Cancer risks in first-degree relatives of BRCA1 mutation carriers: effects of mutation and proband disease status

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ABSTRACT

Introduction It is not known to what extent the risks of breast and ovarian cancer differ for women with different mutations in the BRCA1 genes. We estimated cancer risks for carriers of three founder mutations in the BRCA1 gene in Poland.

Methods We obtained blood samples and pedigrees from 3568 unselected cases of breast cancer, and from 609 unselected patients with ovarian cancer from various hospitals in Poland. A founder BRCA1 mutation was identified in 273 samples (4.3% of the patients with breast cancer and 12.3% of the patients with ovarian cancer). We calculated the risk to age 75 in the first-degree relatives of the carriers using Kaplan-Meir methods.

Results The overall risk of breast cancer to age 75 in the relatives was 33% and the risk of ovarian cancer was 15%. The risk for breast cancer was 42% higher among first-degree relatives of carriers of the C61G missense mutation, compared to other mutations (HR = 1.42; p = 0.10) and the risk for ovarian cancer was lower than average (OR = 0.26; p = 0.03). Relatives of women diagnosed with breast cancer had a higher risk of breast cancer than the relatives of women diagnosed with ovarian cancer (OR = 1.7; p = 0.03).

Discussion The risks of cancer for carriers of founder BRCA1 mutations in Poland vary, both with the mutations type and with the family history of cancer. It is therefore not ideal to counsel all women with a BRCA1 mutation in Poland with average risk figures.
INTRODUCTION
Mutations in the BRCA1 (MIM 113705) gene are found in a substantial proportion of families with multiple cases of breast and ovarian cancer, and women with a BRCA1 mutation are at significantly higher risk of developing breast and ovarian cancer than are the general public. However, uncertainty remains as to the best estimate of risk for gene carriers, and which are the factors that influence the penetrance of the BRCA1 gene. Different methods have been used to measure penetrance - but it is generally accepted that studies based on unselected patient series are superior to those based on cases selected for family history. [1][2] This is because familial cases may be enriched for predisposing cofactors and because families with multiple cases are more likely to be ascertained than are families with a smaller number of affected women. If there are predisposing risk factors that cluster within families then we expect the risk of cancer in close relatives to depend on whether the proband was affected with breast or ovarian cancer, as well as with the mutation itself.

Three founder BRCA1 mutations (5382insC, C61G and 4153delA) comprise over 90% of all detectable BRCA1 mutations in Poland. [3][4] We have conducted population surveys of unselected cases of breast cancer (diagnosed under age 50) and of ovarian cancer cases (diagnosed at any age) in Poland. The patients provided details about cancers in first-degree relatives and underwent genetic testing for the three founder BRCA1 mutations. Using this data we are able to estimate the cumulative incidence of all cancers in the first-degree relatives of the carriers, and to compare the risks by BRCA1 mutation, and by the disease status of the index case (breast or ovarian cancer).

METHODS

Study subjects
In the course of a national breast cancer survey we identified 4596 women diagnosed with breast cancer at age 50 or below at one of 18 centers situated throughout Poland from 1996-2003. [5] We were able to obtain a DNA sample for BRCA1 analysis from 3568 of these. 609 patients with ovarian cancer were interviewed from 1999 to 2004 at eight centers situated throughout Poland. The ovarian cancer patients have been described in detail previously. [6] The study was approved by the ethics board of the Pomeranian Medical University.

Pedigree data
The patient was interviewed in person by a member of the research team. The woman was asked to provide information about cancers in all her first-degree relatives, including type of cancer, age of onset, age of death, and current age for relatives without cancer. None of the diagnoses of cancer in the relatives were confirmed by reference to pathology reports. Patients were unaware of their mutation status at the time of interview.

