Cancer prevalence in 129 breast-ovarian cancer families tested for BRCA1 and BRCA2 mutations

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Background. Women who carry germline mutations in the breast-ovarian cancer susceptibility genes, BRCA1 and BRCA2, are at very high risk of developing breast and/or ovarian cancer. Both genes are tumour suppressor genes that protect all cells from deregulation, and there are reports of their involvement in other cancers that vary and seem to depend on the population investigated. It is therefore important to investigate the other associated cancers in different populations to assist with risk assessments.

Objectives. To assess the cancer risk profile in BRCA-mutation-positive and negative South African breast-ovarian cancer families, mainly of Caucasian origin.

Design. Descriptive study in which the prevalence of all cancers in the pedigrees of BRCA1- and BRCA2-mutation-positive groups and a group of families without mutations in either gene were compared with the general population.

Results. As expected, female breast and ovarian cancer was significantly increased in all three groups. Furthermore, male breast cancer was significantly elevated in the BRCA2-positive and BRCA-negative groups. Stomach cancer prevalence was significantly elevated in the BRCA2-positive families compared with the general population.

Conclusions. These results can be applied in estimation of cancer risks and may contribute to more comprehensive counselling of mutation-positive Caucasian breast and/or ovarian cancer families.

Breast cancer is the most common malignancy among women in South Africa, with a crude incidence rate of 18.5/100 000 recorded between 1993 and 1995. A small but significant percentage (5 - 10%) of breast cancer cases are directly due to an inherited susceptibility. Two tumour suppressor genes involved in early-onset breast and ovarian cancer, BRCA1 and BRCA2, have been mapped and cloned. These two genes explain 20 - 40% of heritable breast cancer cases in various populations over the world. A large linkage and mutation study on 237 families collected by the Breast Cancer Linkage Consortium found that overall BRCA1 accounts for 52% of all families, and BRCA2 for 32%, leaving 16% of the families with a familial breast cancer phenotype unaccounted for. In the study, 81% of the families with both a breast and an ovarian phenotype were BRCA1-positive families while 14% linked to BRCA2. The situation was reversed in families that presented with a male breast cancer phenotype in addition to female breast cancer, where 76% linked to BRCA2 and only a small percentage to BRCA1.

Worldwide many families with a strong history of familial breast cancer have been fully screened for BRCA1 and BRCA2 mutations but none were found. This is especially the case in breast cancer-specific families (no other cancers beside breast cancer in family). While the search for the BRCA1 and BRCA2 genes was helped by the strong association of ovarian cancer in addition to breast cancer with BRCA1 and male breast cancer with BRCA2, the search for other breast cancer-associated genes is more complicated. Studies on BRCA1- and 2-negative breast cancer families showed that the most probable explanation is that there are multiple additional genes with lower penetrance and/or prevalence, each responsible for a small number of families.

The functions of the BRCA genes have not been fully elucidated, but they are broadly classified as tumour suppressor genes with functions in DNA repair and recombination, cell cycle regulation through checkpoint control and transcription regulation. Owing to their function in cell cycle regulation and damage response, mutations in these genes are expected to lead to susceptibility for deregulation and cancer in more than one tissue type. It is unclear why mutations in these two genes are mainly involved in malignancies in the breast and ovaries, but it is thought that some interaction with the female hormones, oestrogen and progesterone, may be responsible.

Mutations within BRCA1 and BRCA2 have been demonstrated to contribute to an increased risk of cancers.
other than breast and ovarian cancer. Friedenson summarised 32 studies (involving >70 000 individuals) that investigated the elevated risks for other cancers, associated with these two genes.\textsuperscript{13} The increased risks range from 20% to 60%, with the most important increases in cancers of the stomach and pancreas. BRCA2 confers an elevated risk to a broader spectrum of cancers than BRCA1. Many reviewed studies, however, had conflicting reports, stressing the importance of contributing genetic factors and environmental influences that may differ between populations.

We studied the occurrence of different types of cancer in 127 Caucasian and 2 non-Caucasian South African families with a positive breast cancer history. Complete mutation analysis allowed division of these families into BRCA1-mutation positive, BRCA2-mutation positive and families with no mutation in either gene. The pedigrees of these three groups of families were compared to determine the respective contribution of BRCA1 and BRCA2 to breast and ovarian cancer and to establish which other cancers may be associated with mutations in these genes.

The study was approved by the Ethics Committee of the University of Pretoria (Protocol 18/98).

**Methods**

**Selection of patients**

Participating families were obtained through a familial cancer clinic at the University of Pretoria. Families willing to participate and with a family history (3 or more cases with breast and/or ovarian cancer) suggestive of inherited susceptibility were included.

