Risk Estimation for Healthy Women from Breast Cancer Families: New Insights and New Strategies

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Abstract

Risk estimation in breast cancer families is often estimated by use of the Claus tables. We analyzed the family histories of 196 counselees; compared the Claus tables with the Claus, the BRCA1/2, the BRCA1/2/BRCAu models; and performed linear regression analysis to extend the Claus tables with characteristics of hereditary breast cancer. Finally, we compared the Claus extended method with the Claus, the BRCA1/2, and the BRCA1/2/BRCAu models. We found 47% agreement for Claus extended method versus Claus model; 39% agreement for Claus extended method versus BRCA1/2 model; 44% agreement for Claus extended model versus BRCA1/2 model; and 66% agreement for Claus extended method versus BRCA1/2 model. The regression formula (Claus extended method) for the lifetime risk for breast cancer was 0.08 + 0.40 * Claus Table + 0.07 * ovarian cancer + 0.08 * bilateral breast cancer + 0.07 * multiple cases. This new method for risk estimation, which is an extension of the Claus tables, incorporates information on the presence of ovarian cancer, bilateral breast cancer, and whether there are more than two affected relatives with breast cancer. This extension might offer a good alternative for breast cancer risk estimation in clinical practice.

Introduction

Risk estimation in familial breast cancer is complicated, and practical problems in the application of risk estimation models have been reported. A significant degree of variability is observed between the outcomes of the various models. This not only has serious implications for individual patient management and service provision, it also complicates multicenter studies evaluating the benefits of genetic testing and surveillance protocols (1–4).

Because DNA analysis for BRCA1 and BRCA2 mutations has been available on a large scale, several mutation probability models have been published (5–8) that estimate the probability of an individual harboring a germline mutation in BRCA1 or BRCA2. These known breast cancer predisposition genes, however, account for only 20–25% of familial aggregation (9). Moreover, the models used do not provide enough information to establish a policy for the large group of breast cancer families with a negative DNA test result for BRCA1 and BRCA2. For healthy women from DNA-negative or untested breast cancer families, risks can be estimated only by examining their pedigrees.

For this risk estimation, the so-called Claus model (10) is still useful, although the familial clustering of breast cancer is explained in this model by a dominant mode of inheritance that is represented by one theoretical gene. The Claus model has been used to make up risk tables, the so-called Claus tables (11), for women with a particular constellation of affected relatives. The Claus tables comprise first- and second-degree affected female relatives of a healthy woman and their ages at diagnosis. Clinical characteristics in the personal and family histories, such as ovarian cancer and bilateral breast cancer, which suggest the presence of a BRCA1 or BRCA2 mutation, are not included. Thus, use of the Claus model and tables may lead to underestimation of the lifetime risk for breast cancer in these families. Nevertheless, the Claus tables are often used by clinicians because they have several advantages. The tables may be used for handwritten pedigrees, and so no computer software is needed. Healthy women from breast cancer families may comparatively easily be divided into risk categories. Depending on the outcome (low, moderate, or high risk), further risk management options may be offered (12–14). Another model, developed by Gail et al. (15), which is based on reproductive factors plus breast biopsies, histology, and first-degree family history, is less useful in clinical genetics because second-degree relatives are not taken into account (16). The same limitation is true for the adaptation of the Claus tables published for women with a first-degree family history of ovarian cancer (17).

Our primary goal was to study the agreement between the Claus tables and several models in breast cancer risk estimation. Estimated lifetime breast cancer risks for healthy women according to the Claus tables (11) were compared with the Claus model (10) and two recently developed risk estimation models: the two-gene model with BRCA1 and BRCA2 (7) and the BRCA1/2/u model (18), a three-gene model that includes, in addition to BRCA1 and BRCA2, a third hypothetical gene called BRCAu. Our secondary goal was to extend the Claus tables according to these new insights into hereditary breast cancer. This method is an extension of the Claus tables; in addition to information on up to two cases of breast cancer in the family.
it also incorporates information on the presence of relatives in the family who had experienced ovarian cancer, bilateral breast cancer, and other breast cancers.

