of the inherited breast/ovarian cancer phenotype in selected families. J Med Genet 2005;42:e31. [PubMed: 15863663]
34. Hartmann C, John AL, Klaes R, et al. Large BRCA1 gene deletions are found in 3% of German high-risk breast cancer families. Hum Mutat 2004;24:534. [PubMed: 15532023]
35. Anonymous. The exon 13 duplication in the BRCA1 gene is a founder mutation present in geographically diverse populations. The BRCA1 Exon 13 Duplication Screening Group. Am J Hum Genet 2000;67:207–12. [PubMed: 10827109]
36. Gutierrez-Enriquez S, de La Hoya M, Martinez-Bouzas C, et al. Screening for large rearrangements of the BRCA2 gene in Spanish families with breast/ovarian cancer. Breast Cancer Res Treat. 2006
37. Casilli F, Tournier I, Sinilnikova OM, et al. The contribution of germline rearrangements to the spectrum of BRCA2 mutations. J Med Genet 2006;43:e49. [PubMed: 16950820]
38. Agata S, Dalla Palma M, Callegaro M, et al. Large genomic deletions inactivate the BRCA2 gene in breast cancer families. J Med Genet 2005;42:e64. [PubMed: 16199546]
39. Lahti-Domenici J, Rapakko K, Paakkonen K, et al. Exclusion of large deletions and other rearrangements in BRCA1 and BRCA2 in Finnish breast and ovarian cancer families. Cancer Genet Cytogenet 2001;129:120–3. [PubMed: 11566341]
40. Barcenas CH, Hosain GM, Arun B, et al. Assessing BRCA carrier probabilities in extended families. J Clin Oncol 2006;24:354–60. [PubMed: 16421416]
41. Hendrickson BC, Judkins T, Ward BD, et al. Prevalence of five previously reported and recurrent BRCA1 genetic rearrangement mutations in 20,000 patients from hereditary breast/ovarian cancer families. Genes Chromosomes Cancer 2005;43:309–13. [PubMed: 15846789]
42. Rohlfs EM, Puget N, Graham ML, et al. An Alu-mediated 7.1 kb deletion of BRCA1 exons 8 and 9 in breast and ovarian cancer families that results in alternative splicing of exon 10. Genes Chromosomes Cancer 2000;28:300–7. [PubMed: 10862036]
43. Ward BD, Hendrickson BC, Judkins T, et al. A multi-exonic BRCA1 deletion identified in multiple families through single nucleotide polymorphism haplotype pair analysis and gene amplification with widely dispersed primer sets. J Mol Diagn 2005;7:139–42. [PubMed: 15681486]
44. Barrois M, Bieche I, Mazoyer S, Champeme MH, Bressac-de Paillerets B, Lidereau R. Real-time PCR-based gene dosage assay for detecting BRCA1 rearrangements in breast-ovarian cancer families. Clin Genet 2004;65:131–6. [PubMed: 14984472]
45. Borg A, Dorum A, Heimdal K, Maehle L, Hovig E, Moller P. BRCA1 1675delA and 1135insA account for one third of Norwegian familial breast-ovarian cancer and are associated with later disease onset than less frequent mutations. Dis Markers 1999;15:79–84. [PubMed: 10595257]
46. Rudkin TM, Hamel N, Galvez M, et al. The frequent BRCA1 mutation 1135insA has multiple origins: a haplotype study in different populations. BMC Med Genet 2006;7:15. [PubMed: 16509964]
47. Vallon-Christersson J, Cayanan C, Haraldsson K, et al. Functional analysis of BRCA1 C-terminal missense mutations identified in breast and ovarian cancer families. Hum Molec Genet 2001;10:353–60. [PubMed: 11157798]

48. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006;295:1379–88. [PubMed: 16551709]

49. Mazoyer S. Genomic rearrangements in the BRCA1 and BRCA2 genes. Hum Mutat 2005;25:415–22. [PubMed: 15832305]

50. Kauff ND, Perez-Segura P, Robson ME, et al. Incidence of non-founder BRCA1 and BRCA2 mutations in high risk Ashkenazi breast and ovarian cancer families. J Med Genet 2002;39:611–4. [PubMed: 12161607]