Laboratory analyses
Three founder mutations in BRCA1 gene (5382insC, C61G, and 4153delA) which cover about 90% of BRCA1 mutations in Poland were studied. Methods have been described elsewhere. [3] [4][5][6]

Statistical analysis
We estimated the age-specific breast, ovarian and total cancer risks for first-degree relatives of mutation carriers for each mutation separately, using Kaplan-Meier survival analyses. Patients were considered to be at risk of cancer from birth until either the development of cancer; death from another cause; the date of patient interview, or until age 75. Cumulative
incidence curves were computed separately for breast cancer, for ovarian cancer and for all cancers combined (any cancer). Curves were computed separately for the each of the three founder mutations. We also calculated the cumulative incidence of breast cancer (and ovarian) cancer for women who were the relatives of probands with breast (or ovarian) cancer. Penetrance curves were compared for mothers and sisters. Statistical significance between curves was compared using the log-rank test. To establish which of these factors were the most relevant for predicting the lifetime cancer risk a Cox proportional hazards model was used which incorporated mutation, proband disease status and relationship (mother versus sisters). In this model the baseline categories were 5382insC, breast cancer diagnosed in the proband and sisters of the proband.

RESULTS
Among the unselected Polish women with cancer in this study, 273 mutation carriers were identified, including 198 probands with breast cancer and 75 probands with ovarian cancer. A mutation was present in 4.3% of the patients with breast cancer and 12.3% of the patients with ovarian cancer. 263 of the pedigrees contained sufficient data for statistical analysis (96%). The cumulative risks of cancer among the first-degree relatives of the BRCA1 mutation carriers are shown in Table 1 and Fig 1. The risk of breast cancer for all female first-degree relatives of all mutation carriers was estimated to be 33% to age 75. Sixty-seven percent of the female relatives had been diagnosed with some type of cancer by the age of 75, compared to 35% of the male relatives.

We observed moderate differences in cancer risk for the subgroups of relatives with each of the three different mutations (Table 3; Figs 2 and 3). In the Cox proportional hazard model, the breast cancer risk for relatives of women with the missense mutation C61G was about 40% higher than that conferred by the more common mutation 5382insC (OR =1.44; p = 0.10).

Differences in risk with different mutations were also seen for ovarian cancer. Only 5% of the female relatives of the C61G mutation carriers were affected with ovarian cancer by age 75, and this represented only 28% of the risk relative to the 5382insC mutation (OR = 0.28; p = 0.04). For all mutations combined, the risk of ovarian cancer to age 75 was 15%.

We compared the risk of cancer in sisters and mothers of the probands to establish if the risk appears to be changing with time. For both breast and ovarian cancer the lifetime risk for sisters exceeded that of mothers (table 2). The hazard ratio for breast cancer (sisters versus mothers) was 2.5 (p = 10^{-4}) and the hazard ratio for ovarian cancer was 3.0 (p = 0.003).

The data was then analyzed with respect to the type of cancer diagnosed in the proband (breast or ovarian). The underlying null hypothesis is that the cancer risk is entirely dependent on the mutation itself, and that other familial factors (genetic and/or environmental) do not play a significant role. The risk of cancer was therefore compared for relatives of probands with breast and ovarian cancer. For ovarian cancer risk in relatives, there was no appreciable difference seen depending on whether the proband had breast or ovarian cancer (Table 3). In contrast, the relatives of breast cancer patients experienced a much greater risk of breast cancer than did the relatives of ovarian cancer patients. A survival analysis using Cox regression estimated that the relatives of ovarian cancer patients experienced approximately only one-half of the risk of breast cancer as did the relatives of breast cancer patients (HR = 0.58; p = 0.03; Table 4).
Finally, we wished to establish whether the observed effect of the proband cancer type on breast cancer risk was due to a different distribution of mutations in the two groups. A multivariate Cox regression was done. In this analysis the hazard ratios were adjusted for specific mutation and relation to the proband (sister versus mother). After adjustment the effect of proband cancer type was still significant - the hazard ratio for breast cancer in relatives of women with ovarian cancer was 0.51 (95% CI 0.31 – 0.84; p = 0.008). Similarly, in the multivariate analysis the effects of the mutation types on cancer risk were essentially unchanged. Because of the possible confounding influence of the C61G mutation on these results we repeated this regression but restricted the probands to women who carried the 5382insC mutation. The results were essentially unchanged.

