Frequency of the CHEK2 1100delC Mutation among Women with Breast Cancer: An International Study

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Abstract

A founder allele in the CHEK2 gene (1100delC) has been associated with an elevated risk of breast cancer. This allele is responsible for the majority of CHEK2-associated breast cancers in women from northern European countries; however, within Europe, it seems to be rare in countries that are close to the Mediterranean. The frequency of the 1100delC allele has not been measured in non-White populations. We measured the frequency of the CHEK2 founder allele in 3,882 breast cancer patients and 8,609 controls from various countries. The allele was not seen among Asian patients (from Pakistan or the Philippines) and was present in 1 of 155 cases from Brazil. Among White women, the allele was present in 1.5% of 825 familial cases of breast cancer and in 0.7% of 1,106 patients with nonfamilial breast cancer. The allele was equally frequent in Jewish and non-Jewish patients. We estimate that the CHEK2 1100delC allele is associated with an odds ratio of 2.6 for breast cancer, which corresponds to a lifetime risk of ~24% in Ontario. [Cancer Res 2008;68(7):2154–7]

Introduction

Following the positional cloning of BRCA1 in 1994 (1) and of BRCA2 in 1995 (2), there has been continued interest in the identification of new genes for hereditary breast cancer. These genes may be roughly divided into two categories—genes with rare alleles, which are associated with a high relative risk of breast cancer (i.e., highly penetrant), and genes with relatively common alleles, which are associated with modest relative risks of breast cancer (i.e., low penetrance genes). It has been suggested that genes in the latter class might account for significant proportion of cancers in the general population.

CHEK2 is one of a few genes that have been clearly associated with an elevated breast cancer risk. A founder allele of CHEK2 (1100delC) predisposes to breast cancer in Europe and North America (3, 4) and other CHEK2 alleles have been implicated in breast carcinogenesis in Finland (5) and in Poland (6). In the initial CHEK2 study, the 1100delC variant was found in 5.1% of individuals with familial breast cancer (but with no BRCA1 or BRCA2 mutation), compared with 1.1% of healthy control subjects (3). In a large follow-up study, 10,860 breast cancer cases from five countries (United Kingdom, the Netherlands, Finland, Germany, and Australia) were studied (4). The highest prevalence of the 1100delC mutation was found among cases from the Netherlands (3.5%) followed by Finland (2.2%), the United Kingdom (1.2%), Germany (0.8%), and Australia (0.7%). The frequencies among controls also varied widely, from 1.8% in the Netherlands to 0.1% in Australia. Elsewhere, the mutation frequency has been estimated to be 0.5% in cases from Poland (6) and 0% in cases from Spain (7). As a whole, these studies suggest that the frequency of the 1100delC mutation varies between countries and that the highest mutation rates are seen in northern European countries. To date, no studies have been conducted in non-European populations. We estimated the prevalence of the CHEK2 1100delC mutation in 3,882 breast cancer patients belonging to various ethnic groups, including women from Asia and South America.

Materials and Methods

DNA samples were available from women who presented for genetic evaluation to the Women’s College Research Institute in Toronto. We also included women who were enrolled in a number of breast cancer studies. For some studies, patients were unselected hospital-based cases of breast cancer. For other studies, patients were preselected on the basis of age of diagnosis, family history, ethnic group, or personal history of cancer. The study was given ethical approval at the Sunnybrook and Women’s College Health Sciences Centre and the University of Toronto, and all patients provide written informed consent.

In addition, 8,609 controls were tested. These women were unaffected with breast cancer. A large number of controls were women who attended a screening clinic for healthy women at Women’s College Hospital or were female students who attended the University of Toronto. For some hospital-based studies, a control group of non-breast cancer patients was also collected and was available for study. French Canadian controls consisted of DNA extracted from cord blood specimens from unselected newborn infants from the Quebec City region (8). Detailed information on ethnic group was taken from all...
cases and controls, and individuals were classified according to ethnic group: White women were divided into Ashkenazi Jewish, French Canadian, and other White.

