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# Breast Cancer Risk Among Male BRCA1 and BRCA2 Mutation Carriers

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## Abstract

Men who carry germline mutations in the BRCA2 gene have a higher risk of developing breast carcinoma than men in the general population. Men who carry germline mutations in the BRCA1 gene may also be at a higher risk for breast carcinoma, but this association is not as well established. We evaluated the risks of developing breast carcinoma for male BRCA1 and BRCA2 mutation carriers in the US population based on data from 1939 families with 97 male subjects with breast carcinoma that were collected from eight centers across the National Cancer Institute's Cancer Genetics Network. At all ages, the cumulative risks of male breast cancer were higher in both BRCA1 and BRCA2 mutation carriers than in noncarriers. The relative risks of developing breast cancer were highest for men in their 30s and 40s and decreased with increasing age. Both the relative and cumulative risks were higher for BRCA2 mutation carriers than for BRCA1 mutation carriers. The estimated cumulative risk of breast carcinoma for male BRCA1 mutation carriers at age 70 years was 1.2% (95% confidence interval [CI] = 0.22% to 2.8%) and for BRCA2 mutation carriers, 6.8% (95% CI = 3.2% to 12%).

Male breast carcinoma accounts for less than 1% of all breast cancer cases in the United States (1,2). It is more common in men with a family history of breast cancer. Both genetic linkage and DNA sequencing data have demonstrated that male breast carcinoma is associated with deleterious germline mutations in BRCA2 (3,4). Several studies have examined the incidence of BRCA2 mutations in men with breast cancer (5–9). In one study that included 237 hereditary breast carcinoma families, 26 families had at least one male member who had been diagnosed with breast carcinoma and in 77%, the disease was linked to mutations in BRCA2 (5). Couch et al. (6) found that 14% of 50 male breast cancer patients who were not selected based on a family history of breast cancer had a deleterious BRCA2 mutation. Easton et al. (7) examined two large BRCA2-linked families that contained four male breast carcinoma cases. The estimated cumulative risk for male breast carcinoma by age 70 years was 6.3%. In a separate study of 164 families with BRCA2 mutations, the estimated cumulative risk of breast cancer for men who carried BRCA2 mutations was 2.8% by 70 years of age and 6.9% by 80 years of age (8). Recently, Risch et al. (9) estimated that the relative risk of breast cancer for male BRCA2 carriers was 102 (95% confidence interval [CI] = 9.9 to 1050).

The association between male breast carcinoma and deleterious germline mutations in BRCA1 is less clear. Initial data suggested that inherited male breast cancer was not linked to germline mutations in BRCA1 (10) and BRCA1 mutations have been detected at very low frequency in several series of unselected male breast cancer patients (11–14). However, a more recent study

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(15) in a series of 10000 individuals reported that 21 of 76 men with breast cancer had mutations in either BRCA1 or BRCA2; more than one-third of those mutations were in BRCA1. Brose et al. (16) estimated a lifetime risk of male breast cancer of 5.8% in BRCA1 mutation carriers, but this estimate was based on families who sought breast cancer risk counseling and was not adjusted for ascertainment. The purpose of our study was to evaluate the risk of breast carcinoma for male BRCA1 and BRCA2 mutation carriers by using a large sample of US family histories.

We used a database that contained detailed family history information for 1948 families with complete pedigrees that were collected from eight centers across the National Cancer Institute's Cancer Genetics Network (CGN). The CGN has been described in detail (17). Nine families were excluded from the analysis because of invalid entries in the pedigree. Among the remaining 1939 families, 676 were of Ashkenazi Jewish ancestry. Seven of the eight centers were high-risk counseling clinics, and one was a population-based clinic. Therefore, most of the families were ascertained based on a family history of breast and/or ovarian cancer. The institutional review boards at each participating institution approved the study protocol.

