Breast Cancer RESEARCH

LETTER

Mutation screening of *RAD51C* in male breast cancer patients

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We read with great interest the paper by Akbari and colleagues [1] in a recent issue of *Breast Cancer Research*. The authors reported on the absence of *RAD51C* mutations in 454 patients with *BRCA1/2*-negative familial breast cancer/ovarian cancer (BC/OC). In the initial report by Meindl and colleagues [2], *RAD51C* mutations were identified in 6 out of 480 patients with *BRCA1/2*-negative familial BC/OC. Interestingly, on the basis of histopathologic features, including intermediate grade (G2), estrogen receptor-positive (ER^+), progesterone receptor-positive (PR^+), and HER2-negative ($HER2^-$) expression, *RAD51C*-associated BCs were found to be similar to *BRCA2*-associated BCs [2]. *BRCA2* is known to play a significant role in male BC (MBC); however, no occurrence of MBC was observed in the six *RAD51C* families described [2].

To investigate the role of *RAD51C* in MBC, we screened for *RAD51C* mutations in 97 MBC patients selected from our population-based series of 126 cases because they were previously found negative for *BRCA1/2*, *CHEK2*, *PALB2*, and *BRIP1* mutations [3,4]. Notably, 25.8% of cases showed a positive first-degree family history of BC or OC or both. The majority of MBCs were invasive ductal carcinomas (74.5%), G2 (53.5%), ER^+ (90.7%), PR^+ (82.6%), or $HER2^-$ (85.4%). Overall, 66% of the MBCs showed an $ER^+/PR^+/HER2^-$ phenotype. All patients provided informed consent to the study. We carried out mutation screening of the nine exons and intron/exon boundaries of *RAD51C* by high resolution melting (HRM) analysis, a rapid closed-tube mutation scanning method with high sensitivity and specificity. Cases displaying abnormal profiles were evaluated by direct sequencing. Primers are available upon request.

We found no truncating *RAD51C* mutations. We identified a novel intronic variant, *IVS3 c.738-16G>T*, in 1 out of 97 MBCs (1%). By *in silico* analysis, performed with Splice Site Prediction (Berkeley Drosophila Genome Project, Lawrence Berkeley National Laboratory, Berkeley, CA, USA) and NetGene 2 Server software (Center for Biological Sequence Analysis, Technical University of Denmark, Lyngby, Denmark), the *IVS3 c.738-16G>T* variant is predicted not to affect splicing. This variant was also identified in 2 out of 173 (1.2%) population controls examined. We also found a neutral polymorphic intronic variant, *IVS6 c.904+34T>C* (rs28363318), in 16 out of 97 (16.5%) MBCs.

Overall, our results, which are based on a relatively large MBC series, are consistent with the findings by Akbari and colleagues [1] and with data on 92 patients with hereditary gynecological cancer in which no deleterious *RAD51C* mutations were identified [5] and would suggest that the impact of *RAD51C* mutations on BC predisposition might be more limited than initially reported. In conclusion, we found no evidence that *RAD51C* mutations may contribute to MBC susceptibility. Further studies on larger MBC series are needed to confirm our findings.

Abbreviations

BC, breast cancer; ER, estrogen receptor; G2, intermediate grade; MBC, male breast cancer; OC, ovarian cancer; PR, progesterone receptor.

Competing interests

The authors declare that they have no competing interests.

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