**DISCUSSION**

Although it is clear that BRCA1 mutations confer a substantial risk for both breast and ovarian cancer, the cancer risk appears to vary between populations, and within populations between individual carriers. Undoubtedly, some of the variance in the risk estimates can be attributed to biases in the methods in the different studies, but there are several reasons to believe that the differences are real. There are three potential sources of variation; first variation in risk between mutations; second, modifying genetic background and third, environmental/lifestyle factors.

In our study we have shown that the risks of breast and ovarian cancer appear to differ significantly with the mutation itself. We found a higher risk of breast cancer and a lower risk of ovarian cancer associated with the missense mutation C61G. The C61G mutation is the most frequent missense change reported to the Breast Cancer Information Core Database (http://research.nhgri.nih.gov/bic/). It was first reported in two families, one of which was a Polish family, and is one of the few missense changes in *BRCA1* that has been determined to be linked to disease using segregation analysis.[15] This mutation targets a critical residue that coordinates binding to a zinc atom in the RING finger domain of *BRCA1*. [16] Mutation at this residue abrogates the ubiquitin ligase activity of BRCA1. [17] [18] Importantly, this mutant seems to be unable to reverse gamma-radiation hypersensitivity of *BRCA1*-null cells.[18] We observed the highest risk of breast cancer and the lowest risk of ovarian cancer to be associated with this mutation. It is not clear of this is a general characteristic of other pathogenic missense mutations or of other mutations which disrupt the RING finger. To our knowledge this is the only common founder mutation in the RING finger.

Several studies have proposed the notion of a genotype-phenotype correlation for *BRCA1* and *BRCA2* in which risk for ovarian or breast cancer vary with mutation position.[7] [8] [19] [20] However, these studies have looked at mutations as a group, with most mutations being frameshift or nonsense mutations which generate truncated proteins. It will be of interest to functionally evaluate the C61G mutation by comparing its activity in breast and ovarian cell lines.

There is also some evidence that families with single mutations in the central part of BRCA1 (nucleotides 2401 to 4190) have a lower than average risk of breast cancer. [8] The risks of breast and ovarian cancers associated with particular mutations are difficult to estimate, because of the high costs of genetic testing, the rarity of mutations in the general population, and the large number of distinct mutations in the gene. At this stage it is only practical to perform mutation specific analyses for founder populations. Antoniou et al. estimated the risks of breast and ovarian cancer in a (mostly) Jewish study population with two BRCA1 founder mutations. [9] They reported the risk of ovarian cancer to age 70 to be substantially higher among carriers of the BRCA1 5382insC mutations (33%) than the 185 del AG
mutations (14%) but the difference was not statistically significant. No apparent differences were noted for breast cancer risks with the two BRCA1 mutations.

We recently reported that the breast cancer risk associated with the Polish 4153delAG mutation was much lower than that of the other two mutations, based on odds ratios generated from unselected Polish breast cancer patients and controls. [10] In the present study, which was based on reported family histories, we did not observe the breast cancer risk for relatives of probands with the 4153delAG mutation to be significantly lower than for the other two mutations, however the number of patients in this group of relatives was small (n = 8). It is not clear yet what is the reason for the difference between the two studies, but in both the actual number of subjects was small.

