

CORRESPONDENCE

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.¹ 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 north 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 Polish study. This was presumably due to the different approaches to offering testing. No results were available for females <18 years old in our study. Mutation testing was entirely at the behest of the unaffected female.

The overall frequency of positive tests was 45% in our series (table 1) and, in contrast to the Polish study, there was a sharp decline in the ratio of positive to negative tests in unaffected women after 40 years of age. Whereas 61.5% of women tested aged <50 years in Poland were positive, the proportion was only 51% in our series. However, intriguingly, the proportion of positive results was substantially higher than 50% in the 30–39 year old cohort suggesting some replication of the results of the Polish study, although these results did not reach statistical significance (p = 0.29). It is possible that women with breast symptoms may be more likely to come forward for testing and then subsequently be diagnosed with breast cancer. Three carriers and three mutation negative women in our series have since developed breast cancer, none of whom had

Table 2 Proportion of unaffected female first degree relatives of *BRCA1/2* mutation carriers testing positive for the family mutation from all four studies

Age at testing	Testing positive	Testing negative	Proportion positive
<30	102	76	57% (p=0.2)
30–49	218	192	54%
50+	47	112	30%
Total	367	380	49%

breast symptoms at the time of testing. There was no difference in the results for *BRCA1* compared to *BRCA2* with 45% testing positive for each gene and no evidence of a difference in age related change. Taking the results from our survey together with those from two similar studies,^{2,3} the results from women <50 years of age reveal that 54% were mutation positive. There was a significant excess of mutation carriers <30 years of age in two previous studies.² However, this excess disappears (table 2) when the results of these two studies are added to those of our study and another study (57% positive; p = 0.2).³

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).^{1,4,5} Indeed, adding the results of the other two studies, only 30% of women >50 years of age were mutation positive. Although there was a very low level of positive tests in those over 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 *BRCA* mutation analysis. Although we have offered testing more widely for two common mutations in *BRCA1/2* in Manchester, the penetrance in these families was still high.⁶ 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*.^{4,7,8} The very low figures published on small numbers of families from population studies have now been addressed by a meta analysis.⁸ 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 consortium² 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.^{9–11}

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.¹² 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*² 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*,¹ 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.

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Table 1 Proportion of unaffected female first degree relatives of *BRCA1/2* mutation carriers testing positive for the family mutation

Age at testing	Testing positive	Testing negative	Untested	Proportion positive	Proportion tested
18–29	16	18	85	47%	29%
30–39	64	46	58	58%	65%
40–49	37	50	45	43%	66%
50–59	16	25	52	39%	44%
60+	1	27	31	4%	47%
Total	134	166	186	45%	52%

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.

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