Materials and Methods
This study included 196 consecutive women from breast and/or ovarian cancer families who sought genetic counseling at the Department of Clinical Genetics of Leiden University Medical Center from 1997 onward. The family histories were investigated by a questionnaire, followed by an interview. All first-, second-, and third-degree relatives on the paternal and maternal sides of the counselee were taken into consideration, and these data were entered into a database. These 196 families consisted of 5492 individuals. The age of each family member was noted in decades. If ages were unknown, estimations were done for each generation, based on the mean age in this generation. Family members with unknown gender (n = 65; all third-degree relatives) were not included in the risk estimation. For affected family members, cancer type and age at diagnosis were noted. For women with (bilateral) breast cancer, the tumors and age at diagnosis were noted. The SPSS 11.0, S-Plus statistical package for Windows and computer program language C were used to analyze the data.

The risk estimation models we used offered lifetime risks for breast cancer in healthy women. Approximately one-third of the women who sought genetic counseling in our department were affected by breast cancer (19). To allow use of all 196 family histories for this study, we included an imaginary sister with breast and/or ovarian cancer as the youngest patient closest to the counselee in the pedigree. This youngest patient with breast and/or ovarian cancer could also be the counselee herself. This was done for all pedigrees; including the pedigrees with a healthy counselee; thus, all pedigrees were similarity dealt with. The imaginary sister was healthy and was 5 years of age. Because of her young age, this imaginary sister did not affect the family history for breast and ovarian cancer and was only an aid for a consistent point of view in each pedigree.

The Claus tables and the three risk estimation models were applied in the same way to the imaginary sister. In each family, a lifetime risk of developing breast cancer was obtained for this sister from the Claus tables. The lifetime risks for breast cancer were computed with the Claus model (10), the BRCA1/2 mutation probability model (7), and the three-gene model BRCA1/2/u (18). The values from the Claus tables were successively compared with the values obtained with these three risk estimation models. In the first comparison, raw data were compared by scatter plots. In the second comparison, the lifetime risks were categorized into four categories that are widely used in clinical practice: 0–10%, 10–20%, 20–30%, and >30%. For comparisons of the four risk estimation models, percentage of agreement and Spearman rank correlation were given.

To extend the Claus tables according to new insights into hereditary breast cancer, we incorporated information on ovarian cancer, bilateral breast cancer, and on whether more than two relatives were affected by breast cancer. Only phenotypic characteristics of the pedigrees were used in the new method, and no genetic information was included. Linear regression was performed. The dependent variable was the lifetime risk computed with the three-gene BRCA1/2/u model. One of the independent variables was the probability found in the Claus tables; the other two were the presence of ovarian cancer and of bilateral breast cancer. To account for breast cancer cases that did not fit in the Claus tables (more than two affected family members), a third independent variable was added.

We then applied the linear regression formula for familial breast cancer risk estimation to the 196 families to create the Claus extended method. For each imaginary sister, the lifetime risk was calculated by the estimated regression formula and compared with the lifetime risk calculated with the Claus, BRCA1/2, and BRCA1/2/u models. Again, raw data were compared by scatter plots, and categorized data were compared by percentages of agreement and Spearman rank correlations.

Results
The characteristics of the 196 family histories are given in Table 1. The mean number of breast cancer cases was 2.5 (SD, 1.4). Among these 196 families, families with ovarian cancer only were also present. This explained the minimum number of breast cancer cases of 0. The maximum number of breast cancer cases was 7. No male breast cancer and almost no bilateral breast or ovarian cancers were reported in third-degree relatives (data not shown). The Claus tables could not exactly account for the clinical characteristics that suggested the presence of hereditary breast cancer in 96 of 196 families (49%).

The results of the four different risk estimation models in these families are shown in Table 2. The Claus tables and the Claus model gave a percentage of agreement of 47% (Spearman rank correlation, 0.58). The Claus tables and the BRCA1/2 model were compared in the same way and showed less agreement (39%; Spearman rank correlation, 0.38). Comparison of the Claus tables and the BRCA1/2/u model gave the highest percentage of agreement, 48% (Spearman rank correlation, 0.52). Scatter plots of the three comparisons are shown in Fig. 1.

