

LETTER

RAD51C germline mutations in breast and ovarian cancer patients

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The two breast cancer genes *BRCA1* and *BRCA2* account for approximately one-half of cases of hereditary breast cancer, and other genes, such as *BRIP1*, *PALB2*, and *P53*, account for a small additional fraction [1]. Recently, it has been proposed that *RAD51C* is also a breast cancer susceptibility gene [2]. A bi-allelic mutation of *RAD51C* was originally found in a family from Pakistan with features of Fanconi anemia [3]. Because several genes in the Fanconi anemia gene family are also breast cancer susceptibility genes (including *BRCA2* (*FANCD1*) [4], *BRIP1* (*FANCF*) [5] and *PALB2* (*FANCN*) [6]), Meindl and colleagues hypothesised that *RAD51C* might be a breast cancer gene [2]. A germline mutation was seen in 6 of 480 (1.3%) breast/ovarian cancer families from Germany, which had previously been found to be negative for mutations in *BRCA1* and *BRCA2*. In each of the six families, the putative mutation co-segregated with the relevant cancers [2]. Each family with a mutation contained at least one case each of breast and ovarian cancer.

In order to confirm these findings, we sequenced the nine coding exons of *RAD51C* in the germline DNA of 454 patients with familial breast/ovarian cancer. The mean age at diagnosis of the breast cancers was 44.7 years (range 21 to 65) and the mean age of diagnosis of the ovarian cancers was 47.9 years (range 23 to 60 years). All patients were previously found to be negative for *BRCA1* and *BRCA2* mutations. Each proband had at least two affected first- or second-degree relatives. Eighty-five percent of the families contained at least one case of ovarian cancer. One-hundred patients were Jewish, 152 were French-Canadian and 202 were of various other ethnic origins. All subjects provided written informed consent to participate in the study. The study protocol was approved by the ethics committee of the Women's College Research Institute, protocol number 2007-0036-B.

We found no deleterious *RAD51C* mutation among the 454 patients. We found a novel c.146-8A>G splicing variant in three of 100 Jewish breast cancer patients, but this variant was also present in 12 of 190 Jewish controls. In addition, we found one polymorphic missense variant (p.126Ala>Thr or rs61758784) in three patients and one (p.287Thr>Ala or rs28363317) in four patients. Based on the prevalence of mutations in the initial report [2], we expected to identify approximately five families with a deleterious germline *RAD51C* mutation. It is of interest that the mutations in the German families were all different, and therefore the discrepant results cannot be explained by the presence of *RAD51C* founder alleles in Germany. Perhaps *RAD51C* mutations are not as common as the initial report suggests.

Competing interests

The authors declare that they have no competing interests.

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