BRCA PRO 6.0 Model Validation in Male Patients Presenting for BRCA Testing

Zahi I. Mitri, Micheline Jackson, Carolyn Garby, Juhee Song, Sharon H. Giordano, Gabriel N. Hortobágyi, Claire N. Singletary, Sahrukh Hashmi, Banu K. Arun, Jennifer K. Litton

University of Texas MD Anderson Cancer Center, Houston, Texas, USA; Baylor Charles A. Sammons Cancer Center, Baylor University Medical Center, Dallas, Texas, USA; University of Texas Health and Science Center at Houston, Houston, Texas, USA

Key Words: BRCA • BRCAPRO • Risk models • Male breast cancer • Cancer genetics • Genetic counseling

Abstract

Background. BRCAPRO is a risk assessment model to estimate the risk of carrying a BRCA mutation. BRCA mutation carriers are at higher risk of developing breast, ovarian, pancreatic, and prostate cancer. BRCAPRO was developed for women and found to be superior to other risk assessment models. The present study evaluated the validity of BRCAPRO at predicting the risk of male patients carrying a BRCA mutation.

Patients and Methods. A total of 146 men who presented for genetic counseling and testing from February 1997 to September 2011, and their test results were included in the present study. BRCAPRO risk assessment for all patients was calculated using the BRCAPRO clinical CancerGene assessment software.

Results. The mean age at presentation was 57 years. Of the 146 patients, 48 had breast cancer, 18 had pancreatic cancer, 39 had prostate cancer, 27 had other primary cancers, and 37 had no cancer. Fifty patients (34%) tested positive for a BRCA mutation (22 BRCA1, 27 BRCA2, and 1 BRCA1 and BRCA2). The mean BRCAPRO score for all patients was 24.96%. The BRCAPRO score was significantly higher for patients who tested positive for a BRCA mutation (46.19% vs. 13.9%, p < .01). The area under the receiver operating characteristics curve was 0.83 for all patients for the BRCAPRO score to predict the risk of carrying a BRCA mutation. At a cutoff point of 30.02%, the sensitivity, specificity, positive predictive value, and negative predictive value were 0.74, 0.81, 0.67, and 0.86, respectively.

Conclusion. BRCAPRO appears to be a valid risk assessment tool for determining the risk of carrying a BRCA mutation in men. The Oncologist 2015;20:593–597

Implications for Practice: Men carrying genetic mutations in the BRCA gene have a greater risk than the general population of developing certain types of cancer, including breast, pancreatic, and prostate cancer. BRCA PRO is a risk assessment model that predicts the risk of carrying a BRCA mutation. The present study aimed at validating BRCAPRO for use with men seen for genetic counseling, whether affected by cancer or not. The data available for 146 patients revealed that BRCAPRO was effective at identifying patients at risk of BRCA mutation. These findings could help in identifying a subset of high-risk patients who should proceed to genetic testing.

Introduction

Hereditary breast and ovarian cancer is attributed to a mutation in either the BRCA1 or BRCA2 gene and is linked in an autosomal dominant manner. Men with mutations in BRCA2 have a greater risk of breast cancer than BRCA1 mutation carriers, and both have a greater risk than the general population [1]. The BRCA mutations carry an increased risk of other malignancies in men, including prostate and pancreatic cancer [1]. Therefore, identifying male carriers of a BRCA mutation is important for the prevention and early detection of these malignancies.

Male breast cancer is rare, accounting for less than 1% of male cancers. The rate of BRCA mutations in male breast cancer patients has been estimated to be 4–40%. Among men with a BRCA mutation, the lifetime risk of breast cancer is approximately 8% for those with BRCA2 mutations and 2% for those with BRCA1 mutations [2–4]. The symptoms at diagnosis include a painless lump, nipple retraction, and/or nipple bleeding [3–5]. Compared with women with breast cancer, male breast cancer is usually diagnosed at a mean age of 67 years versus 62 years in women, at a more advanced stage, and a greater tumor size with lymph node involvement. The pathologic type is most often invasive ductal carcinoma and hormone receptor-positive (estrogen receptor-positive 80–90%, progesterone receptor-positive 73–81%) [4]. The reports of HER-2/neu positivity have been inconsistent, with it initially reported as equivalent to that of female breast cancer but more recently reported at 5%–15% in different studies [6, 7].