For the Claus extended method, the regression formula for the lifetime risk was 0.08 + 0.40 * Claus table + 0.07 * ovarian cancer + 0.08 * bilateral breast cancer + 0.07 * multiple cases, where “Claus Table” stands for the value obtained from the

<table>
<thead>
<tr>
<th>Occurrence of</th>
<th>Number (%) of affected family histories (total = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 relatives</td>
</tr>
<tr>
<td>Bilateral breast cancer</td>
<td>145 (74)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>154 (79)</td>
</tr>
<tr>
<td>Breast and ovarian cancer in one individual</td>
<td>184 (93)</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>191 (96)</td>
</tr>
<tr>
<td>More affected relatives</td>
<td></td>
</tr>
<tr>
<td>First degree</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Second degree</td>
<td>121 (61)</td>
</tr>
</tbody>
</table>

*Mean number of breast cancer cases, 2.5 (SD, 1.4); minimum, 0; maximum, 7. Total of 4467 individuals.
Claus tables, i.e., the lifetime risk of the imaginary healthy sister for breast cancer; "ovarian cancer" is 1 if ovarian cancer is present in at least one first- or second-degree relative and is otherwise 0; "bilateral breast cancer" is 1 if bilateral breast cancer is present in at least one first- or second-degree relative and 0 otherwise; and "multiple cases" is 1 if an additional first- or second-degree relative does not fit in the Claus tables, i.e., more than two affected relatives in the first or second degree.

The SE for the estimated five regression coefficients were 0.013, 0.047, 0.012, 0.011, and 0.0097, respectively. The correlation between the fitted risks and the risks computed with the BRCA1/2 model was 0.75. For Claus-table risks and BRCA1/2, the correlation was 0.48. When we modeled the final regression formula, the variables concerning third-degree relatives were not informative; we therefore decided to remove them from the model. The number of female relatives without breast cancer might also be of importance when performing risk estimation. It appeared, however, that the fit of the regression model was minimally improved by including this information.

Shown in Table 3 are comparisons of the new risk estimation model, (the Claus extended method), the Claus model, the BRCA1/2 model, and the BRCA1/2/u model. The Claus extended method and the Claus model gave an agreement of 37% (Spearman rank correlation, 0.61). The Claus extended method and the BRCA1/2 model showed higher agreement: 44%. The Spearman rank correlation was also higher: 0.70. Comparison of the Claus extended method and the BRCA1/2/u model gave the highest percentage of agreement: 66% (Spearman rank correlation, 0.72). Scatter plots of the three comparisons are given in Fig. 2.

Shown in Fig. 3 is an example of how to use the risk estimation formula. The healthy woman in this sample family would be informed about her lifetime risk for breast cancer. We start with the intercept of 0.08. In this situation the value obtained from the Claus table is 0.25 and should be multiplied by 0.40. The formula subsequently includes the information on ovarian cancer, which equals 0 because there is no ovarian cancer in this family. Bilateral breast cancer and more than two affected first- or second-degree breast cancer patients are present in this family; therefore, these characteristics in the formula have to be multiplied by 1. The lifetime risk based on the Claus table is 0.31.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of lifetime risks for the imaginary sister: Estimations by the Claus tables, the Claus model, the BRCA1/2 model, and the BRCA1/2/u model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Claus tables</td>
</tr>
<tr>
<td></td>
<td>≤10%</td>
</tr>
<tr>
<td>Claus model</td>
<td></td>
</tr>
<tr>
<td>≤10%</td>
<td>13</td>
</tr>
<tr>
<td>10–20%</td>
<td>2</td>
</tr>
<tr>
<td>20–30%</td>
<td>1</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td></td>
</tr>
<tr>
<td>≤10%</td>
<td>4</td>
</tr>
<tr>
<td>10–20%</td>
<td>12</td>
</tr>
<tr>
<td>20–30%</td>
<td>0</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
</tr>
</tbody>
</table>

* The Claus table and the Claus model have 47% agreement (Spearman rank correlation, 0.58).
  The Claus tables and the BRCA1/2 model have 39% agreement (Spearman rank correlation, 0.38).
  The Claus tables and the BRCA1/2/u model have 48% agreement (Spearman rank correlation, 0.52).
In clinical practice, it is important to estimate the lifetime breast cancer risk for healthy women from breast cancer families as a starting point for further policy. In this study, the outcomes based on the Claus tables were compared with the outcomes of three models for the estimation of lifetime breast cancer risk for 196 women from breast cancer families. We observed a moderate agreement between the outcomes of these models, whereas significant variability among the outcomes of several of the investigated models had been reported previously by Tischkowitz et al. (2) and Shannon et al. (4).

