A HIGH PROPORTION OF FOUNDER BRCA1 MUTATIONS IN POLISH BREAST CANCER FAMILIES


1 Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland
2 Prophylactic and Epidemiology Center, Poznani, Poland
3 Department of Cancer Immunology, Great Poland Cancer Center and University School of Medical Sciences, Poznani, Poland
4 Regional Oncology Center, Wroclaw, Poland
5 Institute of Immunology and Experimental Therapy, Wroclaw, Poland
6 Department of Tumor Biology, Maria Skłodowska-Curie Memorial Institute, Gliwice, Poland
7 Department of Clinical Genetics, Bydgoszcz Medical University, Bydgoszcz, Poland
8 Department of Paliomology and Oncology, Regional Oncology Hospital, Olsztyń, Poland
9 Holycross Oncology Center, Kielce, Poland
10 Regional Oncology Center, Białystok, Poland
11 Department of Chemotherapy, Medical Academy, Łódź, Poland
12 Department of Chemotherapy, Regional Hospital, Świdnica, Poland
13 Oncology Diagnostic Center, Legnica, Poland
14 Regional Hospital I, Rzeszów, Poland
15 Department of Gynecology, Medical Academy, Lublin, Poland
16 Cancer Genetics Counseling Unit, Medical University, Lublin, Poland
17 Regional Oncology Center, Kraków, Poland
18 Regional Oncology Hospital, Opole, Poland
19 Regional Hospital, Gorzów Wielkopolski, Poland
20 Regional Oncology Hospital, Zielona Góra, Poland
21 Clinic of Surgical Gynecology and Gynecologic Oncology of Adults and Adolescents, Pomeranian Medical University, Szczecin, Poland
22 Centre for Research in Women’s Health, University of Toronto, Toronto, Canada

Received 21 August 2003; Revised 30 November 2003; Accepted 16 December 2003

Three mutations in BRCA1 (5382insC, C61G and 4153delA) are common in Poland and account for the majority of mutations identified to date in Polish breast and breast-ovarian cancer families. It is not known, however, to what extent these 3 founder mutations account for all of the BRCA mutations distributed throughout the country. This question has important implications for health policy and the design of epidemiologic studies. To establish the relative contributions of founder and nonfounder BRCA mutations, we established the entire spectrum of BRCA1 and BRCA2 mutations in a large set of breast-ovarian cancer families with origins in all regions of Poland. We sequenced the entire coding regions of the BRCA1 and BRCA2 genes in 100 Polish families with 3 or more cases of breast cancer and in 100 families with cases of both breast and ovarian cancer. A mutation in BRCA1 or BRCA2 was detected in 66% of breast cancer families and in 63% of breast-ovarian cancer families. Of 129 mutations, 122 (94.6%) were in BRCA1 and 7 (5.4%) were in BRCA2. Of the 122 families with BRCA1 mutations, 119 (97.5%) had a recurrent mutation (i.e., one that was seen in at least 2 families). In particular, 111 families (91.0%) carried one of the 3 common founder mutations. The mutation spectrum was not different between families with and without ovarian cancer. These findings suggest that a rapid and inexpensive assay directed at identifying the 3 common founder mutations will have a sensitivity of 86% compared to a much more costly and labor-intensive full-sequence analysis of both genes. This rapid test will facilitate large-scale national epidemiologic and clinical studies of hereditary breast cancer, potentially including studies of chemoprevention.

Key words: breast cancer; ovarian cancer; inherited predisposition; BRCA1; BRCA2.

Germline mutations in BRCA1 (MIM 113-705) and BRCA2 (MIM 600185) account for familial clustering in the majority of families with both breast and ovarian cancers and in approximately one-half of families with site-specific breast cancer.1–3 Of the more than 1,000 BRCA1 mutations reported to the Breast Cancer Information Core (BIC) database, many are unique but there are also numerous examples of founder mutations. Founder mutations have been reported in genetic isolates such as Ashkenazi Jews4,5 and the Icelandic,6 Finnish,7 Dutch8,9 and French Canadian10 populations. Founder mutations have also been noted in Slavic countries, including Poland.11 Three BRCA1 mutations (5382insC, C61G and 4153delA) are common in Poland,11 but several other BRCA1 and BRCA2 mutations have also been reported in one or a few families.1–11 Our goal was to describe the frequency of BRCA1 and BRCA2 constitutional mutations in a series of 200 breast cancer and breast-ovarian cancer families representing all regions of Poland.

Grant sponsor: Polish National Scientific Committee; Grant number: KBN No 4PO5A 132 18.