Correspondence: Jennifer Litton, M.D., Department of Breast Medical Oncology, Clinical Cancer Genetics, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1354, Houston, Texas 77030, USA. Telephone: 713-792-2817; E-Mail: JLitton@mdanderson.org Received February 28, 2014; accepted for publication February 5, 2015; published Online First on May 6, 2015. ©AlphaMed Press 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2014-0425

Although the risks for male breast cancer differ, the treatment usually follows guidelines similar to those for women with breast cancer. The risk factors for the development of male breast cancer include, not only BRCA mutations, but also mutations in PTEN and CHEK2, obesity, chest wall radiation, Klinefelter syndrome, gynecomastia, and a positive family history. The increase in risk for men who have female relatives with breast cancer is a 2.5-fold [3–5, 8, 9].

Treatment of male breast cancer usually follows the guidelines for female breast cancer. Small studies have shown a similar benefit for the use of surgery, chemotherapy, and tamoxifen in men with breast cancer [10, 11]. Similarly, the tumor size and lymph node status were found to be independent predictors of overall survival [12]. Limited data are available for radiation therapy and aromatase inhibitor use. A single-institution study showed 5-year survival estimates for male patients with node-positive and node-negative breast cancer of 68.5% and 87.5%, respectively [12].

Genetic counseling was historically recommended for patients whose pretest probability exceeded 10% [13]. This 10% cutoff has been abandoned, and the National Comprehensive Cancer Network guidelines recommend testing according to the patient’s personal and family history of cancer [14]. BRCAPRO is a risk assessment model that has been validated to determine the probability of carrying a BRCA1 and BRCA2 mutation [15]. It has been found to be superior to other risk assessment models [16] and comparable to the results from experienced genetic counselors [17]. BRCAPRO was also found to be a useful tool to determine the need for testing in male breast cancer patients with no significant family history in a study by Zanna et al. [18]. This model has not yet been validated, to our knowledge, as a predictor of carrying a BRCA mutation in a cohort of affected and unaffected men who present for testing. We retrospectively report the accuracy of the BRCAPRO model and evaluated the mutation carrier rate in this cohort.

**Materials and Methods**

**Study Sample**

A medical record review of men who presented to the Clinical Cancer Genetics Program at the University of Texas MD Anderson Cancer Center for genetic counseling and underwent genetic testing was conducted as a part of an institutional review board-approved study. A total of 146 men with BRCA test results from February 1997 to September 2011 were identified in the study. One patient with both a BRCA1 and a BRCA2 mutation was included in the aggregate analysis of BRCA mutations but excluded from the separate analysis of each BRCA mutation. The electronic medical record and pedigree were reviewed, and data were collected for analysis for 146 male patients.