51. Phelan CM, Kwan E, Jack E, et al. A low frequency of non-founder BRCA1 mutations in Ashkenazi Jewish breast-ovarian cancer families. Hum Mutat 2002;20:352–7. [PubMed: 12402332]

52. Evans DG, Lalloo F, Wallace A, Rahman N. Update on the Manchester Scoring System for BRCA1 and BRCA2 testing. J Med Genet 2005;42:e39. [PubMed: 15994864]

53. Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 2004;91:1580–90. [PubMed: 15381934]

54. Eng C, Brody LC, Wagner TM, et al. Interpreting epidemiological research: blinded comparison of methods used to estimate the prevalence of inherited mutations in BRCA1. J Med Genet 2001;38:824–33. [PubMed: 11748305]

55. Capalbo C, Ricevuto E, Vestri A, et al. BRCA1 and BRCA2 genetic testing in Italian breast and/or ovarian cancer families: mutation spectrum and prevalence and analysis of mutation prediction models. Ann Oncol 2006;17(Suppl 7):vii34–vii40. [PubMed: 16760289]

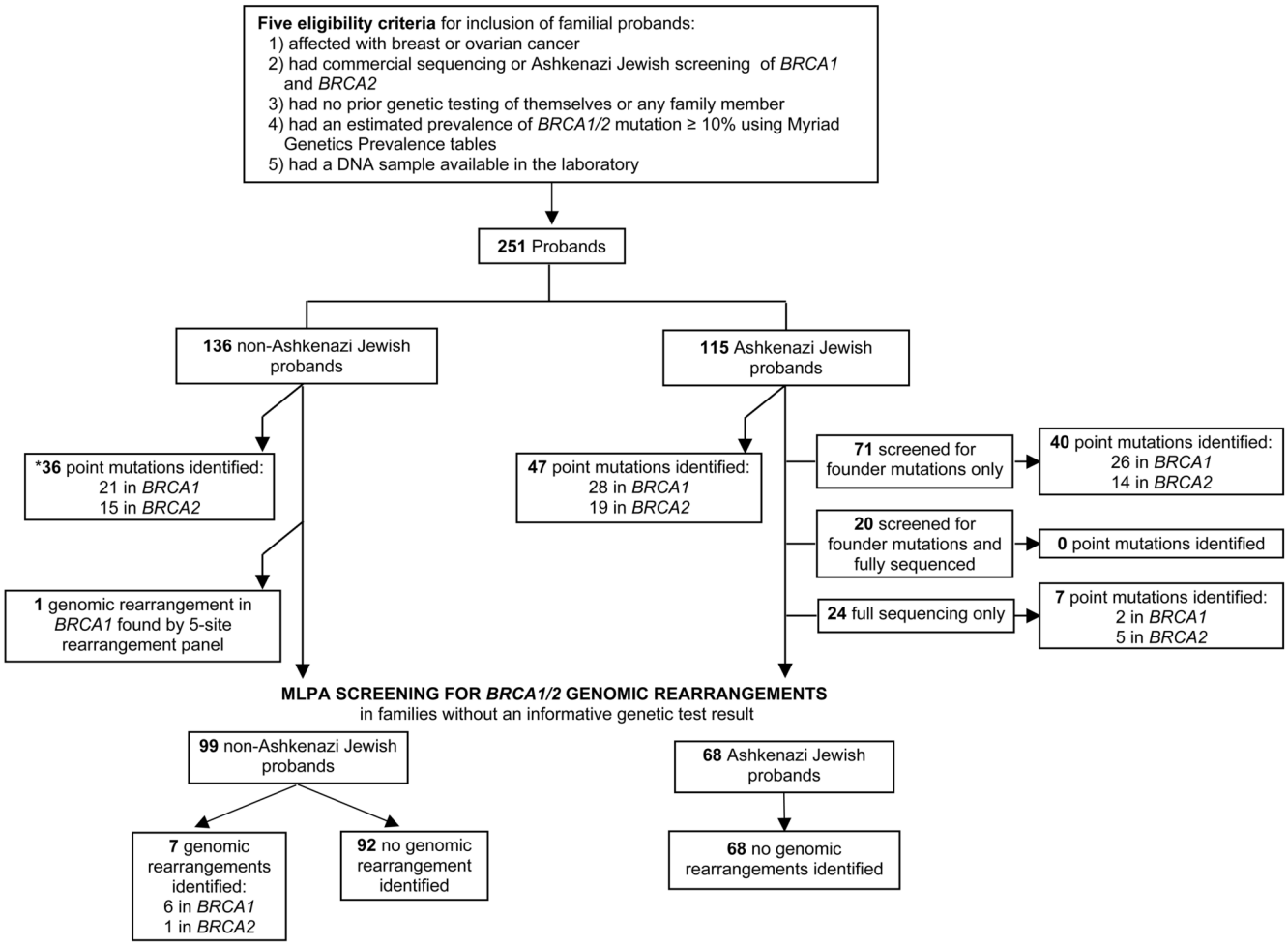


**Figure 1.**

Analytical strategy of the study and numbers of patients identified in each group. *Mutations are listed in Supplementary Table 1