*Correspondence to: Polabska 4, 70115 Szczecin, Poland.
Fax: +48-91-4661533. E-mail: gorskib@sci.pam.szczecin.pl

© 2004 Wiley-Liss, Inc.
motion was detected in 122 families (61%) and a BRCA2 mutation, in 7 (3.5%) families (Tables II, III). All 7 BRCA2 mutations were unique (i.e., none seen in more than one family). Six of the 7 BRCA2 mutations were found in families with site-specific breast cancer, and one was found in a breast–ovarian cancer family. Of the 122 BRCA1 mutations, 119 (97.5%) were found in more than one family. The 3 most common mutations accounted for 111 of the 122 (91.0%) BRCA1 mutations detected and for 86.0% of all detected mutations. The 5382insC mutation alone accounted for the majority of mutations (68 families). Three other recurrent BRCA1 mutations were seen but much less commonly (Table II).

BRCA1 mutations were almost equally frequent in families with site-specific breast cancer (60%) or the breast–ovarian cancer syndrome (62%). Overall, a BRCA1 mutation was identified in 66% of site-specific breast cancer families and in 63% of breast– ovarian cancer families. There was less difference in the distribution of individual mutations between families with and without ovarian cancer, with the possible exception of the 4153delA mutation. Of the 12 families with this specific mutation, 9 had one or more cases of ovarian cancer. There were no clear differences in the prevalence of mutations by geographic region (Table IV).

All of these mutations are associated with truncated proteins and are therefore believed to be deleterious. In addition, 5 BRCA2 variants of the missense type were seen in 11 different families (Table III). These variants have not been shown to be of functional consequence. No unclassified variants were observed in the BRCA1 gene.

RESULTS

We screened 200 Polish families with either site-specific breast cancer (100 families) or breast– ovarian cancer (100 families). The characteristics of these families are presented in Table I. A BRCA1 mutation was detected in 122 families (61%) and a BRCA2 mutation, in 7 (3.5%) families (Tables II, III). All 7 BRCA2 mutations were unique (i.e., none seen in more than one family). Six of the 7 BRCA2 mutations were found in families with site-specific breast cancer, and one was found in a breast–ovarian cancer family. Of the 122 BRCA1 mutations, 119 (97.5%) were found in more than one family. The 3 most common mutations accounted for 111 of the 122 (91.0%) BRCA1 mutations detected and for 86.0% of all detected mutations. The 5382insC mutation alone accounted for the majority of mutations (68 families). Three other recurrent BRCA1 mutations were seen but much less commonly (Table II).

BRCA1 mutations were almost equally frequent in families with site-specific breast cancer (60%) or the breast–ovarian cancer syndrome (62%). Overall, a BRCA1 mutation was identified in 66% of site-specific breast cancer families and in 63% of breast– ovarian cancer families. There was less difference in the distribution of individual mutations between families with and without ovarian cancer, with the possible exception of the 4153delA mutation. Of the 12 families with this specific mutation, 9 had one or more cases of ovarian cancer. There were no clear differences in the prevalence of mutations by geographic region (Table IV).

All of these mutations are associated with truncated proteins and are therefore believed to be deleterious. In addition, 5 BRCA2 variants of the missense type were seen in 11 different families (Table III). These variants have not been shown to be of functional consequence. No unclassified variants were observed in the BRCA1 gene.
BRCA1 MUTATION IN POLISH BREAST CANCER

We observed equally high frequencies of mutations in families with and without ovarian cancer. This is perhaps surprising given previous results, but in the present study the average age at diagnosis was younger in the site-specific breast cancer families than in the breast–ovarian cancer families (46.6 vs. 50.2 years).

Polish people are ethnically distinct, but within Poland geographic mixture has been achieved largely due to extensive immigration after the Second World War. We did not observe a greater than expected degree of variation in the prevalence or spectrum of mutations seen in different regions of Poland; therefore, we consider that the current panel is appropriate for testing women in all Polish centers. However, our sample size from individual centers was small, and significant differences in the frequency and spectrum of BRCA1 mutations between regions cannot be excluded.

The proportion of families with breast–ovarian cancers and BRCA1 mutations in Warsaw may be lower than that reported here (E. Skasko, personal communication). It is also possible that unrecognized mutations in genes other than BRCA1 or BRCA2 are present to different degrees in cancer families in different regions of Poland and that these uncounted mutations have contributed to the observed variation.

Similarly, we did not see a clear difference in the spectrum of BRCA1 or BRCA2 mutations in families with and without ovarian cancer. Therefore, our data do not support the notion of an ovarian cancer cluster region in BRCA2 (nucleotides 3035–6629).27 However, the number of families in our study with BRCA2 mutations was small (n = 6), and only one of these contained a case of ovarian cancer.

We did not evaluate the spectrum or frequency of large rearrangements in BRCA1 or BRCA2. This type of mutation is likely to be missed by our sequencing technique. In some series, these large rearrangements have contributed up to 30% of the burden of mutations.28 It is possible therefore that the total frequency of mutations is even higher than the 64% observed. To date, founder deletions or rearrangements have not been identified in Eastern Europe.

