

# A protein truncating *BRCA1* allele with a low penetrance of breast cancer

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In the 10 years since the identification of the *BRCA1* gene, many cancer families have been tested throughout the world, and there is ongoing interest in estimating the cancer risks for women with mutations in this gene. There is some evidence that families with mutations in the central part of *BRCA1* (nucleotides 2401 to 4190) have a higher than expected ratio of ovarian to breast cancers, due to a lower than average risk of breast cancer.<sup>1</sup> The absolute and relative risks of breast and ovarian cancers associated with different mutations have been difficult to quantify, in part because of the large number of different mutations in the gene, the rarity of mutations in the general population, and the expense of testing. The majority of established *BRCA1* mutations are protein truncating, although a number of deleterious missense mutations have also been identified.<sup>2</sup>

Poland is ideally suited to the study of the genetic epidemiology of *BRCA1* mutations because the country is ethnically homogeneous, and because three common *BRCA1* mutations comprise 91% of all *BRCA1* mutations found in the population.<sup>3</sup> Since 1999, we have tested large numbers of unselected cancer patients and cancer families throughout Poland.<sup>3-5</sup> To estimate the prevalences and relative risks associated with each of the three founder mutations, we genotyped 2012 unselected cases of breast cancer, 364 unselected cases of ovarian cancer, and 2000 population controls. The breast cancer patients were consecutively diagnosed from eight hospitals throughout Poland. Patients were unselected for age (range 21 to 80 years) or for family history, and had been diagnosed between 1999 and 2002. The ovarian cancer patients were from two hospitals in Szczecin, Poland, and have been described previously.<sup>3</sup> The control population consisted of 1000 newborn children from throughout Poland and 1000 adults unaffected with cancer from the practices of family physicians in Szczecin.

The distribution of mutations is shown in table 1. The 4153delA allele is under-represented among breast cancer patients in this distribution and the ratio of breast to ovarian cancers with this mutation is atypical. Among carriers of the 5382insC mutation, the odds ratio for breast cancer is 10.9 (95% confidence interval (CI) 3.9 to 30.4).

Among carriers of the 4153delA mutation, the odds ratio for breast cancer is 1.0 (95% CI 0.06 to 16.2). The equivalent odds ratios for ovarian cancer for the 5382insC mutation and the 4153delA mutation are 43.6 (15.2 to 125.3) and 50.0 (6.2 to 400) respectively.

To confirm the hypothesis that the 4153delA *BRCA1* mutation confers a comparatively low risk of breast cancer, we compared the ratio of breast to ovarian cancers in an independent set of families who had been referred to the hereditary cancer clinic of the Szczecin because of two or more cases of breast or ovarian cancer. These families had been referred for genetic counselling to cancer genetics clinics throughout Poland. At the time the pedigrees were created, no patient in these families had undergone prophylactic mastectomy or had taken tamoxifen as a preventive measure.

## Key points

- Three founder mutations in the *BRCA1* gene contribute to the burden of hereditary breast and ovarian cancer in Poland.
- We estimated the relative risk for breast and ovarian cancer associated with each of these three mutations by studying 2012 unselected cases of breast cancer, 364 unselected cases of ovarian cancer, and 2000 population based controls.
- The odds ratios for ovarian cancer for the two common mutations were 43.6 (95% confidence interval 15.2 to 125.3) for the 5382insC mutation and 50.0 (6.2 to 400) for the 4153delA mutation. In contrast, those for breast cancer were 10.9 (3.9 to 30.4) for the 5382insC mutation and 1.0 (0.06 to 16.2) for the 4153delA mutation.
- This large survey suggests that a common truncating mutation in *BRCA1* may have a dramatic effect on increasing the risk of ovarian cancer, but appears to have little or no effect on modifying breast cancer risk.

Typically, pedigrees contained at least first and second degree relatives of the proband.

These families contained a total of 979 cases of breast cancer and 376 cases of ovarian cancer (not all of these have been genotyped for the family mutation). A founder mutation has been found in 460 of these families. Among the 44 families with the 4153delA mutation, there were 51 breast and 74 ovarian cancers. Among the 416 families with one of the other two mutations there were 928 breast and 302 ovarian cancers (odds ratio 0.22;  $p < 10^{-15}$ ). Breast cancer is clearly under-represented in families with the 4153delA mutation.

These two independent observations indicate that, compared with the other two *BRCA* mutations, the penetrance of the 4153delA founder mutation is low for breast cancer (but is comparable for ovarian cancer). Our results support the conclusions of Thompson and Easton<sup>1</sup> that mutations in the central part of the gene, prior to nucleotide 4190, confer similar risks of ovarian cancer, but reduced risks of breast cancer, compared with other mutations. The biological reason

**Table 1** Distribution of *BRCA1* founder mutations in cancer cases and controls (number (%))

	C61G	4153delA	5382insC	Total
Breast	15 (0.7%)	1 (0.05%)	43 (2.1%)	59 (2.9%)
Ovarian	13 (3.6%)	8 (2.2%)	28 (7.7%)	49 (13.5%)
Controls	1 (0.05%)	1 (0.05%)	4 (0.2%)	6 (0.3%)

for the different risks is unknown. Interestingly, the situation is different for Ashkenazi Jews; women in this population group with the two common founder mutations in *BRCA1* face similar risks of breast and ovarian cancer.<sup>1-6</sup> Our sample is relatively small, and it is likely that the risk of breast cancer in carriers of the 4153delA mutation is elevated and that further studies will be required to estimate with accuracy the extent of this risk. It will be helpful to have mutation specific risks for counselling women in Poland so that they can make informed choices regarding preventive surgery.

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