**Figure 2 a.**

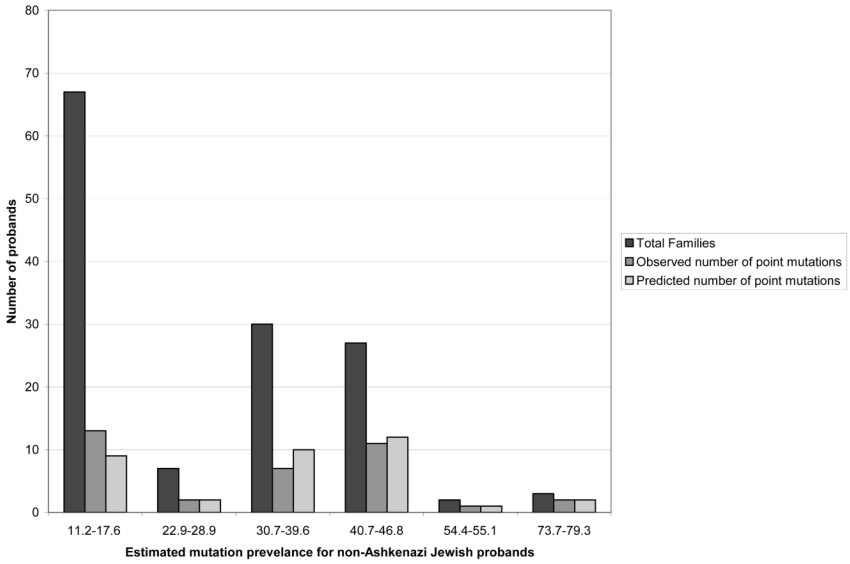


**Figure 2 b.**

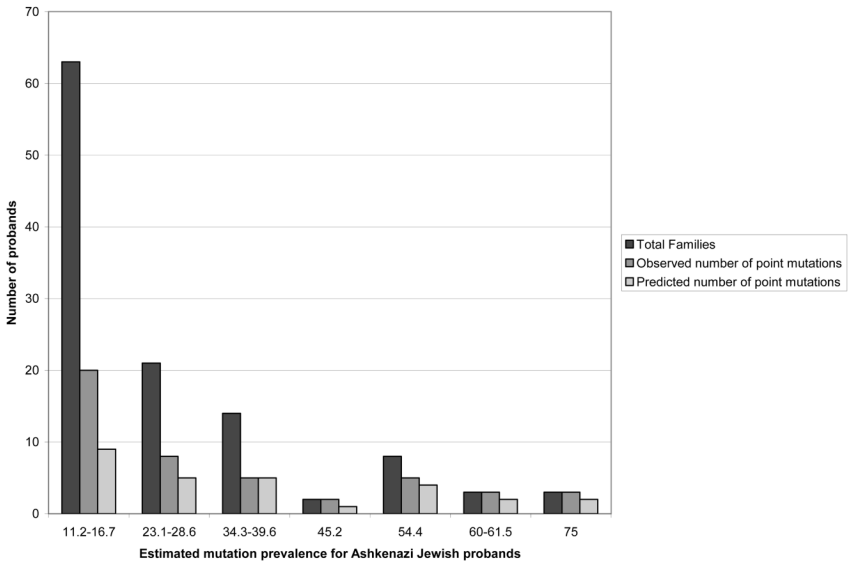


**Figure 2.**

Figure 2a. The total number of non-Ashkenazi Jewish probands in each estimated mutation prevalence, group showing the estimated and observed number of point mutations

Figure 2b: The total number of Ashkenazi Jewish probands in each mutation prevalence group, showing the estimated and observed number of point mutation

**Table 1**
Characteristics of all probands

| Characteristics | | Family N° (%) |
|---|---|---|
| **Ethnicity**, All probands (N=251) | | |
| *Non-Ashkenazi Jewish* | | 136 (54) |
| European | | 119 (87) |
| African American | | 16 (12) |
| Latin American | | 1 (1) |
| *Ashkenazi Jewish* | | 115 (46) |
| **Cancer history** | | |
| ***Non-Ashkenazi Jewish*** | | **136 (100)** |
| Breast only* | | 90 (66) |
| | Age of breast diagnosis: | |
| | <30 | 3 (2) |
| | 30–39 | 33 (25) |
| | 40–49 | 46 (33) |
| | 50–59 | 7 (5) |
| | ≥ 60 | 1 (1) |
| Ovarian only | | 13 (9) |
| Breast and Ovarian | | 11 (8) |
| Bilateral Breast | | 14 (11) |
| Bilateral Breast and Ovarian Cancer | | 3 (2) |
| Male Breast | | 5 (4) |
| ***Ashkenazi Jewish*** | | **115 (100)** |
| Breast only | | 71 (62) |
| | Age of breast diagnosis: | |
| | <30 | 3 (2.5) |
| | 30–39 | 19 (16) |
| | 40–49 | 35 (31) |
| | 50–59 | 10 (9) |
| | ≥ 60 | 4 (3.5) |
| Ovarian only | | 13 (11) |
| Breast and Ovarian | | 6 (5) |
| Bilateral Breast | | 21 (18) |
| Bilateral Breast and Ovarian Cancer | | 2 (2) |
| Male Breast | | 2 (2) |

*Cancer history percentage shown is the percent of total non-Ashkenazi Jewish or Ashkenazi Jewish groups