We estimate the sensitivity of an assay based on the 6 common BRCA1 mutations to be 92% and that of an assay based on the 3 most common mutations to be 86%. This means that it should be possible to classify most individuals into carriers and noncarriers with little expense and minimal misclassification. This will be important as future epidemiologic studies are designed. Also, it should be feasible to identify relatively large numbers of carriers for intervention and screening studies at limited cost. We estimate that the cost of DNA extraction and testing of the common BRCA1 mutations is 50 Euros per assay, or 100 Euros per patient including genetic counseling. The sensitivity of 86% for the mutation panel described here should be adequate for most clinical purposes, though it is possible that the 86% estimate of sensitivity is high due to sampling error. There may be individual families with strong aggregations of cancer and for whom the initial mutation screen is negative. For these women, full gene screening may be justified. It may also be prudent to offer screening with this “Polish panel” for women of Polish origin who reside in other countries.29

### TABLE IV - FREQUENCY OF BRCA1 MUTATION DETECTION AMONG DIFFERENT REGIONS OF POLAND

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of families studied</th>
<th>Number of BRCA1 mutations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolnośląskie</td>
<td>15</td>
<td>9</td>
<td>60%</td>
</tr>
<tr>
<td>Kajawsko-Pomorskie</td>
<td>11</td>
<td>9</td>
<td>81%</td>
</tr>
<tr>
<td>Lubelskie</td>
<td>12</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>Lubuskie</td>
<td>6</td>
<td>5</td>
<td>83%</td>
</tr>
<tr>
<td>Łódzkie</td>
<td>13</td>
<td>6</td>
<td>46%</td>
</tr>
<tr>
<td>Małopolskie</td>
<td>17</td>
<td>11</td>
<td>64%</td>
</tr>
<tr>
<td>Mazowieckie</td>
<td>24</td>
<td>12</td>
<td>50%</td>
</tr>
<tr>
<td>Opolskie</td>
<td>6</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>Podkarpackie</td>
<td>12</td>
<td>8</td>
<td>66%</td>
</tr>
<tr>
<td>Podlaskie</td>
<td>7</td>
<td>4</td>
<td>57%</td>
</tr>
<tr>
<td>Pomorskie</td>
<td>11</td>
<td>3</td>
<td>27%</td>
</tr>
<tr>
<td>Szasie</td>
<td>24</td>
<td>16</td>
<td>66%</td>
</tr>
<tr>
<td>Świętokrzyskie</td>
<td>7</td>
<td>5</td>
<td>71%</td>
</tr>
<tr>
<td>Warmińsko-Mazurskie</td>
<td>7</td>
<td>6</td>
<td>85%</td>
</tr>
<tr>
<td>Wielkopolskie</td>
<td>18</td>
<td>10</td>
<td>55%</td>
</tr>
<tr>
<td>Zachodniopomorskie</td>
<td>9</td>
<td>7</td>
<td>77%</td>
</tr>
</tbody>
</table>

### TABLE V - PREVIOUS REPORTS ON THE FREQUENCY OF BRCA1 GENE MUTATIONS IN POLAND

<table>
<thead>
<tr>
<th>City and reference</th>
<th>5382insC</th>
<th>C61G</th>
<th>4153delA</th>
<th>Other</th>
<th>% of families with mutations (number of families studied)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bydgoszcz25</td>
<td>4</td>
<td>1</td>
<td></td>
<td>NE</td>
<td>50% (4) 43% (7) 45% (11)</td>
</tr>
<tr>
<td>Gdańsk12</td>
<td>NE</td>
<td>3</td>
<td></td>
<td>1</td>
<td>14% (21) 66% (3) 19% (21)</td>
</tr>
<tr>
<td>Gdańsk17</td>
<td>4</td>
<td>2</td>
<td></td>
<td>3</td>
<td>11% (9) 72% (11) 45% (20)</td>
</tr>
<tr>
<td>Gliwice13</td>
<td>11</td>
<td>1</td>
<td></td>
<td>4</td>
<td>38% (13) 58% (19) 50% (32)</td>
</tr>
<tr>
<td>Poznan4</td>
<td>2</td>
<td>NE</td>
<td></td>
<td>NE</td>
<td>0% (7) 66% (3) 20% (10)</td>
</tr>
<tr>
<td>Poznan10</td>
<td>5</td>
<td>5</td>
<td></td>
<td>NE</td>
<td>55% (9) 0% (2) 45% (11)</td>
</tr>
<tr>
<td>Szczecin11</td>
<td>16</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>34% (35) 66% (27) 48% (62)</td>
</tr>
<tr>
<td>Warsaw16</td>
<td>6</td>
<td>2</td>
<td></td>
<td>1</td>
<td>NG          NG</td>
</tr>
</tbody>
</table>

NE, not examined. NG, not given.
REFERENCES


30. Stawicka M. Clinical features and epidemiology of hereditary breast cancer in female population of Poznan. Pomeranian Medical University, Szczecin, Poland (dissertation).