The genomic DNA was extracted from the peripheral blood with PureGene DNA Isolation Kit (Gentra Systems) according to the protocol provided. Two sets of PCR primers were used to screen for the CHEK2 1100delC mutation. Specific primers for the CHEK2 exon 10 on chromosome 22 were designed to avoid all other homologous sequences in the genome (forward primer 5'-TTAATTTAAGCAAAATTAAATGTC-3', reverse primer 5'-GGCATGGTGGTGTGCATC-3'). The PCR products were then re-amplified with nested primers, which were designed to amplify the region encompassing the site of CHEK2 1100delC. The forward primer contained one base substitution to generate a restriction site for restriction enzyme ScaI within the wild-type allele after PCR amplification. The forward primer sequence was 5'-CCCTTTTGTACTGAATTTTAGAGTA-3' (a T to G substitution at position 1097). The reverse primer was 5'-ACAAGAACTTCAGGCGCCAAGTAG-3'. Then, the 116-bp PCR products from the second amplification were digested with the restriction enzyme ScaI and incubated overnight at 37°C (2.5 units per sample, Roche Molecular Biochemicals), which digests only the wild-type allele but not the mutant allele. Restriction enzyme digest products were separated on 3% agarose gels visualized with ethidium bromide. The wild-type allele is cut into bands of 92 and 24 bp (the 24-bp band usually runs out of the gel). The mutant allele cannot be cut by the enzyme. Mutations were

<p>| Table 1. CHEK2 1100delC mutations in breast cancer cases and controls by ethnicity |
|------------------------------------------|-----------------|-----------------|-----------------|---------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Positive</td>
<td>Number</td>
<td>Total</td>
</tr>
<tr>
<td>Jewish</td>
<td>320</td>
<td>4</td>
<td>1.3%</td>
<td>180</td>
</tr>
<tr>
<td>French Canadian</td>
<td>560</td>
<td>4</td>
<td>0.7%</td>
<td>6460</td>
</tr>
<tr>
<td>Other White</td>
<td>1566</td>
<td>15</td>
<td>1.0%</td>
<td>1223</td>
</tr>
<tr>
<td>All Whites</td>
<td>2449</td>
<td>23</td>
<td>0.9%</td>
<td>7863</td>
</tr>
<tr>
<td>Brazil</td>
<td>155</td>
<td>1</td>
<td>0.7%</td>
<td>377</td>
</tr>
<tr>
<td>Pakistan</td>
<td>376</td>
<td>0</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Filipino</td>
<td>342</td>
<td>0</td>
<td>0%</td>
<td>7</td>
</tr>
<tr>
<td>Other/mixed/unknown</td>
<td>560</td>
<td>4</td>
<td>0.7%</td>
<td>322</td>
</tr>
</tbody>
</table>

