**ORIGINAL ARTICLE**

**Risk Modeling in Breast Cancer**

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**Abstract:** Woman with *BRCA-1* or *BRCA-2* mutations have a significantly increased risk for breast cancer. While genetic testing can provide valuable information concerning this increased risk and the proposed benefit of risk-reducing interventions, the absolute breast cancer risk conferred by *BRCA-1* and *BRCA-2* mutations remains to be fully determined. The American Society of Clinical Oncology (ASCO) guidelines indicate that testing should be considered in women whose mutation probability is greater than 10%. None of the currently available approaches for determining BRCA gene mutation probability are 100% accurate. The computer program BRCAPRO is a useful adjunct for estimating these probabilities, but limitations inherent in mathematical models make it essential that genetic counselors are involved in decisions to perform genetic testing.

Although less than 10% of breast cancers are linked to genetic mutations, such as *BRCA-1* and *BRCA-2*, women who carry these mutations are at very high risk for breast cancer, and the information provided by genetic testing is invaluable for making informed decisions related to breast cancer risk management. The absolute risk of breast cancer conferred by a *BRCA* gene mutation remains debatable. Data from a linkage consortium study (1) suggest that a woman with a *BRCA* gene mutation has an 85% probability of developing breast cancer. Looking at unselected families where the proband was affected with breast cancer, the probability of breast cancer development ranges from approximately 35% to 70%, with the penetrance as low as 26% in families with unaffected probands. No one number accurately expresses the risk of breast cancer associated with *BRCA* mutations; incompletely understood modifying factors make this risk very high for some families, and not so high for others.

Genetic testing can be of value in deciding on risk-reducing interventions such as chemoprevention, prophylactic surgery, and surveillance (Table 1). Controversy still remains as to whether *BRCA-1* mutation carriers derive significant benefit from therapy with tamoxifen. There remain a significant number of *BRCA* mutation carriers who do not opt for prophylactic surgery and choose surveillance instead.

| Table 1. Issues Specific to *BRCA* Gene Mutation Carriers |
|----------------------------------------------------------|
| **Surveillance**                                          |
| - Mammographic density                                   |
| - Mammographically occult cancers                        |
| **Chemoprevention**                                      |
| - Tamoxifen questionable for *BRCA-1* carriers            |
| **Prophylactic surgery**                                 |
| - Oophorectomy and/or mastectomy                         |

Universal genetic testing has some major drawbacks, namely the high cost and the frequency of mutations of uncertain clinical significance that occur in unselected families. To meet this challenge, the American Society of Clinical Oncology (ASCO) has devised guidelines suggesting it is reasonable to consider testing in women whose mutation probability is greater than 10% (2). Determining mutation probability requires an overview of the woman’s family. *BRCA* gene mutations are autosomal dominant; thus approximately half of the members of any generation in a very large family will have the mutation. Age at breast cancer diagnosis differs in *BRCA* mutation carriers compared to the general population, with a median age of approximately 44 years as compared to age 55 years for sporadic breast cancers (Fig. 1) (3). In addition, there tends to be multiple or bilateral cancers in families affected by *BRCA* gene mutations. Associated cancers, such as ovarian cancer, run in these families as well.

Most mathematical models, such as Couch, Shattuck-Eldens, Frank, and Hartge, are generally combinations of either counting cancers or calculating mean age at cancer diagnosis. An effective model, although seldom used,
perhaps because of its presumed complexity, is the computer model BRCAPRO, a Bayesian calculation (3,4). This model improves on what was known at birth, based on the frequency of BRCA gene mutations in specific populations.

**EXAMPLES**

**Example 1**

Consider a 70-year-old Caucasian woman without breast cancer. The cumulative probability that this woman would have developed breast cancer by age 70 if she had a gene mutation would be 0.787 based on the Breast Cancer Linkage Consortium data. The cumulative probability of breast cancer for this woman in the absence of a mutation would be 0.075. The likelihood ratio is derived by dividing the probability of no cancer development if she were a gene mutation carrier by the probability of no cancer development without the mutation. A factor related to the frequency of mutated BRCA genes in the population (in this case 1/832) completes the calculation. Based on this calculation, this woman’s probability of carrying a BRCA gene mutation is 0.00028, an improvement over the 0.00012 probability had she been evaluated at birth (Table 2). BRCAPRO incorporates a similar calculation based on the presence or absence of ovarian cancer and then combines all of the calculations for every individual in a family to derive the probability that a given family carries a BRCA gene mutation.

