Non-random transmission of mutant alleles to female offspring of BRCA1 carriers in Poland

J Gronwald, B Gorski, T Byrski, T Huzarski, A Jakubowska, J Menkiszak, S A Narod, J Lubinski

C onstitutional mutations in the BRCA1 gene predispose to an autosomal dominant syndrome of breast and ovarian cancer. The lifetime penetrance of BRCA1 gene mutations is high; approximately 50% of women with mutations will be affected by cancer by the age of 50 years, and over 80% of women with mutations will be affected with cancer by the age of 75 years. At birth, it is expected that 50% of the children of a carrier parent will inherit a mutant allele. If the mortality in carriers is higher in carriers than in non-carriers, then the proportion of carriers among offspring is expected to decline with age. Similarly, among unaffected women, the proportion of carriers is expected to decline with age. For example, if the gene is 50% penetrant by the age of 50 years, then one third of a sample of healthy 50 year old female offspring of carriers are expected to be carriers. Under the assumption that a mutant allele is transmitted to 50% of offspring, it is therefore possible to estimate age-specific penetrance values of the BRCA1 gene by counting the relative number of carriers and non-carriers in a sample of healthy offspring, of varying ages, of carrier parents.

Three founder mutations in BRCA1 are common in Poland (5382insC, C61G, and 4153delA). In an attempt to estimate the age-specific penetrance of these three mutations, we systematically reviewed the genotypes of mothers and daughters in a selected group of 387 families from the Hereditary Cancer Center. The probands (mothers) were drawn from three sources: (a) 44 carrier probands were found in 490 consecutive cases of breast cancer diagnosed in women under 50 years of age; (b) 46 carrier probands were found in 347 consecutive ovarian cancer cases diagnosed at any age; and (c) 297 carrier probands were found among women with a family history of breast or ovarian cancer who were referred for genetic counselling. In these latter families, the proband refers to the individual who first received genetic testing in the family, and of the probands, 127 were affected with breast cancer, 35 were affected with ovarian cancer, 135 had neither form of cancer.

In total, 387 carrier probands were identified, of whom 247 had one or more daughters. To avoid the possibility of selection bias we included only families in which the mothers received their genetic test result before any of the daughters were tested (218 of 247). Of these 218, 91 mothers had one or more daughters who were tested for the mutation and 127 had daughters who were not tested. The 91 carrier mothers had 141 daughters, of whom 126 were tested (range 1–4 daughters per mother). Fifty nine of the 91 mothers had breast cancer, 21 had ovarian cancer and 11 were unaffected. Four of the daughters had been affected by breast cancer and were excluded. None of the unaffected daughters had ovarian cancer or had a child affected with cancer. Thus, 122 unaffected daughters were tested. The mean age of the daughters was 26.5 years (range 7–50 years) (mutation results were not offered to daughters under the age of 18 years). The prevalence of mutations in the daughters by age is given in the table. In total, 75 of 122 unaffected daughters (61.5%) were carriers of the mutation; 61 would have been expected under a transmission ratio of 50% (p = 0.011). Surprisingly, there was no evidence of declining prevalence of mutations with increasing age of the daughters. Among women aged 20 years or above, 63 carriers and 33 non-carriers were identified (p = 0.002).

Results were similar for each of the three groups of probands. Among the tested daughters of the unselected cases of breast cancer 18 mutations were observed (15 expected), among the daughters of the unselected cases of ovarian cancer 12 mutations were observed (nine expected), and among the daughters of the mothers referred to the genetics clinics 45 carriers were observed (37 expected). Results were similar for the three mutations studied; among daughters of mothers with the 5382insC mutation 46 carriers were observed (36.5 expected); among daughters of mothers with the G61C mutation 16 mutations were observed (12.5 expected); and among daughters of mothers with the 4153delA mutation 13 mutations were observed (12 expected). For comparison purposes, we also tested 63 sons of the carrier mothers; 30 mutations were found (31.5 expected).

In summary, we observed a greater frequency than expected of carriers among daughters, but not among sons, of carriers of BRCA1 founder mutations in Poland. As a result, it was not possible to estimate the penetrance in these families by using the method of unaffected carriers. The reason for the surprisingly high observed frequency of carriers is not known, nor is it easy to explain the lack of decline in mutation prevalence with increasing age. If our results are due to a selective advantage for carriers then this
selection appears not to have been in operation for women born in the last 20 years. These data raise the possibility that the high frequency of founder BRCA1 mutations in Poland, and possibly in other populations may be due to a selective advantage to carriers. Future studies will extend these observations to other populations with founder effects.

Out data suggests that the selective advantage is restricted to females. If a female embryo carrying a BRCA1 mutation is more likely to survive to birth than a non-carrier female embryo, then carriers of BRCA1 mutations should have more daughters than sons. In support of this, among the children of the 57 probands unselected for family history, 73 were daughters and 53 were sons (p = 0.07). The lack of stillbirths and early deaths in this cohort suggests that any selective advantage must be operating very early in utero or during gametogenesis, possibly during oocyte selection.

By studying only the unaffected offspring of carrier mothers we believe that we have limited possible biases in our study design. Fewer than 50% of unaffected first degree relatives are expected to carry the mutation. Results were similar for each of the BRCA mutations and for each of the three groups of probands. Only women who were tested after the identification of the mutation in the mother were included.

In summary, we found that a greater number of daughters than expected inherited the deleterious BRCA1 allele. If confirmed, this finding has important implications both for genetic counselling and for the calculation of penetrance estimates using pedigree-based methods.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of carriers</th>
<th>Number of non-carriers</th>
<th>Proportion of carriers (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>12</td>
<td>14</td>
<td>46</td>
<td>0.69</td>
</tr>
<tr>
<td>20-29</td>
<td>38</td>
<td>18</td>
<td>68</td>
<td>0.080</td>
</tr>
<tr>
<td>30-39</td>
<td>16</td>
<td>10</td>
<td>61.5</td>
<td>0.24</td>
</tr>
<tr>
<td>40-50</td>
<td>9</td>
<td>5</td>
<td>64</td>
<td>0.29</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>47</td>
<td>61.5</td>
<td>0.011</td>
</tr>
</tbody>
</table>

**Table 1** Mutation frequency by age among unaffected daughters of carrier mothers

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