**Table 2**

Characteristics of non-Ashkenazi Jewish families*

| | All Families (n = 136) | *BRCA1* Point Mutation Positive Families (n = 21) | *BRCA2* Point Mutation Positive Families (n = 15) | *BRCA1* Genomic Rearrangement Positive Families (n = 7) | *BRCA2* Genomic Rearrangement Positive Families (n = 1) | All Mutation Positive Families (n = 44) | All Mutation Negative Families (n = 92) | p value† |
|---|---|---|---|---|---|---|---|---|
| **Familial Characteristics** | | | | | | | | |
| Any Breast Cancer (%) | 134 (99) | 21 (100) | 15 (100) | 7 (100) | 1 (100) | 44 (100) | 90 (98) | 0.55 |
| Breast Cancer <50 y (%) | 130 (96) | 20 (95) | 15 (100) | 7 (100) | 1 (100) | 43 (98) | 87 (95) | 0.55 |
| Br/Ov Cancer in the same individual (%) | 22 (16) | 6 (29) | 4 (27) | 1 (14) | 0 | 11 (25) | 11 (12) | 0.05 |
| Any Ovarian Cancer (%) | 63 (46) | 14 (67) | 8 (53) | 4 (57) | 1 (100) | 27 (61) | 36 (39) | 0.02 |
| Male Breast Cancer (%) | 9 (7) | 1 (5) | 1 (6) | 0 | 1 (100) | 3 (7) | 6 (7) | >0.99 |
| Pancreatic Cancer (%) | 9 (7) | 1 (5) | 5 (33) | 0 | 0 | 6 (14) | 3 (3) | 0.03 |
| Prostate Cancer (%) | 26 (19) | 7 (33) | 3 (9) | 2 (29) | 1 (100) | 13 (29) | 13 (14) | 0.04 |
| **Proband Characteristics** | | | | | | | | |
| Breast Cancer Only (%) | 90 (66) | 9 (43) | 10 (67) | 4 (57) | 0 | 23 (52) | 67 (73) | 0.02 |
| Bilateral Breast Cancer (%) | 15 (11) | 4 (19) | 1 (7) | 2 (29) | 1 (100) | 8 (18) | 7 (8) | 0.08 |
| Ovarian Cancer Only (%) | 13 (10) | 3 (14) | 1 (7) | 1 (14) | 0 | 5 (11) | 8 (9) | 0.75 |
| Br/Ov Cancer in the same individual (%) | 13 (10) | 4 (19) | 2 (13) | 0 | 0 | 6 (14) | 7 (8) | 0.34 |
| Male Breast Cancer (%) | 5 (4) | 1 (5) | 1 (7) | 0 | 0 | 2 (5) | 3 (3) | >0.99 |
| Breast Cancer Average Age Dx | 43.1 | 40.4 | 43.5 | 35.7 | --- | 40.8 | 44.0 | 0.14‡ |
| Ovarian Cancer Average Age Dx | 57.5 | 51 | 59 | --- | --- | 53.7 | 60.3 | 0.57 |

*includes up to fourth degree relatives

†comparison of all mutation positive and negative families using two-tailed Fisher Exact test

‡comparison of average age of diagnoses using Krushal Wallis test

*Cancer Res*. Author manuscript; available in PMC 2009 September 28.

**Table 3**

Description of genomic rearrangements

| Gene | Exon(s) | Type of genomic change | Myriad II model estimated mutation prevalence† | Phenotype proband | Family history (# of cases)‡ | | | | | Ethnicity |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Primary Cancer(s) (Age of Dx) | Br Ca | Br Ca Dx < 50 | Male Br Ca | Ov Ca | Br/Ov Ca | |
| *BRCA1* | 1–2 | Deletion | 17.6 | Breast ca (45) | 1 | 1 | --- | 1 | --- | White (Irish/English/German) |
| *BRCA1* | 3 | Deletion | 46.8 | Ovarian ca (54) | 2 | 1 | --- | --- | 1 | White (Italian) |
| *BRCA1* | 8–9 | Deletion | 17.6 | Breast ca (29) | 1 | 1 | --- | 1 | --- | African-American |
| *BRCA1* | part of 11–12 | Deletion | 17.6 | Breast ca (39) | 1 | 1 | --- | 1 | --- | White (Western Europe) |
| *BRCA1* | 14–20* | Deletion | 16.3 | Bilateral breast ca (27, 33) | 2 | 2 | --- | --- | --- | White (British) |
| *BRCA1* | 21–24 | Deletion | 16.3 | Bilateral breast ca (45, 47) | 3 | 2 | --- | --- | --- | White (Irish/German) White |
| *BRCA1* | 21–24 | Deletion | 30.7 | Breast ca (29) | 6 | 5 | --- | --- | --- | (German/British/Italian/Czech) White |
| *BRCA2* | 1–13 | Deletion | 11.2 | Bilateral breast ca (55, 55) | 6 | 4 | 1 | 1 | --- | (Scottish/English/German/Norwegian) |

*Identified by the Myriad Genetics 5-site rearrangement screen

†Using 1st and 2nd degree relatives

‡Up to 4th degree relatives included in family history