We assembled a total of 129 (127 Caucasian and 2 non-Caucasian) families: 81/129 (62.8%) were Afrikaners, mainly descended from Dutch, German and French immigrants to the South African Cape during the early 17th century;\textsuperscript{14} Ashkenazi Jewish families represented 15.5% (20/129), 12.4% (16/129) were of British/UK origin, and 2.32% (3/129) were of Dutch descent. In addition, there were single families of Afrikaner-Lebanese, Austrian, Belgian, German, German-British, Polish and Portuguese descent. The 2 non-Caucasian families were a black South African and a South African Indian family.

A blood sample from index individuals (affected with breast and/or ovarian cancer) in these families was obtained with informed consent, and the two BRCA genes were screened for mutations using single-strand conformation polymorphism and heteroduplex analysis (SSCP/HA), protein truncation test (PTT) and multiplex ligation-dependent probe amplification (MLPA) methods. Of the 129 families, 26 tested positive for a mutation in BRCA1 and 43 for a mutation in BRCA2, while 60 remained unassigned (‘BRCA negative’) after full screening.\textsuperscript{15,16} The three groups were analysed to determine the prevalence of cancer in family members.

**Pedigree analysis**

Information regarding cancer cases in the families were obtained from the index individuals and were not verified with pathological reports. The reliability of the information, especially for more distant relatives, may be lower than that for first- and second-degree relatives’ cancers. Females and males included in the analysis were only from the branches of the pedigree (paternal or maternal) that were believed to carry mutations in one of the BRCA genes. Only the index cases were screened for mutations; none of the other family members in the pedigree were screened. The assumptions of the inheritance of the mutation were based primarily on the occurrence of breast and ovarian cancer in females and secondarily on other cancers in all individuals. Where there were cancers in both branches of the family, the branch with the most cancers in the closest relatives were included. For the previous generations, all males and females in the pedigrees were included, up to the generation where the first reported case appeared. Persons in more current generations were included only if they were born before 1960 (~40 years old at time of analysis). This therefore excludes very young persons who would not yet have developed cancer.

The number of females in the pedigrees was used in calculations for female-specific cancers, and the same applies for the male-specific cancers. In the case of cancer affecting both the female and male populations the unknown gender counts were included. Bilateral cases (in females and males) were counted as two separate cases, but only the age at first diagnosis was used in calculations regarding age.

For the chi-square test the expected number of cancer cases was obtained by multiplying the population risk with the total number of individuals in the group. The population risk in South African individuals for 1993 - 1995 was obtained from the National Cancer Registry (NCR).\textsuperscript{17} The Cancer Registry data are limited in that they only supply information on histopathologically confirmed tumour data and not on population-based data. These data are at best a minimal estimate of ‘population’ risks. Cancer risks in the Caucasian population of South Africa were used for the calculations, since the majority of the study families were of Caucasian origin (only 2 families were non-Caucasian, i.e. 1 black in the BRCA-negative group and 1 Indian in the BRCA1-positive group). For the chi-square tests for cancers, which are not gender specific, the mean between the cancer risk of Caucasian males and females in South Africa was used.

**Results**

Mutation-positive families constituted 53% of the total families. The BRCA2-positive families were largely site-specific breast cancer families (33/43), compared with the BRCA1-positive families (6/26) (Table I). The total number of individuals in all the pedigrees included was 3 682 with an average of 28.5
Male breast cancer had a higher prevalence than expected in the BRCA-positive groups. In all three groups prostate, colon, bladder and lung cancers and melanoma had a significantly lower prevalence than expected. Overall, the prevalence of cancers in total was higher in all three study groups ($p<0.00001$) compared with what would be expected from the general Caucasian population data (Table II).

**Discussion**

**Breast cancer**

Breast cancer prevalences for the BRCA1-positive group and the BRCA-negative group were similar ($p=0.843$) (Table I). The BRCA2-positive group had a significantly higher prevalence of breast cancer than the BRCA1-positive group ($p=0.015$) and the BRCA-negative group ($p=0.009$), which seems to indicate that a higher breast cancer risk is associated with BRCA2 than with BRCA1 (Table I). Generally BRCA2 mutation penetrance for lifetime risk of breast cancer is lower than for BRCA1 mutation carriers, resulting in a later age of onset.\(^\text{11}\) This was also apparent in our study, where more BRCA1-positive individuals than BRCA2-positive individuals were diagnosed with breast cancer below the age of 50 years (Table I).