**Example 2**

This is a 40-year-old woman without breast cancer; family history includes breast cancer diagnosed in the father and the father’s sister, in addition to a history of breast and ovarian cancer on the mother’s side of the family. Using BRCAPRO, it can be seen that there is a 1.9% probability that this woman has a BRCA-1 mutation and a 42.8% probability that she has a BRCA-2 mutation, for an overall probability of 44%. Based on that result, the probability that she will develop breast cancer over time, up to age 85 years, is 40%; the probability of ovarian cancer is about 13% by age 85 years.

A recent study validated the use of BRCAPRO in determining BRCA gene mutation probabilities (5), comparing the results using the BRCAPRO model versus non-computer-based risk assessment conducted by eight genetic risk counselors. A total of 148 gene-tested families, consisting of 2025 women with a mean of 14 family members per pedigree, were assessed (Table 3). Eighty-five families were mutation negative and 63 were mutation positive. Ninety-five percent of the former group had one breast cancer and 97% of the latter group had one breast cancer. BRCAPRO was found to have greater overall discrimination than the majority of the counselors, as well as greater specificity (Fig. 2). The analysis revealed a significant caveat concerning families with a mutation probability less than 10%. Sixteen percent of families with a BRCAPRO probability less than 10% actually did have a BRCA gene mutation. Similarly 8–29% of families assigned a mutation probability less than 10% by the counselors were found to have a BRCA gene mutation. According to the investigators, this underscores the necessity of viewing the 10% threshold as a guideline rather than as a rigid criterion for testing. A second caveat concerns the 95% mutation probability. Twenty-six percent of families with a BRCAPRO probability of 95% had no BRCA gene mutation discovered by complete

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**Table 2. BRCAPRO: A Bayesian Example**

| 70-year-old Caucasian woman without breast cancer |
|-----------------------------------------------|
| Cumulative probability of breast cancer by age 70 with mutation = 0.787. |
| Cumulative probability of breast cancer by age 70 without mutation = 0.075. |
| Likelihood ratio (LR) is the probability of no cancer with mutation/probability of no cancer without mutation |
| LR = 1 / 0.787/1 = 0.705 |
| p(M/H) = LR / LR + 832 = 0.23 / 0.23 + 832 = 0.00028 |
| (cf. 0.0012 at birth) |

**Table 3. BRCAPRO versus Genetic Risk Counseling**

| Sample Characteristics | Mutation negative (%) | Mutation positive (%) | ρ |
|------------------------|-----------------------|-----------------------|---|
| Number                 | 85                    | 63                    |   |
| Any breast cancer      | 81 (95)               | 61 (97)               | 0.96 |
| Mean no. of breast cancers | 2.5                | 2.7                  | 0.52 |
| Mean age for breast cancer (years) | 49.1             | 43.2                  | <0.01 |
| Any ovarian cancer     | 26 (31)               | 31 (49)               | 0.03 |
| Mean no. of ovarian cancers | 0.45              | 0.71                  | 0.05 |
| Mean age for ovarian cancer (years) | 54.4             | 52.0                  | 0.37 |

Information on 2025 individuals (mean of 14 per family).
sequencing. This figure was 0–35% of families assigned a mutation probability of 95% by the counselors. The investigators concluded that individuals with a 95% mutation probability must be treated as mutation carriers regardless of the test result when it comes to intervention planning.

Further validation of the use of BRCAPRO as an accurate predictor of risk has been provided by an additional analysis of 300 families (6). An analysis is currently under way of 802 families from 11 Cancer Genetics Network clinics that will evaluate four different ways of calculating BRCAPRO compared to a variety of other models.

**REFERENCES**

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