Of the 1939 families included in this analysis, 87 families (4.5%) had one or more male members with breast carcinoma; the total number of male subjects with breast carcinoma was 97. Only one person in each family, i.e., the proband, was genotyped. In 45 families (52%), the male breast cancer patient was the proband. Of the 87 probands, 23 (26%) had detectable BRCA2 mutations and six (7%) had detectable BRCA1 mutations. The median age at diagnosis of male breast cancer was 64 years (range = 24–87 years). There were three male subjects with contralateral breast cancer. Table 1 presents information for the 97 male breast cancer subjects.

We estimated the risk of breast cancer for men who carried a BRCA1 or BRCA2 mutation by assuming that the age-conditional probability of developing cancer at age $t$ was that of a noncarrier multiplied by the relative risk at that age [RR($t$)], which was defined as $\exp(\alpha + \beta \times t)$, where $\alpha$ quantifies the relative risk at age 0 and $\beta$ quantifies the change in relative risk with respect to age. We assumed that the age-conditional probabilities of developing cancer for noncarriers were the same as those for the US male population (18). We also assumed that the relative risks were the same for Ashkenazi Jewish and non-Ashkenazi Jewish individuals but that the relative risks differed between BRCA1 mutation carriers and BRCA2 mutation carriers.

**CONTEXT AND CAVEATS**

**Prior knowledge:** Men who carry germline mutations in the BRCA2 gene have a higher risk of developing breast carcinoma than men in the general population. However, the association between germline mutations in the BRCA1 gene and the risk of breast carcinoma in men is not as well established.

**Study design:** A retrospective study of the risk of developing breast carcinoma for male BRCA1 and BRCA2 mutation carriers in the United States based on data from 1939 families with 97 men with breast carcinoma that were collected from eight centers across the National Cancer Institute's Cancer Genetics Network.

**Contribution:** At all ages, the cumulative risks of male breast cancer were higher in both BRCA1 and BRCA2 mutation carriers than in non-carriers. The relative risks of developing breast cancer were highest for men in their 30s and 40s and decreased with increasing age. Both the relative and cumulative risks were higher for BRCA2 mutation carriers than for BRCA1 mutation carriers.

**Implications:** These risk estimates are important for determining appropriate risk management strategies for the male members of families with germline mutations in BRCA1 or BRCA2.

**Limitations:** No information about family members' ethnicity group other than their Ashkenazi Jewish ancestry was available, precluding estimates of the penetrance of mutations in BRCA1 and BRCA2 for African Americans.

Because our study included subjects who pursued mutation testing for BRCA1 and BRCA2, it included a greater representation of families with a history of breast and ovarian cancer than studies that have examined unselected cases of male breast cancer. To correct for possible selection bias, we used a retrospective likelihood approach (19), in which each family's contribution to the likelihood of penetrance parameters is the probability of the genetic test results conditioning on the observed family history. This approach produces unbiased estimates of risk provided that the probability of including a family in the study depends only on the family history (19) and not on other information relevant to the presence of a genetic mutation (e.g., linkage score). Because all subjects included in this study were the first person in their family to be tested for a BRCA1 or BRCA2 mutation, this approach gives unbiased estimates in our study, even though the selection of subjects into the study involves, to some extent, the subjects' own preferences.

Table 2 presents the estimated age-specific cumulative risks and relative risks of developing breast cancer for male BRCA1 and BRCA2 mutation carriers. Prospective cancer risks are provided in the BRCAPRO program (20,21). At all ages, the cumulative risks of male breast cancer were higher in both BRCA1 and BRCA2 mutation carriers than in noncarriers. The estimated cumulative risk of breast carcinoma for male BRCA1 mutation carriers at age 70 years was 1.2% (95% CI = 0.22% to 2.8%), and for BRCA2 mutation carriers, 6.8% (95% CI = 3.2% to 12%). The relative risks of developing male breast cancer were highest for men in their 30s and 40s and decreased with increasing age. This trend was particularly pronounced in BRCA2 mutation carriers: the relative risk at age 30 years was 22.3 times that at age 70 years.