**Mutation Detection**

BRCA testing was performed at the Myriad Genetics Laboratory for all the patients, except for 1 test, which was performed at the Oxford Radcliffe Hospitals Genetics Laboratories (Oxford, U.K.). The results included positive, negative, or a variant of unknown significance. Three men were found to have variants of unknown significance, later reclassified as negative results.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Descriptive statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age presentation</td>
<td>57.45 ± 14.47, 59 (18, 87)</td>
</tr>
<tr>
<td>BRCAPRO score</td>
<td>24.96 ± 26.62, 12.07 (0.02, 100)</td>
</tr>
<tr>
<td>BRCA1 score</td>
<td>10.17 ± 19.3, 1.06 (0, 97.06)</td>
</tr>
<tr>
<td>BRCA2 score</td>
<td>14.08 ± 21.86, 3.23 (0.01, 99.64)</td>
</tr>
<tr>
<td>BRCA1 and BRCA2 score</td>
<td>0.71 ± 6.68, 0.01 (0, 80.69)</td>
</tr>
<tr>
<td>Ashkenazi</td>
<td>40 (27.4)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>48 (32.9)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>18 (12.3)</td>
</tr>
<tr>
<td>Other cancer</td>
<td>27 (18.5)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>39 (26.7)</td>
</tr>
<tr>
<td>BRCA test positive</td>
<td>50 (34.2)</td>
</tr>
<tr>
<td>BRCA1 test positive</td>
<td>22 (15.1)</td>
</tr>
<tr>
<td>BRCA2 test positive</td>
<td>27 (18.5)</td>
</tr>
<tr>
<td>BRCA1 and BRCA2 test positive</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Reason for test, known family mutation</td>
<td>50 (34.2)</td>
</tr>
<tr>
<td>Reason for test, personal history</td>
<td>97 (66.4)</td>
</tr>
<tr>
<td>Reason for test, family history</td>
<td>75 (51.4)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, median (minimum, maximum) or n (%).

**BRCAPRO Score Calculation**

All the men had their BRCAPRO score calculated using the BRCAPRO 6.0 model. This model uses a Bayesian model, which takes into account proband data, affected and unaffected family member data, and population data. The variables included in the model were a personal history of cancer, first- and second-degree family history, age at cancer diagnosis, current age or age at death, ethnicity, Ashkenazi Jewish ancestry, and history of risk-reducing surgery [15]. The population-based data in BRCAPRO includes mutation prevalence and disease penetrance. In the Ashkenazi Jewish population, the prevalence of BRCA1 and BRCA2 mutations has been estimated at 1.22% and 1.36%, respectively [15, 19, 20]. Disease penetrance at age 70 for both carriers and noncarriers of BRCA mutations has been estimated at 0.69 and 0.67 for breast cancer and 0.29 and 0.19 for ovarian cancer [21, 22]. The BRCAPRO model is available through the Cancer-Gene assessment software (http://www4.utsouthwestern.edu/breasthealth/cagene/).

**Statistical Analysis**

All variables of interest were summarized using descriptive statistics, including the mean, SD, range, and median for continuous variables and frequency (percentage) for categorical variables. The patient characteristics were summarized according to the BRCA mutation status. The two groups, with and without a BRCA mutation, were compared in each variable using the two-sample t test or Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher’s exact test for the categorical variables. Univariate logistic regression models were fitted considering the BRCA mutation status as a response variable (each BRCA separately and in aggregate).
Table 2. Patient characteristics according to BRCA mutation status (n = 146)

<table>
<thead>
<tr>
<th>Variable</th>
<th>BRCA mutation (n = 50)</th>
<th>No BRCA mutation (n = 96)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age presentation</td>
<td>52.12 ± 16.7, 55 (18, 78)</td>
<td>60.23 ± 12.37, 60 (19, 87)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BRCAPRO score</td>
<td>46.19 ± 29.23, 49.44 (0.02, 100)</td>
<td>13.9 ± 16.73, 5.97 (0.05, 51.16)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BRCA1 score</td>
<td>20.88 ± 25.91, 5.31 (0, 97.06)</td>
<td>4.6 ± 11.41, 0.73 (0.02, 49.94)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BRCA2 score</td>
<td>23.34 ± 30.52, 3.93 (0.01, 99.64)</td>
<td>9.26 ± 13.42, 3.03 (0.03, 49.77)</td>
<td>.1391</td>
</tr>
<tr>
<td>BRCA1 and BRCA2 score</td>
<td>1.99 ± 11.38, 0.08 (0, 80.69)</td>
<td>0.04 ± 0.15, 0 (0, 1.22)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ashkenazi</td>
<td>15 (30)</td>
<td>25 (26)</td>
<td>.61</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4 (8)</td>
<td>44 (45.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>5 (10)</td>
<td>13 (13.5)</td>
<td>.54</td>
</tr>
<tr>
<td>Other cancer</td>
<td>7 (14)</td>
<td>20 (20.8)</td>
<td>.31</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>10 (20)</td>
<td>29 (30.2)</td>
<td>.19</td>
</tr>
<tr>
<td>Reason for test, known family mutation</td>
<td>36 (72)</td>
<td>14 (14.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Reason for test, personal history</td>
<td>17 (34)</td>
<td>80 (83.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Reason for test, family history</td>
<td>22 (44)</td>
<td>53 (55.2)</td>
<td>.20</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, median (minimum, maximum) or n (%).