**Ovarian cancer**

Previously the cumulative risk for ovarian cancer in BRCA2 was established at 11% versus 39% for BRCA1.\(^\text{17}\) A study on breast ovarian cancer families with at least two cases of ovarian cancer showed these families to be four times more likely to carry a BRCA1 mutation than a BRCA2 mutation.\(^\text{18}\) Likewise, in our study 9.6% of individuals in the BRCA1-positive group had ovarian cancer compared with 1.9% in the BRCA2-positive group (Table I), indicating a significant difference between the two groups ($p<0.001$).

**Male breast cancer**

Our study supported our expectation that a BRCA2-mutation-positive genotype would result in fewer ovarian cancer cases and more male breast cancer cases than in the BRCA1-positive group, as in other studies.\(^\text{19}\) (Table I). Interestingly, in the BRCA-negative group the male breast cancer prevalence also appeared to be increased compared with what was expected for the general population (Table II). However, this may not be a true reflection as we selected families for the presence of male and female breast cancers. In the BRCA-negative group the 5 male cases each came from different families (1 case per family), whereas the 8 breast cancer cases observed in the BRCA2-positive group came from only 3 families (2.7 cases per family). It was reported previously that once an index case presents with male breast cancer in a BRCA2-positive family a number of other cases also emerge in the rest of the family.\(^\text{20}\) This could possibly indicate gene-gene interactions that modify the prevalence based on the general Caucasian population risk\(^\text{1}\).

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Table I. Family information, cancer cases and prevalence in the different study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>BRCA1+</th>
<th>BRCA2+</th>
<th>BRCA2-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families (N)</td>
<td>26</td>
<td>43</td>
<td>60</td>
</tr>
<tr>
<td>With BC &amp; OV</td>
<td>18</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>With only BC</td>
<td>6</td>
<td>33</td>
<td>48</td>
</tr>
<tr>
<td>With only OV</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Females (N)</td>
<td>456</td>
<td>719</td>
<td>834</td>
</tr>
<tr>
<td>Males (N)</td>
<td>337</td>
<td>545</td>
<td>663</td>
</tr>
<tr>
<td>Unknown gender (N)</td>
<td>5</td>
<td>82</td>
<td>41</td>
</tr>
<tr>
<td>Cancer cases (cases/family) (N)</td>
<td>219 (8.4)</td>
<td>375 (8.7)</td>
<td>342 (5.7)</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>Female BC (bil. BC)</td>
<td>24.6 (3.94)</td>
<td>31.0 (3.89)</td>
</tr>
<tr>
<td></td>
<td>Diag. &gt;50 yrs</td>
<td>18.1</td>
<td>28.7</td>
</tr>
<tr>
<td></td>
<td>Diag. ≤50 yrs</td>
<td>69.1</td>
<td>55.4</td>
</tr>
<tr>
<td></td>
<td>OV</td>
<td>9.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Male BC</td>
<td>0.3</td>
<td>1.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Cancers other than BC and OV</td>
<td>7.8</td>
<td>9.7</td>
<td>7.2</td>
</tr>
<tr>
<td>All cancers</td>
<td>27.4</td>
<td>27.9</td>
<td>22.2</td>
</tr>
</tbody>
</table>

\(BC = \) breast cancer, \(OV = \) ovarian cancer, Prevalence = \(N\) of cancer cases/\(N\) of individuals (female and/or male depending on the cancer type) × 100, bil. BC = bilateral breast cancer, Diag. = age at breast cancer diagnosis.
penetrance of male breast cancer in certain BRCA2-positive families.

Other cancers

Of the other cancers recorded in the families, only stomach cancer in the BRCA2-positive group showed a significantly increased prevalence compared with the general population (Table II).

Prostate, colon, bladder and lung cancers and melanoma appear to have a lower than expected prevalence in all three groups, probably because of incomplete reports of all cancers in the families. Some of these cancers have a high population risk, e.g. prostate cancer with a 1 in 14 lifetime risk. Incomplete reporting will affect the cancers with a higher population risk to a greater extent than those with a lower risk. To illustrate the point: if 30% of all cancers in a group of 1 346 individuals (similar in size to the BRCA2-positive group) were not reported, it would lead to 11 cases of unreported colon cancer (similar in size to the BRCA2-positive group) were not reported.

Another consideration could be that the under-reported cases are not the same over all the cancer categories but that there are preferential reports on breast and ovarian cancer, as this study focused on these cancers. The clinic that collected the families for this study tried to limit this tendency by informing patients of the importance of recording all cancers before gathering their pedigree information. However, a bias may still remain and will persist in studies that rely on secondary information supplied by the family rather than on hospital and pathology records.