The Claus model is a useful tool for risk estimation for healthy women in breast cancer families, although no data on ovarian cancer, bilateral breast cancer, male breast cancer, or on more than two affected first- or second-degree relatives can be included (10). The Claus model was developed in the early 1990s, before the BRCA1 and BRCA2 susceptibility genes for breast cancer were found. In this model, the mutant allele on one theoretical gene is supposed to explain all familial clustering of breast cancer. This gene is supposed to be autosomal dominant, and the mutant allele frequency was 0.0033. For practical use, the Claus tables, based on the Claus model, were produced. Although the Claus model was used to produce the Claus risk tables, only moderate agreement was observed between these two variants of the risk estimation model. The moderate correlation between these risk estimation tools could be explained as follows. The Claus tables give risks based on a maximum of at most two affected subjects, without accounting for unaffected family members. Thus, in families with up to two affected family members, the tables give a higher risk than the method based on the whole pedigree. For small pedigrees, the effect is limited. For larger breast cancer families, with more healthy women, the risk will be somewhat lower than when the Claus tables are used (14). For family histories with more than two breast cancer cases, the Claus tables might give an underestimation of the lifetime risk. No independent validation has been reported for the Claus model.

### Table 3: Comparison of lifetime risks for the imaginary sister: Estimations by the Claus extended method, the Claus model, the BRCA1/2 model, and the BRCA1/2/u model

<table>
<thead>
<tr>
<th></th>
<th>≤10%</th>
<th>10–20%</th>
<th>20–30%</th>
<th>&gt;30%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Claus model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>0</td>
<td>33</td>
<td>10</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>10–20%</td>
<td>0</td>
<td>24</td>
<td>34</td>
<td>4</td>
<td>62</td>
</tr>
<tr>
<td>20–30%</td>
<td>0</td>
<td>8</td>
<td>17</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>≥30%</td>
<td>0</td>
<td>2</td>
<td>25</td>
<td>32</td>
<td>59</td>
</tr>
<tr>
<td><strong>BRCA1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>0</td>
<td>24</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10–20%</td>
<td>0</td>
<td>41</td>
<td>57</td>
<td>4</td>
<td>102</td>
</tr>
<tr>
<td>20–30%</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>≥30%</td>
<td>0</td>
<td>2</td>
<td>13</td>
<td>32</td>
<td>47</td>
</tr>
<tr>
<td><strong>BRCA1/2/u</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>0</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>10–20%</td>
<td>0</td>
<td>44</td>
<td>15</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>20–30%</td>
<td>0</td>
<td>13</td>
<td>58</td>
<td>15</td>
<td>86</td>
</tr>
<tr>
<td>≥30%</td>
<td>0</td>
<td>1</td>
<td>12</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0</td>
<td>67</td>
<td>86</td>
<td>43</td>
<td>196</td>
</tr>
</tbody>
</table>

* The Claus extended method and the Claus model have 37% agreement (Spearman rank correlation, 0.61).
* The Claus extended method and the BRCA1/2 model have 44% agreement (Spearman rank correlation, 0.70).
* The Claus extended method and the BRCA1/2/u model have 66% agreement (Spearman rank correlation, 0.72).

Fig. 2. Comparison of lifetime risks for an imaginary sister. Comparisons of estimations obtained with the Claus extended method versus the Claus model (top), the BRCA1/2 model (middle), and the BRCA1/2/u model (bottom) are presented as scatter plots.
familial clustering of breast cancer, it is probable that addi-

\( \text{BRCA1} \)

describe all familial clustering of breast cancer. Because

\( \text{BRCA1} \)

compared with the outcome of genetic testing (24).

For the BRCAPRO model, validation has been reported in

\( \text{BRCA1} \)

fully explain familial aggregation of familial breast cancer (9).

However, a model that incorporates only the \( \text{BRCA1} \)

and \( \text{BRCA2} \) genes is not suitable for breast cancer risk estimation because the deleterious \( \text{BRCA1} \) and \( \text{BRCA2} \) mutations do not

fully explain familial aggregation of familial breast cancer (9). For the BRCAPRO model, validation has been reported in

which the outcome of the BRCAPRO risk estimation was

improved by inclusion of this variable. The scatter plot changed

only marginally, and the final formula became more compli-

cated to use (data not shown). We therefore decided not to

include this variable. The same was true for two or more cases

of ovarian cancer in one individual. The Claus extended method is

not a reliable risk estimation method for healthy female rela-

tives of male breast cancer patients.

To improve risk estimation in clinical practice, we ex-

tended the Claus tables according to new insights into heredi-

tary cancer. A new formula for risk estimation in familial breast cancer was obtained by including several characteristics of hereditary breast cancer in a linear regression analysis, the so-called Claus extended method. This model also uses information on the presence of ovarian cancer, bilateral breast cancer, and whether there are more than two affected breast cancer relatives. Similar to the Claus model, only phenotypic characteristics of the family histories were taken into account. The Claus extended method we developed gives a lower agreement with the Claus model than the Claus tables but better agreement with the BRCA1/2 and BRCA1/2/u models because

in the latter two models ovarian cancer, bilateral breast cancer, and breast cancer among males were also included.