RESULTS

From February 1997 to September 2011, 146 men who had undergone genetic counseling and testing were identified and eligible for the present analysis. The patient characteristics of the 146 male patients are summarized in Table 1. The mean ± SD age at presentation was 57 ± 14 years (range 18–87). The mean BRCAPRO score for all the patients was 24.96%. Forty patients (27%) were Ashkenazi Jewish. Of the 146 patients, 48 had breast cancer, 18 had pancreatic cancer, 39 had prostate cancer, 27 had other primary cancers, and 38 had no cancer. Also, 26 patients had more than one tumor. Fifty patients (34%) tested positive for a BRCA mutation (22 had BRCA1, 27 had BRCA2, and 1 had both). The reason for testing was a known family mutation (KFM) in 50 patients, a personal history of cancer in 79 patients, and a family history in 75 patients.

The patient characteristics according to BRCA mutation status are summarized in Table 2. The patients who tested positive for a BRCA mutation were significantly younger than the patients who tested negative (52 vs. 60 years, p < .01). The BRCAPRO score was significantly higher for the patients who tested positive for a BRCA mutation (46.19% vs. 13.9%, p < .01). Of the 48 patients with breast cancer, 4 were in the BRCA mutation group and 44 in the BRCA-negative group (p < .01).

The area under the ROC curve was 0.83 for all patients for a BRCAPRO score to predict the risk of carrying a BRCA mutation (Fig. 1). The cutoff point suggested by the closest value to the left upper corner was 30.02%. The sensitivity, specificity, PPV, and NPV at this cutoff point were 0.74, 0.81, 0.67, and 0.86, respectively. Using a BRCAPRO score cutoff point of 10%, which historically in the published data has been used as a threshold for testing, the sensitivity, specificity, PPV, and NPV were 0.86, 0.59, 0.52, and 0.89, respectively.

A multivariable logistic regression analysis identified the BRCAPRO score and KFM as two significant variables in predicting carriers of a BRCA mutation. The results of this analysis suggested different cutoff points for those who were tested because of a KFM and for those who were tested for reasons not related to a KFM, 13.20% and 53.96%, respectively (Fig. 2).
In the present study, we evaluated the BRCAPRO as a risk assessment tool for carrying a BRCA mutation. The group of male patients with and without a personal history of breast cancer in the present study represents a population in which BRCAPRO has not been extensively evaluated. Our study found that the BRCAPRO model does have utility and reasonable sensitivity, specificity, PPV, and NPV for men who are being evaluated for genetic testing.

The BRCAPRO score has been validated as a counseling tool for determining the risk of carrying a BRCA mutation in families in which at least one member underwent genetic testing in a study that included several genetic counseling centers [15]. Multiple other research groups have also evaluated the BRCAPRO tool in various settings. In a study by Euhus et al. [17], the risk of carrying a BRCA gene mutation in 148 pedigrees from families who had undergone BRCA gene testing was evaluated using BRCAPRO and by eight experienced genetic counselors. The median area under the ROC curves for the eight genetic counselors was 0.67 compared with 0.71 for BRCAPRO. Overall, compared with the genetic counselors, BRCAPRO had equal sensitivity and higher specificity at predicting the risk of carrying a BRCA mutation. In that study, the genetic counselors performed better on all measures when provided with the BRCAPRO information compared with being unaware of it [17].

