Transmission of mutant alleles to female offspring of BRCA1 carriers in Poland

Three founder mutations in BRCA1 are common in Poland (5382insC, C61G, and 4153delA). At birth, it is expected that 50% of the children of a parent who carries a BRCA1 mutation will inherit a mutant allele. However, in a recent paper we observed a greater than expected frequency of mutation carriers among daughters (but not among sons) of women with BRCA1 mutations in Poland. We observed 75 carrier daughters and 47 non-carrier daughters of 122 carrier sons) of women with BRCA1 mutations in Poland. We observed 75 carrier daughters and 47 non-carrier daughters of 122 carrier mothers (transmission ratio 61.5%; p = 0.01 for difference). Recently, de la Hoya et al. have undertaken a similar study in a Spanish and Dutch cohort and have also observed a higher ratio of carrier daughters (58% in those <30 years of age). However, Evans et al. have found no evidence of non-random transmission in an English cohort. Because of the potential importance of these observations for genetic counsellors and for our understanding of BRCA1 genetics, we repeated this study on an unselected series of breast cancer patients. This study is superior in design to our earlier study in that the mutation carriers were drawn from a pool of unselected breast cancer patients and all first degree relatives were accounted for and offered genetic testing.

In the course of a national breast cancer survey we identified 4596 women with breast cancer diagnosed before age 50 from 1996 to 2003 at one of 18 centres situated throughout Poland. Three of the 18 centres did not participate in the study. We were able to obtain a DNA sample for 2871 of these patients for BRCA1 analysis. Among these women 154 mutation carriers were identified (5.4%). Through pedigree review, we identified 187 sisters and 134 daughters of these 154 women. We requested a blood sample from all female first degree relatives. We completed testing on 125 sisters (69% of total sample) and 109 daughters (81%). The BRCA1 mutation was present in 57 of the 109 daughters (52%) and in 67 of the 125 (54%) sisters. Of the 125 sisters, 41 had breast cancer (22%). Of these, 23 were tested and 22 were found to be positive. The other 146 sisters were unaffected; of these, 102 were tested and 45 (43%) were positive. Assuming the same distribution of carriers and non-carriers in the 62 untested sisters (18 affected and 44 unaffected), we estimate that 103 of the sisters were positive for the family mutation and 84 were negative (p = 0.08). The estimated transmission ratios for daughters (52%) and for sisters (55%) are lower than that which we reported previously for daughters (62%) and are closer to the expected values of 50%.

However, as we saw in the first paper, there was a suggestion that the transmission ratio varied with year of birth. Among women in the first study who were born between 1971 and 1980, there were 38 carriers and 18 non-carriers (transmission ratio 68%). In the present study the proportion was 60% (33 of 55). When the data from the two independent studies were merged, the possibility of an effect by calendar year was supported to a modest degree (table 1). However, there is no consistent trend here, this was a post hoc comparison, and there were no significant differences between the rows.

In summary, our new data do not clearly support our earlier claim that there is a greater than expected probability of transmission of the mutant BRCA1 allele to daughters of carrier families. However, a modest excess of carriers over non-carriers is consistent with a modest excess of mutant alleles to female offspring in BRCA1 carriers.

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Competing interests: none declared

References

Table 1 Number of mutation positive and negative first degree female relatives of BRCA1 mutation carriers in Poland

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Number positive</th>
<th>Number negative</th>
<th>Transmission ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>10</td>
<td>11</td>
<td>48%</td>
<td>0.8</td>
</tr>
<tr>
<td>1951–1960</td>
<td>40</td>
<td>29</td>
<td>58%</td>
<td>0.3</td>
</tr>
<tr>
<td>1961–1970</td>
<td>36</td>
<td>28</td>
<td>64%</td>
<td>0.003</td>
</tr>
<tr>
<td>1971–1980</td>
<td>71</td>
<td>40</td>
<td>64%</td>
<td>0.003</td>
</tr>
<tr>
<td>1981–present</td>
<td>42</td>
<td>49</td>
<td>64%</td>
<td>0.003</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>157</td>
<td>56%</td>
<td>0.03</td>
</tr>
</tbody>
</table>
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