We included 196 consecutive breast and/or ovarian cancer families in our study. These families consisted of breast-cancer-only families, combined breast and ovarian cancer families, and ovarian-cancer-only families. It is likely that hereditary ovarian cancer is a variant of the hereditary breast-ovarian cancer syndrome (29, 30). Moreover, because healthy women from these ovarian-cancer-only families also had questions about their risk for breast cancer, we decided not to exclude these ovarian-cancer-only families (\( n = 8 \)).

During the regression analysis, the occurrence of breast and ovarian cancer in one individual was included as an extra independent variable. The fit of the linear regression was not improved by inclusion of this variable. The scatter plot changed only marginally, and the final formula became more complicated to use (data not shown). We therefore decided not to include this variable. The same was true for two or more cases of ovarian cancer in the family and the presence of male breast cancer as separate variables. In now presented Claus extended method, male breast cancer counts as just another case of breast cancer as a separate variable. The Claus extended method agrees better with the BRCAPRO/2 and BRCA1/2/u models than the Claus tables; however, there are still family histories that were not assigned to the same risk category according to BRCAPRO/2 and the Claus extended method, the so-called outliers. Family histories which gave a lifetime risk >30% with the BRCAPRO/2 model and a lifetime risk of 20–30% according the Claus extended method are characterized by male breast cancer, two or more cases of ovarian cancer, and breast and ovarian cancer in one individual. The Claus extended method is not a reliable risk estimation method for healthy female relatives of male breast cancer patients.

The group of family histories that gave a lifetime risk >30% with the Claus extended model and a lifetime risk of 20–30% with BRCAPRO/2 were characterized by breast and ovarian cancer in one family or were very large families. This might be an overestimation according to the Claus extended model, although all of these families had histories that justified breast surveillance.

An additional finding in this dataset is the limited infor-
mation on third-degree relatives. Not only was this information limited as to the characteristics of the families, but for the linear regression model as well. This might have been caused by the lack on information of third degree relatives, and underreporting of ovarian cancer or bilateral breast cancer in the third degree. This is in agreement with our previous simulation study in which the inclusion of cousins in individual risk estimation of hereditary breast cancer was of little significance (31).

The formula we obtained is easy to use and simplifies risk estimation in familial breast cancer. The formula starts with an intercept of 0.08. This is the population risk for breast cancer and the basis for further risk estimation. The value of the Claus table should be multiplied by 0.40. The formula subsequently includes the information on ovarian cancer, bilateral breast cancer, and more than two affected first- or second-degree breast cancer patients. These characteristics in the formula are 1 or 0. To obtain the formula, the value of the Claus table has to be multiplied once, and the other values may be added. The outcome of the formula gives the lifetime risk for a healthy imaginary sister of the index patient, closest to the counselee, and might reflect the lifetime risk of the counselee herself if she is healthy (Fig. 3). A risk of 25% is considered as a moderate risk and a risk of 33% is considered as a high risk. For each risk category, the breast surveillance will differ (12–14). The thresholds for surveillance are not evidence based. The existing guidelines for surveillance are usually based on the Claus model, which is not validated; the presented Claus extended method in our study also is not validated. Obviously, validating these methods needs to be a research goal in the near future.

A new method for risk estimation in clinical practice should be more accurate than the Claus tables, and it should also be possible to use on hand-written pedigrees. Although software is available for commonly used risk estimation models for familial breast cancer, clinicians have to know what they are actually estimating, and an understandable risk estimation should be available to clinicians (16, 32). In addition, an easily applicable risk estimation model for hand-written pedigrees is very practical in a clinical setting. In our opinion, the Claus extended method meets these criteria.

In conclusion, we studied the agreement between the Claus tables and several models of breast cancer risk assessment. We present a new method for risk estimation that is an extension of the Claus tables and incorporates new insights into hereditary cancer. It therefore also uses information on the presence of ovarian cancer, bilateral breast cancer, and the presence of more than two relatives with breast cancer. This extension should be investigated in other databases to test whether this may offer a good alternative for breast cancer risk estimation in clinical practice.

Acknowledgments
We acknowledge the assistance of Thomas E. M. Crijnen in preparing this manuscript.

References

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