We found that the risk of breast cancer in first-degree relatives differed significantly, depending on whether the proband was diagnosed with breast or ovarian cancer. This was not the case for ovarian cancer risk. These observations are consistent with the earlier reports of Moslehi et al [11] and of Warner et al [12], who used identical methods in Jewish populations of unselected ovarian cancer and breast cancer patients respectively. They also found that the risk of breast cancer varied, depending on the type of cancer in the proband, but the risk of ovarian cancer was about the same. The data from these two studies is summarized in Figure 6. Together the studies suggest that it is likely that there are modifying genetic risk factors for breast cancer, but not necessarily for ovarian cancer. There are modifying non-genetic risk factors for ovarian cancer in BRCA1 carriers, such as oral contraceptives [13] and breastfeeding (unpublished data), but these risk factors do not necessarily cluster within families.

We also observed that the risks of breast and ovarian cancer were higher in the sisters of the probands than in the mothers, confirming previous reports. [2] [21] This observation suggests that non-genetic factors are also important in influencing the risk of both breast and ovarian cancer and that the prevalence of these risk factors has increased in Poland over the last generation.

The baseline cancer risks to age 75 in Poland are approximately 1.5% for ovarian cancer and 5% for breast cancer. [14] Therefore, based on the observed risks in first-degree relatives, the average penetrances of the BRCA1 founder mutations are estimated to be 46% for breast cancer and 25% for ovarian cancer. However, the means for individual mutations vary considerably.

There are several strengths of our study. Ours is a large single-center study of unselected breast and ovarian cancer patients originating in a well defined, ethnically-homogeneous group residing in one country. We believe this to be close to the ideal study design. We had very few patients who did not agree to participate when approached. Subjects were unaware of their genetic status at the time the family history was obtained, both patients populations were studied using the same methods, and by the same investigators and interviewers. Our total number of carriers in this study was 273, compared to a total of 196 in the Antoniou study (which was based on a meta-analysis of 22 population-based studies from many different countries). [9] Nevertheless, some of our individual risk estimates were imprecise and it will be important to continue to accrue patients to these two studies and to re-examine this question in the future.
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COMPETING INTERESTS
The authors state that they have no competing interests that could interfere or influence the publication of this manuscript.

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Table 1. Estimated cumulative risks for breast, ovary and other cancers for first-degree relatives of patients with founder BRCA1 mutations

<table>
<thead>
<tr>
<th>Cancer Site in relatives</th>
<th>BRCA1 Mutation Type</th>
<th>1st degree relatives with cancer /total</th>
<th>Cancer Risk to age of 50</th>
<th>Cancer Risk to age of 75</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>5382insC</td>
<td>60 /557</td>
<td>0.15</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>C61G</td>
<td>32/226</td>
<td>0.23</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>4153delA</td>
<td>8/68</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Any BRCA1</td>
<td>100/851</td>
<td>0.18</td>
<td>0.33</td>
</tr>
<tr>
<td>Ovary</td>
<td>5382insC</td>
<td>29/557</td>
<td>0.04</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>C61G</td>
<td>3/226</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>4153delA</td>
<td>6/68</td>
<td>0.08</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Any BRCA1</td>
<td>38/851</td>
<td>0.03</td>
<td>0.15</td>
</tr>
<tr>
<td>Other</td>
<td>5382insC</td>
<td>22/557</td>
<td>0.03</td>
<td>0.15</td>
</tr>
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<td></td>
<td>C61G</td>
<td>117/226</td>
<td>0.05</td>
<td>0.36</td>
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<td></td>
<td>4153delA</td>
<td>1/68</td>
<td>0.02</td>
<td>0.02</td>
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<td></td>
<td>Any BRCA1</td>
<td>40/851</td>
<td>0.04</td>
<td>0.19</td>
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<td>0.61</td>
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<td>Any BRCA1</td>
<td>178/851</td>
<td>0.25</td>
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</tr>
<tr>
<td><strong>Men</strong></td>
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<tr>
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<td>7/70</td>
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<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Any BRCA1</td>
<td>70/816</td>
<td>0.03</td>
<td>0.35</td>
</tr>
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</table>
Table 2. Estimated cumulative risks for breast and ovary cancer for mothers and for sisters of patients with founder BRCA1 mutations

