Non-random transmission of mutant alleles to female offspring in BRCA carriers

We were most interested to read the report of Gronwald and colleagues suggesting that there was non-random transmission of the mutant BRCA1 gene to female offspring in a Polish cohort. We have undertaken a similar analysis in an English cohort but found no evidence for non-random transmission.

Gronwald et al reported that 61.5% of unaffected female offspring carried the mutant allele and this ratio did not decrease with age (as might be expected from the exclusion of affected females at advancing age). We have analysed the ratio of positive predictive tests in first degree relatives of proven mutation carriers from 284 BRCA1 and BRCA2 families from central and northern western England. Like Gronwald et al, we excluded women who were affected with cancer or whose daughter was affected as they were potential obligate carriers. We did not include branches of the family where the mutation status of the parent was unknown even if it was a mother with breast or ovarian cancer in a family with a known mutation. This excluded the possibility of including the testing of daughters of potential phenocopies. We did not reach the level of 89% uptake of predictive testing achieved with the daughters of 91 female mutation carriers in the Gronwald and colleagues suggesting that evidence for non-random transmission.

We were most interested to read the report of 91 female mutation carriers in the UK. Like Gronwald et al, we excluded women who were affected with cancer or whose daughter was affected as they were potential obligate carriers. We did not include branches of the family where the mutation status of the parent was unknown even if it was a mother with breast or ovarian cancer in a family with a known mutation. This excluded the possibility of including the testing of daughters of potential phenocopies. We did not reach the level of 89% uptake of predictive testing achieved with the daughters of 91 female mutation carriers in the Gronwald and colleagues suggesting that evidence for non-random transmission.

We suspect that differences in the ascertainment strategies may explain the differences between the findings in Poland and the UK. Thus, in the UK families penetrance appears to be high with <33% of unaffected females older than 50 years of age testing positive (as would be expected with a 50% penetrance by that age). Indeed, adding the results of the two other studies, only 30% of women >50 years of age were mutation positive. Although there was a very low level of positive tests in those aged 60 years of age, we had excluded seven living affected female mutation carriers whose daughters had developed breast or ovarian cancer. The UK families were nearly all selected on the basis of having at least three (and usually four) or more affected relatives with breast/ovarian cancer. In contrast, the Polish families were much less highly selected because the presence of common founder mutations in the Polish population allows a lower threshold for initiating BRCA1 mutation analysis. Although we have offered testing more widely for two common mutations in BRCA1/2 in Manchester, the penetration in these families was still high. Family and epidemiological studies have demonstrated that approximately 70–80% of BRCA1 and BRCA2 mutation carriers develop breast cancer in their lifetime, although the risk is a little lower for BRCA2. The very low figures published on small numbers of families from population studies have now been addressed by a meta-analysis. An important practical point is that penetrance estimates provided in genetic counselling sessions should be modified according to how the family was ascertained. Thus, families which are similar to those from the linkage consortium should be provided with higher risk estimates, whereas those ascertained with fewer affected relatives should be quoted a range including the lower estimates derived from population based studies.

Uptake of genetic testing is age related, with high uptake in unaffected females in their thirties and forties and lower uptakes outside this age group. In particular the lower uptake in older women reflects the reduced interest in testing by those at risk women without daughters who may feel they are past the personal risk period for their family. We did include results from daughters who had a father who carried the mutation although this represents <10% (29) of the tested females. The results were not altered by excluding this subset (48% tested positive); although de la Hoya et al did show a lower proportion of carriers born to carrier fathers, this was with only 59 tested daughters. In summary, although our findings differ from those of Gronwald et al, we suggest that the hypothesis that there may be a selective advantage for the BRCA1 mutant allele in utero merits further investigation and that further studies should also include BRCA2 families and possibly also those who inherited the mutation from their father.

Table 1

<table>
<thead>
<tr>
<th>Age at testing</th>
<th>Testing positive</th>
<th>Testing negative</th>
<th>Untested</th>
<th>Proportion positive</th>
<th>Proportion tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>16</td>
<td>18</td>
<td>85</td>
<td>47%</td>
<td>29%</td>
</tr>
<tr>
<td>30–39</td>
<td>64</td>
<td>46</td>
<td>58</td>
<td>65%</td>
<td>56%</td>
</tr>
<tr>
<td>40–49</td>
<td>37</td>
<td>50</td>
<td>45</td>
<td>6%</td>
<td>66%</td>
</tr>
<tr>
<td>50–59</td>
<td>16</td>
<td>25</td>
<td>52</td>
<td>43%</td>
<td>44%</td>
</tr>
<tr>
<td>60–69</td>
<td>6</td>
<td>31</td>
<td>27</td>
<td>47%</td>
<td>1%</td>
</tr>
<tr>
<td>Total</td>
<td>134</td>
<td>166</td>
<td>186</td>
<td>45%</td>
<td>52%</td>
</tr>
</tbody>
</table>

These results include four mutation carriers and two non-carriers who have subsequently developed breast or ovarian cancer and exclude seven tested females over 60 years of age who had an affected daughter with breast/ovarian cancer who had tested positive.

Table 2

<table>
<thead>
<tr>
<th>Age at testing</th>
<th>Testing positive</th>
<th>Testing negative</th>
<th>Proportion positive</th>
<th>Proportion tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>102</td>
<td>76</td>
<td>57%</td>
<td>p = 0.2</td>
</tr>
<tr>
<td>30–49</td>
<td>49</td>
<td>195</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>50–69</td>
<td>47</td>
<td>112</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>367</td>
<td>380</td>
<td>49%</td>
<td></td>
</tr>
</tbody>
</table>

References


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D G Evans, A Shenton, S Sharif, E Woodward, F Lalloo and E R Maher

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