<p>| Table 2. Description of cases with CHEK2 mutations |
|------------------------------------------|-----------------|-----------------|---------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Pedigree</th>
<th>ID no.</th>
<th>Ethnicity</th>
<th>First cancer</th>
<th>Second cancer(s)</th>
<th>Age of diagnosis of breast cancer (y)</th>
<th>Breast cancers in first-degree relatives</th>
<th>Breast cancers in all relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCP066</td>
<td>23246</td>
<td>Irish/Scottish</td>
<td>Breast</td>
<td></td>
<td>48</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>BRP0085</td>
<td>24114</td>
<td>Brazilian</td>
<td>Breast</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CR2800</td>
<td>4717</td>
<td>English/Dutch</td>
<td>Breast</td>
<td></td>
<td>29</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>CR3569</td>
<td>11072</td>
<td>Norwegian</td>
<td>Breast</td>
<td></td>
<td>51</td>
<td>2</td>
<td>5 (1 male)</td>
</tr>
<tr>
<td>CR4420</td>
<td>13442</td>
<td>Unknown</td>
<td>Breast</td>
<td></td>
<td>40</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CR4522</td>
<td>17809</td>
<td>German/Scottish/Swedish</td>
<td>Breast</td>
<td></td>
<td>39</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CR4731</td>
<td>20571</td>
<td>Unknown</td>
<td>Breast</td>
<td></td>
<td>46</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CR4911</td>
<td>24925</td>
<td>Ashkenazi Jewish</td>
<td>Breast</td>
<td></td>
<td>46</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EW069</td>
<td>13122</td>
<td>Jewish</td>
<td>Breast</td>
<td></td>
<td>44</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>EW154</td>
<td>1369</td>
<td>Irish</td>
<td>Breast</td>
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<td>41</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>EW190</td>
<td>1362</td>
<td>Irish</td>
<td>Breast</td>
<td></td>
<td>35</td>
<td>1</td>
<td>2</td>
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<tr>
<td>FC0071</td>
<td>4321</td>
<td>Unknown</td>
<td>Breast</td>
<td></td>
<td>39</td>
<td>1</td>
<td>3</td>
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<tr>
<td>FRC0065</td>
<td>25866</td>
<td>French Canadian</td>
<td>Breast</td>
<td></td>
<td>38</td>
<td>—</td>
<td>—</td>
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<tr>
<td>FRC0251</td>
<td>82666</td>
<td>French Canadian</td>
<td>Breast</td>
<td></td>
<td>49</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FRC0387</td>
<td>29613</td>
<td>French Canadian</td>
<td>Breast</td>
<td></td>
<td>38</td>
<td>—</td>
<td>—</td>
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<tr>
<td>MG1031.0</td>
<td>4580</td>
<td>Unknown</td>
<td>Breast</td>
<td>Breast/Uterine</td>
<td>47</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>MTR1790</td>
<td>785</td>
<td>German/Welsh</td>
<td>Breast</td>
<td>Breast/Thyroid</td>
<td>65</td>
<td>0</td>
<td>0</td>
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<tr>
<td>PMH1024</td>
<td>3857</td>
<td>German</td>
<td>Breast</td>
<td></td>
<td>—</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PMH1304</td>
<td>10108</td>
<td>Scottish</td>
<td>Breast</td>
<td></td>
<td>65</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PMH1316</td>
<td>10204</td>
<td>British</td>
<td>Breast</td>
<td>Colon/Appendix</td>
<td>55</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PMH1488</td>
<td>10535</td>
<td>Irish</td>
<td>Breast</td>
<td>Skin</td>
<td>70</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>W0971</td>
<td>13122</td>
<td>Dutch/Scottish</td>
<td>Breast</td>
<td></td>
<td>39</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>W9173</td>
<td>3672</td>
<td>English/Irish</td>
<td>Breast</td>
<td>Cervical</td>
<td>49</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>W9348</td>
<td>3489</td>
<td>Ashkenazi Jewish</td>
<td>Breast</td>
<td></td>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>W9724</td>
<td>14666</td>
<td>French Canadian/Scottish</td>
<td>Breast</td>
<td>Breast</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>W9747</td>
<td>16328</td>
<td>Dutch</td>
<td>Breast</td>
<td>Hodgkin</td>
<td>52</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>W9819</td>
<td>20663</td>
<td>Ashkenazi Jewish</td>
<td>Breast</td>
<td></td>
<td>—</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
confirmed by direct sequencing with Cy5/Cy5.5 Dye Primer Cycle Sequencing Kit and OpenGene Automated DNA Sequencing System (Visible Genetics).

**Results**

A total of 3,882 women with breast cancer was tested for the 1100delC CHEK2 mutation. The women were participants in a number of different studies that were designed to estimate the frequencies of various cancer-predisposing alleles in various populations. In some studies, patients were unselected, but for others, patients were selected on the basis of ethnic group, age of diagnosis, a positive family history of cancer, or a personal history of cancer. Therefore, the results are presented separately for the different ethnic groups and for subgroups defined by age of onset, family history, and past cancer history.

A mutation was found in 23 of 2,449 (0.9%) White breast cancer patients. These 23 women were almost all from North America (with European origins). Among Whites, the mutation frequencies were similar for French Canadian patients (0.7%; 4 of 560), Jewish patients (1.3%; 4 of 320), and White women of other ethnic origins (1.0%; 15 of 1,566); the frequency of the mutation in unselected controls was 0.3% for both the French Canadian and other White groups. There was no mutation detected among the Jewish controls, but this sample was relatively small (n = 180).

Brazilian women represent a mixed group, with ancestors of African, Portuguese, Hispanic, and other European origins. One mutation was found among 155 Brazilian patients (0.7%). No mutation was seen among 718 Asian patients (342 Filipino, 376 Pakistani). The mutation prevalences and odds ratios for breast cancer for the different ethnic groups are presented in Table 1. A detailed analysis of the ethnicity of the CHEK2-positive families revealed a dominance of families of English, Scottish, and Irish descent (12 of 28 families; Table 2).