<table>
<thead>
<tr>
<th>Cancer Site in relatives</th>
<th>BRCA1 Mutation Type</th>
<th>1st degree relatives with cancer /total</th>
<th>Cancer Risk to age of 50</th>
<th>Cancer Risk to age of 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Sisters</td>
<td>57/356</td>
<td>0.27</td>
<td>0.42</td>
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<tr>
<td></td>
<td>Mothers</td>
<td>41/254</td>
<td>0.10</td>
<td>0.25</td>
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<tr>
<td></td>
<td>Any BRCA1</td>
<td>100/851</td>
<td>0.18</td>
<td>0.33</td>
</tr>
<tr>
<td>Ovary</td>
<td>Sisters</td>
<td>18/356</td>
<td>0.06</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Mothers</td>
<td>20/254</td>
<td>0.01</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Any BRCA1</td>
<td>38/1158</td>
<td>0.02</td>
<td>0.15</td>
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Table 3 Comparison of risks of cancer in relatives, by proband mutation.

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<tr>
<th>Mutation in proband</th>
<th>HR (95%CI) P-value</th>
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</thead>
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<td></td>
<td>Breast cancer</td>
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<tr>
<td>5382insC</td>
<td></td>
</tr>
<tr>
<td>N=557</td>
<td>1</td>
</tr>
<tr>
<td>4153 del A</td>
<td>1.12 (0.53-2.34) 0.77</td>
</tr>
<tr>
<td>N=68</td>
<td></td>
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<tr>
<td>C61G</td>
<td>1.44 (0.93-2.21) 0.10</td>
</tr>
<tr>
<td>N=226</td>
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Table 4 Comparison of risks in relatives by proband cancer type

<table>
<thead>
<tr>
<th>Proband cancer type</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast cancer</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N=624</td>
<td></td>
<td></td>
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<tr>
<td>Ovarian cancer</td>
<td>0.58 (0.36-0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>N=227</td>
<td></td>
<td></td>
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</tbody>
</table>
Figure Legends

Figure 1. Cumulative incidence of breast and ovarian cancer in female first-degree relatives of 263 BRCA1 carriers.

Figure 2. Cumulative incidence of breast cancer in female first-degree relatives of 263 BRCA1 mutation carriers, by mutation.

Figure 3. Cumulative incidence of ovarian cancer in female first-degree relatives of 263 BRCA1 carriers.

Figure 4. Cumulative incidence of breast cancer in female first-degree relatives of 263 BRCA1 carriers, by cancer type in proband.

Figure 5. Cumulative incidence of ovarian cancer in female first-degree relatives of 263 BRCA1 carriers, by cancer type in proband.

Figure 6. Summary of cancer risk estimates in Ashkenazi Jewish women. Cancer risks in first degree relatives of mutation carriers, by cancer type in proband.
Figure 1. Cumulative incidence of breast and ovarian cancer in 851 female first-degree relatives of 263 BRCA1 mutation carriers.
Figure 2. Cumulative incidence of breast cancer in 851 female first-degree relatives of 263 BRCA1 mutation carriers, by mutation

Cumulative incidence of breast cancer in first-degree relatives by mutation

P=0.25
Figure 3. Cumulative incidence of ovarian cancer in 851 female first-degree relatives of 263 BRCA1 mutation carriers, by mutation.
Figure 4. Cumulative incidence of ovarian cancer in 851 female first-degree relatives of 263 BRCA1 mutation carriers, by cancer type in proband.
Figure 5. Cumulative incidence of breast cancer in 851 female first-degree relatives of 263 BRCA1 mutation carriers, by cancer type in proband.
Figure 6. Summary of cancer risk estimates in Ashkenazi Jewish women. Cancer risks in first-degree relatives of mutation carriers, by cancer type in proband.

Risk of breast and ovarian cancer in Ashkenazi Jewish women

Cumulative incidence of cancer in first-degree relatives of BRCA mutation carriers

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