CORRESPONDENCE

Phenocopies in breast cancer 1 (BRCA1) families: implications for genetic counselling

There is interest in testing the hypothesis that the non-carrier sisters of women with a breast cancer 1 (BRCA1) mutation face a greater than expected risk of breast cancer. Genetic testing on 3568 women with breast cancer under the age of 50 years was performed. These cases were unselected for family history. Genetic testing was offered to 261 sisters of 188 mutation-positive cases. One of 72 mutation-negative sisters was diagnosed with breast cancer. Of the 17 sisters diagnosed with breast cancer, only one was a phenocopy. Thus, we are unable to confirm the hypothesis that the non-carrier sisters of mutation carriers face a risk of breast cancer beyond that of the general population.

In the process of counselling women from families with a known breast cancer 1 (BRCA1) mutation, we often encounter healthy women who are found to have a negative test. This is usually a source of great relief for the woman, and traditionally the genetic counsellor or physician offers the opinion that the residual risk is low—that is, approximately that of women in the general population. In Canada and the USA, the risk to the population is approximately 8% to age 75 years, and in Poland it is about 5%. In a recent paper from the UK, Smith and colleagues suggest that the residual risk is, in fact, much greater than this. They estimate that the risk of breast cancer in a non-carrier first-degree relative of a BRCA1 or BRCA2 mutation carrier is about five times higher than expected. This translates into a lifetime risk of 25–40%, depending on the baseline risk in the country of origin. They attribute this observation to the effect of low-risk genes segregating in the family, and which modify the risk of breast cancer in BRCA carriers and non-carriers alike.

This is an interesting hypothesis with important implications, and the claim warrants close scrutiny. Smith *et al*[1] examined the distribution of mutations in 1444 women from 277 families in which a BRCA mutation was found. According to the pedigree and clinic notes, breast cancer had been reported in 28 (11%) of 258 of the women who tested negative for the mutation. They found that 13 (12%) of 107 of the first-degree relatives with breast cancer had a negative mutation test result. We believe that these findings may be influenced by the population studied and by the choice of statistical analysis. In the Smith study, patients were referred for genetic counselling. They qualified for testing if they were from a family with multiple cases of breast and/or ovarian cancer. For example, a family with two sisters affected with breast cancer might be offered testing, whereas a family with one affected woman would not. We infer, therefore, that a family with a genetic case and a phenocopy might be offered testing but that a sibship with a genetic case alone would not. The more cases of breast cancer, the more likely testing will occur. That is, the presence of phenocopies in the family increases the likelihood that testing would be conducted; hence, the greater than expected number of phenocopies observed in the families. Consider another scenario: suppose we were to do a parallel study on non-familial cases of breast cancer (ie women with no affected first-degree relative). A small number of these cases would test positive for BRCA mutations. The risk of breast cancer in the non-carrier sisters of the mutation-positive probands would (by definition) be zero.

There are two ways in which selection bias might be eliminated. First, we could concentrate only on incident cancers that occur in relatives after the date of ascertainment. Second, we could study cases of breast cancer that were unselected for family history. Smith *et al* provide some data for the first scenario. Among women who were initially unaffected, three breast cancers arose in 153 mutation-negative women, after a mean follow-up period of 5 years, versus 1.4 expected (SIR = 2.1; 95% CI 0.4 to 6.2). The second approach is to study a series of breast cancers, unselected for family history.

Methods

We have previously reported on a cohort of 3568 unselected breast cancer patients diagnosed before the age of 50 years from 18 hospitals in Poland. BRCA1 testing was performed on all cases and 198 mutations were found (5.5%).[2] We were able to study 188 of the 198 pedigrees in more detail. All living sisters of the 188 probands were invited for testing. There were 261 sisters of the 188 probands; 228 of the sisters were alive and 33 had died. Forty-three of the sisters were affected with breast cancer and 218 were unaffected. Genetic testing was performed on 140 (54%) sisters including 61% of the living sisters. We tested 17 (40%) of the 43 sisters with breast cancer and 123 (56%) of the 218 women without breast cancer.

Results

Breast cancer was reported in only 1 (1.4%) of 72 non-carrier sisters compared with 28 (11%) of 258 non-carrier sisters in the Smith study. Only 1 (5.8%) of the 17 affected sisters was a phenocopy (compared with 13 (12%) of 107 cases in the Smith study). Assuming that one-half of the 261 sisters in our study carry a BRCA1 mutation and assuming the same rates of mutation positives in the tested and untested women in our study (adjusted for breast cancer status and vital status), we estimate that there are 130.5 non-carrier sisters in our study, of whom 2.5 have breast cancer. On the basis of their age distribution and the cancer rates for Poland,[3] the expected number of breast cancer cases in the non-carrier relatives is about 1.2. The observed odds ratio of 2 is, in fact, similar to that derived from the prospective analysis of Smith and colleagues. However, on the basis of these small numbers, we are unwilling to conclude that there is a greater than expected incidence of breast cancer in non-carrier sisters of women with a BRCA1 mutation. It is possible that future studies will provide compelling evidence to support this claim, and at that time we will modify our currently held position that these women face the same risk of breast cancer as do women in the general population.

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