Because the 1100delC mutation seemed to be limited to White patients, the remaining analyses are restricted to 2,449 White women with breast cancer (Brazil excluded). The prevalence of mutations in White breast cancer patients, categorized by age and family history, are presented in Table 3. Among the White patients, 825 women had a family history of breast cancer (one or more first- or second-degree relatives with breast cancer) and 1,106 had no family history. Family history data was missing from 518 cases. White women with familial breast cancer were five times more likely to harbor a CHEK2 mutation than were White controls (odds ratio, 5.2; 95% confidence interval, 2.6-10.5; P < 0.0001). White women with nonfamilial breast cancer were 2.6 times more likely to harbor a mutation than were unaffected White controls (odds ratio, 2.6; 95% confidence interval, 1.1-5.8; P = 0.05).

Of the White women, 1,588 had previously been tested for the presence of a BRCA1 or BRCA2 mutation (Table 4). No CHEK2 mutation was seen among 307 breast cancer patients with a BRCA mutation. The prevalences of CHEK2 mutations were 1.4% among those women with no BRCA mutation detected (18 of 1,280) and 0.5% among those who were untested for BRCA mutations (4 of 858). Among the familial cases without a BRCA mutation, the prevalence of CHEK2 mutations was 2.4% (11 of 453).

One proband was homozygous for the CHEK 1100delC mutation. Homozygosity was confirmed by two assays, first by the restriction enzyme assay and subsequently by DNA sequencing. The proband was diagnosed with bilateral breast cancer (ages 47 and 61 years) and with uterine sarcoma at age 58 years.

We examined the family histories of the 28 probands with a CHEK2 mutation. Sixteen of the probands with a mutation had a positive family history of breast cancer (58%). We identified 51 cases of breast cancer among the first-, second-, and third-degree relatives of the 28 probands. Of these, 11 were tested for the CHEK2 mutation (the others were unavailable for testing or were deceased). Only 5 of the 11 affected relatives who were tested for CHEK2 were also positive for the mutation.

A mutation was present in 1.2% of women diagnosed with breast cancer under the age of 50 years, versus 0.6% of women diagnosed after the age of 50 years (P = 0.14). One hundred thirty-seven of the 2,449 patients had multiple primary breast cancers (5.6%), and 359 patients had cancer at a second site (14.7%). The frequency of CHEK2 mutations in women with multiple primary breast cancer (0.7%) was similar to that of women with a single case of breast cancer (0.8%). The frequency of the 1100delC mutation in women with breast cancer and another cancer was 1.7% (odds ratio, 2.1; P = 0.13).

In summary, White ethnicity, age of onset below age 50 years, and a positive cancer family history were risk factors for the presence of a CHEK2 mutation. Mutations were equally frequent in women with unilateral and bilateral breast cancer and were not found in women with a BRCA mutation.

**Discussion**

We estimated the prevalence of the CHEK2 1100delC mutation in breast cancer patients from various ethnic groups. The first goal of this study was to identify populations for which appreciable numbers of women with breast cancer carry the CHEK2 1100delC allele and which might benefit from genetic testing. Our second goal was to estimate the magnitude of the risk increase associated with this single mutation in these populations. We included patients from several Asian countries and from Brazil. We did not identify a mutation in patients from Pakistan and the Philippines.

### Table 3. CHEK2 mutations by age and family history, White women

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Familial</th>
<th></th>
<th>Nonfamilial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Positive</td>
<td>%</td>
</tr>
<tr>
<td>&lt;39</td>
<td>216</td>
<td>6</td>
<td>2.8%</td>
</tr>
<tr>
<td>40-49</td>
<td>280</td>
<td>4</td>
<td>1.4%</td>
</tr>
<tr>
<td>50-59</td>
<td>167</td>
<td>1</td>
<td>0.6%</td>
</tr>
<tr>
<td>60+</td>
<td>154</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>All</td>
<td>825</td>
<td>12</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