Table III presents reports\(^2\) that showed associations with various types of cancers compared with our study. As many of the cancers in our study had few reported cases, one must be careful to attach significance to the difference in prevalence between the groups. However, stomach and prostate cancer each had 40 or more reported cases. Stomach cancer had a significantly \((p=0.00001)\) elevated prevalence in the BRCA2 families compared with the general population and had twice the prevalence compared with the BRCA1-positive group. Although prostate cancer was not significantly elevated in the BRCA-mutation-positive groups compared with the general population, it is still interesting that the BRCA2-positive group had a 5 times higher prevalence compared with the BRCA1-positive group (Table III).

The BRCA-negative group

Just what the families that constitute the BRCA-negative group signify is uncertain. They may represent a diverse group of families with the hypothetical BRCA3 gene, families with genes of lower penetrance, families with mutations in high-penetrance genes that are very rare, or just families with BRCA1 or 2 mutations that were missed by the methods employed. Our methods are supposed to have a 71% - 79% sensitivity,\(^2\) giving an estimate of 27 - 37 families in the BRCA-

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**Table II. Comparison of observed cancer prevalence in the study groups with the expected prevalence**

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Pop. risk</th>
<th>BRCA1+ Observed cases</th>
<th>Expected cases</th>
<th>p-value</th>
<th>BRCA2+ Observed cases</th>
<th>Expected cases</th>
<th>p-value</th>
<th>BRCA- Observed cases</th>
<th>Expected cases</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>13</td>
<td>112</td>
<td>35.08</td>
<td>&lt;0.00001</td>
<td>223</td>
<td>55.31</td>
<td>&lt;0.00001</td>
<td>209</td>
<td>64.15</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Male breast</td>
<td>476</td>
<td>1</td>
<td>0.71</td>
<td>0.728</td>
<td>8</td>
<td>1.14</td>
<td>5</td>
<td>1.39</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>120</td>
<td>44</td>
<td>3.80</td>
<td>&lt;0.00001</td>
<td>14</td>
<td>5.99</td>
<td>0.001</td>
<td>18</td>
<td>6.95</td>
<td>0.0003</td>
</tr>
<tr>
<td>Prostate</td>
<td>14</td>
<td>3</td>
<td>24.07</td>
<td>0.00001</td>
<td>25</td>
<td>38.93</td>
<td>0.0205</td>
<td>12</td>
<td>47.36</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Colon</td>
<td>35.5</td>
<td>4</td>
<td>22.48</td>
<td>0.00008</td>
<td>5</td>
<td>37.92</td>
<td>&lt;0.00001</td>
<td>8</td>
<td>43.32</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Stomach</td>
<td>120.5</td>
<td>7</td>
<td>6.62</td>
<td>0.8829</td>
<td>24</td>
<td>11.17</td>
<td>0.001</td>
<td>17</td>
<td>12.76</td>
<td>0.2337</td>
</tr>
<tr>
<td>Liver</td>
<td>264.5</td>
<td>1</td>
<td>3.02</td>
<td>0.2446</td>
<td>8</td>
<td>5.09</td>
<td>0.196</td>
<td>6</td>
<td>5.61</td>
<td>0.9388</td>
</tr>
<tr>
<td>Brain</td>
<td>339.5</td>
<td>1</td>
<td>2.35</td>
<td>0.377</td>
<td>2</td>
<td>3.96</td>
<td>0.3231</td>
<td>6</td>
<td>4.53</td>
<td>0.4892</td>
</tr>
<tr>
<td>Melanoma</td>
<td>50.5</td>
<td>3</td>
<td>15.80</td>
<td>0.0011</td>
<td>3</td>
<td>26.65</td>
<td>&lt;0.00001</td>
<td>5</td>
<td>30.46</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pancreas</td>
<td>512</td>
<td>2</td>
<td>1.56</td>
<td>0.7234</td>
<td>4</td>
<td>2.63</td>
<td>0.3973</td>
<td>3</td>
<td>3.00</td>
<td>0.9975</td>
</tr>
<tr>
<td>Bladder</td>
<td>75.5</td>
<td>0</td>
<td>10.57</td>
<td>0.0011</td>
<td>3</td>
<td>17.83</td>
<td>0.0004</td>
<td>4</td>
<td>20.37</td>
<td>0.0003</td>
</tr>
<tr>
<td>Kidney</td>
<td>357</td>
<td>2</td>
<td>2.24</td>
<td>0.8749</td>
<td>1</td>
<td>3.77</td>
<td>0.1531</td>
<td>2</td>
<td>4.31</td>
<td>0.2655</td>
</tr>
<tr>
<td>Lung</td>
<td>47.5</td>
<td>4</td>
<td>16.8</td>
<td>0.0016</td>
<td>8</td>
<td>28.34</td>
<td>0.0001</td>
<td>9</td>
<td>32.38</td>
<td>0.0003</td>
</tr>
<tr>
<td>Thyroid</td>
<td>348</td>
<td>1</td>
<td>2.29</td>
<td>0.3929</td>
<td>0</td>
<td>3.87</td>
<td>0.0489</td>
<td>3</td>
<td>4.42</td>
<td>0.499</td>
</tr>
<tr>
<td>Throat</td>
<td>290.5</td>
<td>1</td>
<td>2.75</td>
<td>0.291</td>
<td>4</td>
<td>4.63</td>
<td>0.7682</td>
<td>5</td>
<td>5.29</td>
<td>0.8961</td>
</tr>
<tr>
<td>Uterus</td>
<td>108</td>
<td>1</td>
<td>4.22</td>
<td>0.1152</td>
<td>10</td>
<td>6.66</td>
<td>0.1931</td>
<td>1</td>
<td>7.72</td>
<td>0.0151</td>
</tr>
<tr>
<td>Cervix</td>
<td>93</td>
<td>3</td>
<td>4.90</td>
<td>0.3875</td>
<td>4</td>
<td>7.73</td>
<td>0.1773</td>
<td>0</td>
<td>8.97</td>
<td>0.0026</td>
</tr>
<tr>
<td>Other cancers</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified cancers</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cases</td>
<td>6.5</td>
<td>219</td>
<td>122.7692</td>
<td>&lt;0.00001</td>
<td>375</td>
<td>207.08</td>
<td>&lt;0.00001</td>
<td>342</td>
<td>236.62</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Pop. risk = given as N, where N is the Caucasian population risk \((1/N)\) \((Sitas et al., 1998^3)\); Observed cases = the number of cancer cases counted from pedigrees in each of the three groups (BRCA1-positive, BRCA2-positive and BRCA-negative families); Expected cases = expected cancer cases in the families calculated through multiplying the Caucasian population risk by the total number of individuals in each of the three groups; p-value = the probability that the observed number of cancer cases is in accordance with expected number of cancer cases in general Caucasian population; \(\text{bold font} \) = higher prevalence than general Caucasian population; \(\text{italics} \) = lower prevalence than general Caucasian population.
negative group, which might have BRCA1/2 mutations that were missed by the current screening methods. However this still leaves 23 - 33 families in which the breast cancer phenotype can be ascribed to either rare high-penetrant genes or low-penetrant genes that might segregate in these families together with polymorphisms in other genes that enhance cancer penetrance.