Our study has several strengths. First, the US cohort that we used to examine male breast cancer risk is the largest to date, contains families of Ashkenazi Jewish and other ancestries, and provided risk estimates for BRCA1 and BRCA2 mutation carriers in the US population. Such risk estimates are important for determining appropriate risk management strategies for the male members of families with germline mutations in BRCA1 or BRCA2. Our cumulative risk estimates for BRCA2 mutation carriers are similar to those reported by Easton et al. (7) and Risch et al. (9). Second, to our knowledge, this study is the first to characterize the risks for male BRCA1 mutation carriers in an unbiased fashion with a large cohort. Our demonstration that BRCA1 mutations are associated with an elevated risk of male breast cancer, but that those risks are still substantially lower than those in BRCA2 mutations carriers, confirms previous suggestions (2,10) that the link between BRCA1 mutations and male breast carcinoma is weaker than that between BRCA2 mutations and male breast cancer.

A potential limitation of our approach is that the values we used for the BRCA1 and BRCA2 mutated allele frequencies were fixed at values derived from the literature instead of estimated from the data. For individuals of Ashkenazi Jewish ancestry, we used mutated allele frequencies of 0.0060 and 0.0067 for BRCA1 and BRCA2, respectively, according to a meta-analysis of published estimates (22). For individuals who were not of Ashkenazi Jewish ancestry, we used mutated allele frequencies of 0.00058 and 0.00067 for BRCA1 and BRCA2, respectively (23,24). Risch et al. (9) recently published mutated allele frequencies of 0.0016 and 0.0035 for BRCA1 and BRCA2, respectively, for individuals not of Ashkenazi Jewish

ancestry living in Ontario, Canada. This BRCA2 mutated allele frequency is fivefold larger than the frequency we used. To test the robustness of our risk estimates with respect to allele frequency, we repeated the analysis with the higher allele frequencies. As a result, the cumulative risks by age 80 years decreased from 1.8% (95% CI = 0.3% to 4.5%) to 1.5% (95% CI = 0.3% to 3.9%) for BRCA1 and from 8.3% (95% CI = 3.9% to 15%) to 5.1% (95% CI = 2.0% to 11.0%) for BRCA2. The relative risks at younger ages were also smaller than the ones we estimated in the original analysis (e.g., the relative risks for BRCA1 and BRCA2 mutation carriers at age 30 years were 24 [95% CI = 2.4 to 102] and 430 [95% CI = 68 to 1759], respectively). The relative risks gradually decreased with increasing age, and the relative risks at age 80 years (e.g., 11 [95% CI = 1.7 to 34) for BRCA1 mutation carriers and 16 [95% CI = 5.1 to 42] for BRCA2 mutation carriers) were similar to the ones estimated in our original analysis (Table 2). These similar risk estimates suggest that our approach was robust across a range of allele frequencies.

Another limitation of our study is that we had no information about family members' ethnicity group other than their Ashkenazi Jewish ancestry. Therefore, we were not able to estimate the penetrance of mutations in BRCA1 and BRCA2 for African Americans, for whom the male-to-female ratio for breast carcinoma is higher than it is for white populations (2,25).

The male penetrance estimates reported here have been incorporated into the current version of the BayesMendel genetic counseling software and which is available to genetic counselors through the CaGene software package (26).