**NOTE:** Age of diagnosis was missing on 23 subjects.

### Table 4. CHEK2 mutations by BRCA status and by multiple primary cancer status, White women only (n = 2,449)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>n</th>
<th>Positive</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>One breast cancer</td>
<td>1,953</td>
<td>16</td>
<td>0.8%</td>
</tr>
<tr>
<td>Multiple breast cancers</td>
<td>137</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Breast and other cancer</td>
<td>359</td>
<td>6</td>
<td>1.7%</td>
</tr>
<tr>
<td>BRCA mutation positive</td>
<td>307</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>BRCA mutation negative</td>
<td>1,280</td>
<td>18</td>
<td>1.4%</td>
</tr>
<tr>
<td>Not tested</td>
<td>858</td>
<td>4</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
(therefore, controls from these countries were not tested). The founder mutation was restricted to women of European origin, including Ashkenazi Jews and French Canadian women. The mutation was found in a single woman from Brazil (of mixed European ancestry). This particular mutation is the most important founder allele in European countries and other CHEK2 variants do not seem to make a substantial contribution to breast cancer susceptibility in western Europe or North America (9–11). However, it is possible that other CHEK2 variants are responsible for the predisposition in other countries. For example, a splice-site mutation in CHEK2 IVS2+G>A has been found to be associated with breast cancer predisposition in Poland (12), and, in Ashkenazi Jewish women, the CHEK2 S428F variant increases breast cancer risk by ~2-fold (13).

The observed relative risk of breast cancer associated with the 1100delC mutation in White women with familial breast cancer was ~5-fold. However, the 1100delC allele did not segregate completely with the presence of breast cancer in the families. Incomplete segregation is characteristic of two-gene models for cancer and can be an impediment to gene mapping through linkage analysis (14). For studies of genes in this class, it may be best to conduct association studies of familial cases. For familial cases, the odds ratio was about 5 and an effect of this size is amenable to an association study, even if the allele frequency is relatively rare. However, it is important to note, for counseling purposes, that observing a 5-fold risk does not imply that unaffected women from these same families face a 5-fold risk of breast cancer; their lifetime risk is actually similar to that estimated for nonfamilial cases (below). The observed odds ratio of 5 is a consequence of the case-control design—that is, any gene which is associated with a substantial increase in the risk of breast cancer is more likely to be present in a familial case than in a nonfamilial case because it will result in familial aggregation; for example, if a genetic variant doubles the risk of breast cancer in whomever it is present, it is more likely to be present in a patient with an affected sister than in a singleton case.

From our nonfamilial cases, we estimate a relative risk of 2.6 associated with the 1100delC mutation. Based on the risk to age 74 years for breast cancer in Ontario of 9% (15), this corresponds to a penetrance of roughly 23% penetrance to age 74 years. Previously, the increased risk for breast cancer associated with the CHEK2 1100delC mutation has been estimated at between 1.4- and 4.7-fold. In a similar study of unselected breast cancer cases from New York, Offit and colleagues (11) found the frequency of the allele among 300 cases to be 1.0% and among 1,665 controls to be 0.3%. These figures are similar to ours. In Offit et al.’s study and ours, there was no difference in the allele frequency between Ashkenazi and non-Ashkenazi controls. Because of the penetrance of ~25%, and because most of these breast cancer are estrogen receptor positive, some authors have advocated that unaffected CHEK2 carriers be offered tamoxifen as chemoprevention (16).

In previous studies, patients with a mutation in BRCA1 or BRCA2 were excluded from CHEK2 analysis under the premise that the familial predisposition had been explained. Our data are consistent with this assumption; we found no CHEK2 mutation in 307 White women with breast cancer and a BRCA mutation. It is unlikely that women with a BRCA mutation will be found to harbor a CHEK2 mutation. However, it is impractical to offer screening for CHEK2 as a standalone genetic test; it is better to add the test for selected CHEK2 mutations as part of a wider mutation screen, at least for patients with breast cancer from women with northern and eastern European origins. The additional cost for adding this single allele to a mutation panel is minimal, and a single-step multiallelic approach is more practical than a sequential approach. Our study was of a single allele of CHEK2—it is possible that this allele is very rare in non-European populations but that other CHEK2 alleles may be founder alleles elsewhere. It is important that ethnic-specific studies be conducted in different populations of breast cancer patients to confirm or exclude CHEK2 as a contributing factor.

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References

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