Huo et al. [23] evaluated the performance of the BRCAPRO model in 292 minority families, including African American, Hispanic, Asian American, and other minorities. The area under the ROC curve for all patients was 0.75. The model performed the best in the Hispanic group, with an area under the ROC curve of 0.83 [23]. James et al. [16] compared BRCAPRO with other risk assessment models for the prediction of carrying a BRCA mutation in 246 families who had undergone BRCA gene testing. BRCAPRO was found to be superior to other models, with an area under the ROC curve of 0.78 to predict the risk of carrying any BRCA mutation, 0.85 for BRCA1 and 0.71 for BRCA2. Previous studies across the literature used a cutoff score of 10% to consider testing because of the 1996 American Society of Clinical Oncology statement guidelines on genetic testing. Using a 10% cutoff to determine the risk of carrying a BRCA mutation, James et al. [16] reported sensitivity and specificity for the BRCAPRO model of 0.79 and 0.61, respectively. These results are comparable to those from our analysis. We report areas under the ROC curve for BRCA, BRCA1, and BRCA2 of 0.79 and 0.61, respectively. These results are comparable to, if not slightly higher than, some of the previously published data.

Our study had several limitations. Because it was a retrospective medical record review from a single institution, the information was obtained from the documentation in the electronic medical record and at the genetic counseling visit. Although large for a single institution, larger collaborations would improve the power of these estimations. Because the family histories could not always be verified, they could have included recall bias or other missing information. The pathologic data were not available assessment for all family members to review their cancer types or their genetic testing results, when applicable. Moreover, our institution is a tertiary referral center, which causes a referral bias, with several patients referred because of a known family history of malignancy. Finally, the clinical utility
of this tool is still limited in practice for male breast cancer patients, for whom the current guidelines recommend universal genetic counseling and BRCA testing.

**CONCLUSION**

BRCAPRO appears to be a valid risk assessment tool for determining the risk of carrying a BRCA mutation in the male patient population. This should be validated further in a larger prospective trial to identify patients with a high pretest probability who should proceed to genetic testing.

**ACKNOWLEDGMENTS**

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**REFERENCES**


**AUTHOR CONTRIBUTIONS**

Conception/Design: Jennifer K. Litton, Michelle Jackson, Carolyn Garby, Sharon Giordano, Claire N. Singletary, S. Shahrukh Hashmi

Provision of study material or patients: Jennifer K. Litton, Michelle Jackson, Carolyn Garby, Sharon Giordano, Gabriele N. Hortobágyi, Banu Arun

Collection and/or assembly of data: Jennifer K. Litton, Zahi Mitri, Michelle Jackson, Carolyn Garby, Juhee Song, Sharon Giordano, Claire N. Singletary, Gabriel N. Hortobágyi, S. Shahrukh Hashmi, Banu Arun

Data analysis and interpretation: Jennifer K. Litton, Zahi Mitri, Michelle Jackson, Carolyn Garby, Juhee Song, Sharon Giordano, Claire N. Singletary, Gabriel N. Hortobágyi, S. Shahrukh Hashmi, Banu Arun

Manuscript writing: Jennifer K. Litton, Zahi Mitri, Michelle Jackson, Carolyn Garby

Final approval of manuscript: Jennifer K. Litton, Zahi Mitri, Michelle Jackson, Carolyn Garby, Juhee Song, Sharon Giordano, Claire N. Singletary, Gabriel N. Hortobágyi, S. Shahrukh Hashmi, Banu Arun

**DISCLOSURES**

Jennifer K. Litton: Biomarin, Novartis (steering committee membership) (C/A), Biomarin, Novartis, Bristol-Meyer Squibb (RF); Gabriel N. Hortobágyi: Peregrine, Novartis, Pfizer, Antigen Express (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patient holder; (SAB) Scientific advisory board

**Note:** This article is available for continuing medical education credit at CME.TheOncologist.com.

**EDITOR’S NOTE:** See the related commentary, “Male Breast Cancer: A Study in Small Steps,” on page 584 of this issue.