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## Table 1

Male breast cancers, grouped by family

| Mutated gene | Mutation | Ethnicity | Age at first diagnosis [*], y | No. of female breast cancers in family [†] |
|---|---|---|---|---|
| BRCA1 | 633delC | Other | 46[‡] | 2 |
| BRCA1 | 2931CC→G | Other | 64[‡] | 1 |
| BRCA1 | 2985del5 | Other | 73 | 4 |
| BRCA1 | 5149del5 | Other | 51 | 3 |
| BRCA1 | 5296del4 | Other | 68 | 4 |
| BRCA1 | Exon 13 dup | Other | 42 | 4 |
| BRCA2 | 379delG | Other | 79, 49[‡] | 1 |
| BRCA2 | 1128insG | Other | 48[‡] | 2 |
| BRCA2 | 3034del4 | Other | 52,[‡§] | 3 |
| BRCA2 | Y1894X | Other | 64, 70[‡] | 1 |
| BRCA2 | 6174delT | Other | 46[‡] | 0 |
| BRCA2 | 6174delT | Other | 61[‡] | 0 |
| BRCA2 | 6174delT | Other | 75[‡] | 2 |
| BRCA2 | 7989delC | Other | 53, 70[‡] | 5 |
| BRCA2 | 1538del4 | Other | 66 | 6 |
| BRCA2 | 1982delA | Ashkenazi Jewish | 85, 71 | 4 |
| BRCA2 | 2041insA | Other | 51 | 4 |
| BRCA2 | 3034del4 | Other | 47 | 4 |
| BRCA2 | 3945delA | Other | 66, 42 | 4 |
| BRCA2 | 4075delGT | Ashkenazi Jewish | 70 | 2 |
| BRCA2 | 5482delC | Other | 70 | 1 |
| BRCA2 | 5849del4 | Other | 62, 65 | 7 |
| BRCA2 | 5950delCT | Other | 65 | 1 |
| BRCA2 | 6051delA | Other | 58 | 2 |
| BRCA2 | 6174delT | Other | 49 | 3 |
| BRCA2 | 6174delT | Ashkenazi Jewish | 61 | 1 |
| BRCA2 | 6659delA | Other | 49 | 4 |
| BRCA2 | 9538delAA | Other | 50 | 5 |
| BRCA2 | Q3066X | Other | 26 | 5 |
| None found | — | 18 Ashkenazi Jewish | 60 (13.7)[‖] | 1.56 (1.29) |
| None found | — | 44 Other | 64 (12.2) | 1.45 (1.38) |

[*] When more than one breast cancer was diagnosed in a single man, the age at each diagnosis is presented for BRCA1 and BRCA2 mutation carriers, and the mean age at diagnosis (standard deviation) is presented for noncarriers.

[†] The mean number of female breast cancers (standard deviation) is presented for noncarriers.

[‡] Carriage of a mutation was confirmed by genotype analysis.

[§] This man had contralateral breast cancer. Cancer in the second breast was diagnosed at age 55 years.

[‖] This group includes two men with contralateral male breast cancer: one was diagnosed at ages 58 and 59 years, and the other was diagnosed at age 45 years for both breasts. Both patients were genotyped, but no mutation was found.

**Table 2**

Age-specific cumulative risks and relative risks of developing breast cancer for male BRCA1 and BRCA2 mutation carriers and noncarriers*

| Age, y | Cumulative breast cancer risk, % (95% CI) | | | RR (95% CI) | |
|---|---|---|---|---|---|
| | BRCA1 mutation carrier | BRCA2 mutation carrier | No BRCA1 or BRCA2 mutation† | BRCA1 mutation carrier | BRCA2 mutation carrier |
| 30 | $1.7 \times 10^{-2}$($6.8 \times 10^{-4}$ to 0.12) | 0.18 (0.027 to 0.85) | $1.2 \times 10^{-4}$ | 89 (6 to 505) | 936 (201 to 3277) |
| 40 | 0.12 (0.012 to 0.58) | 1.2 (0.3 to 3.6) | $1.9 \times 10^{-3}$ | 41 (6 to 170) | 396 (129 to 986) |
| 50 | 0.3 (0.052 to 1.2) | 2.7 (0.94 to 6.6) | $8.5 \times 10^{-3}$ | 23 (5 to 61) | 178 (76 to 344) |
| 60 | 0.62 (0.13 to 1.7) | 4.7 (1.9 to 9.5) | $2.7 \times 10^{-2}$ | 16 (3 to 40) | 84 (38 to 158) |
| 70 | 1.2 (0.22 to 2.8) | 6.8 (3.2 to 12) | $6.7 \times 10^{-2}$ | 12 (1 to 34) | 42 (15 to 91) |
| 80 | 1.8 (0.3 to 4.5) | 8.3 (3.9 to 15) | 0.12 | 11 (0.3 to 34) | 22 (5 to 57) |

*CI = confidence interval; RR = relative risk.

†The cumulative risk estimates for noncarriers were obtained from the Surveillance, Epidemiology, and End Results database, which does not provide 95% CIs.