Conclusion

BRCA2 has been implicated in increased susceptibility to a larger range of cancers than BRCA1. This was also seen in our study, where the prevalence of breast, ovarian, male breast and stomach cancer was significantly increased in the BRCA2-positive group. Although cancers of the liver, prostate and uterus were more prevalent in the BRCA2-positive group than the other two groups, this was not significantly elevated compared with the general population.

Both BRCA1 and BRCA2 genes play an important role in the aetiology of familial breast cancer in South Africa. Reports have suggested mutation-specific cancer prevalence for the classically BRCA-associated cancers and other cancers. We report on the cancer risk profile in BRCA-mutation-positive and negative Caucasian breast-ovarian cancer families collected in South Africa. Our results regarding cancer risks in BRCA-mutation-positive families largely agree with published data. This allows for more comprehensive counselling of Caucasian mutation-positive breast and breast-ovarian cancer families regarding their risks of breast-ovarian cancer and of other associated cancers.

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References

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Table III. Comparison with other studies showing association of BRCA genes with cancers other than breast and ovarian

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>BRCA1*</th>
<th>BRCA2*</th>
<th>Current study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1</td>
<td>BRCA2</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>3</td>
<td>2</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Significant elevated prevalence compared to the general population 2 times higher prevalence than BRCA1 families (not significant, p=0.069)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>2</td>
<td>5</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>5 times higher prevalence than BRCA1 families (significant, p=0.0004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td></td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>5 times higher prevalence than BRCA1 families</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>1</td>
<td></td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>6 times higher prevalence than BRCA1 families</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>1</td>
<td>1</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Less than 1.5 times difference between groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>-</td>
<td>1</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Less than 1.5 times difference between groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>3</td>
<td>2</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Less than 1.5 times difference between groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>4</td>
<td>2</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Less than 1.5 times difference between groups</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Number of studies that found a positive association with the gene. Information from Friedenson (2005).