BRCA1 and BRCA2 mutations in breast cancer patients from Saudi Arabia

To the Editor

We were pleased with the results of a report entitled BRCA1 and BRCA2 mutations in breast cancer patients from the Kingdom of Saudi Arabia[1] since they give further support to our consanguinity model of cancer.[2,3] The authors of the paper leave an impression that BRCA1 and BRCA2 mutations are going to be an important contributor to the etiology of breast cancer in Arab women. We would like to suggest that the opposite is likely due to the following arguments: 1) Until now and to the best of our knowledge, there is no single Arab woman with breast cancer that was proven to be due to BRCA1 and BRCA2 mutation namely both allele mutations found in tumor tissue. Although the authors did not look for both BRCA1 and BRCA2 mutation alleles in cancer tissue, the paper implies that might be the case in at least 2 patients. First is a Palestinian carrier with 2483delGACT mutation found in leukocytes. There is a very low risk for second allele mutation in this woman due to her old age (68 years) and negative family history. Being a new mutation, its association with breast cancer has not been known. Second, an Egyptian carrier with Arg841Trp who is at higher risk due to lower age (45 years) and positive family history. However, the overall risk is not very high because the patient age is above the mean age for Arab women with breast cancer (41 years) and her mother developed breast cancer at old age (65 years). 2) The BRCA1 and BRCA2 mutation carrier rate among 29 Arab women with breast cancer is 2/29 (7%) and those mutations may not be deleterious. The BRCA1, BRCA2 polymorphism, and unclassified variants cannot be counted. This is a significantly lower carrier rate in breast cancer patient than approximately 30% found among Japanese and Caucasians breast cancer patient that the authors were referring to. 3) The mean age of Arab with breast cancer was 41, which increases the chance of finding BRCA1 and BRCA2 mutations. However, only one previously confirmed deleterious mutation was found among 29 patients. The patient age and mutation prevalence suggest a different genetic milieu in Arab women. Unfortunately, for this study the important family history data were not provided separately for Arab and Asian patients. 4) The native populations of the Gulf countries have consanguinity rate of approximately 50% and higher in some parts. Consanguinity increases the chances of homozygosity but BRCA1 or BRCA2 homozygous were never documented despite large number of patients tested worldwide. We have argued that BRCA1 and BRCA2 mutations are lethal tumor genes in animal experiments and in humans namely homozygotes are aborted or die early or are unable to reproduce. Thus, with a long history of consanguineous marriages, the lethal cancer mutations were eliminated from the gene pool.[2,3] This in part explains why native population of the Gulf countries have one of the lowest incidence of breast cancer in the world.[4]

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Reply from the Author

We have recently reported on the analysis of the BRCA1 and BRCA2 genes in a hospital-based cohort of breast cancer patients from the Kingdom of Saudi Arabia (KSA) (El-Harith et al[1]). In their correspondence, Dr. Denic and Dr. Al-Gazali suggest that BRCA1 and BRCA2 gene mutations may not contribute much to the genetic susceptibility towards breast cancer in Arab populations and argue that this should be discussed in the context of the high degree of consanguinity. In response to their interpretation we first wish to point out that an accurate estimation of the relative frequency of BRCA1 and BRCA2 mutations in Arab breast cancer patients cannot be deduced from the results of our relatively small pilot study, and we did not claim this nor did we intend to give this impression. In fact we do not know yet whether BRCA1 and BRCA2 mutations are an "important" contributor to the etiology of breast cancer in KSA, but our study provides first evidence that such mutations are present and must be taken into consideration as contributors. Denic and Al-Gazali argue that loss of heterozygosity at the BRCA1 and BRCA2 gene loci is not a general finding in Arab breast cancer patients without a positive family history. But this is very indirect evidence, and allelic loss at these loci occurs only in a minor proportion of breast tumors in patients from other populations as well, which does not preclude BRCA1 and BRCA2 from being an important genetic predisposition towards breast cancer. We do not know whether our mutation carriers have lost their wildtype allele at the respective gene loci but postmenopausal disease and a negative family history would not a priority exclude this possibility nor do these features exclude a disease-causing role for the identified germline mutations. There are several examples in the literature where bonafide BRCA1 and BRCA2 mutations have been found in patients who have an advanced age at onset and no positive family

history, and there is evidence that in a population-wide context some half of the BRCA1 and BRCA2 carriers may not develop the disease at all (Struewing et al[5] and Thorlacius et al[6]). Denic and Al-Gazali,[2] furthermore, consider the 7% frequency of mutation carriers in our Saudi patient cohort to be significantly lower than in other populations. However, as our hospital-based series was unselected for family history, a 7% frequency would seem to fit well within the range observed in population-based studies of unselected breast cancer patients from Europe, North America, Australia or Asia. In such cohorts, the prevalence of BRCA1 and BRCA2 mutations is somewhere between 2-13%, without obvious ethnic differences (reviewed by Liede and Narod[7]). We think that we have no proof at present to conclude that BRCA1 and BRCA2 mutations occur at a significantly lower frequency in KSA than in other parts of the world. Again, much larger cohort sizes of Arab patients would be needed to address this question properly. It is also difficult to draw conclusions from clinical and family data of single cases, and a comparison of Arab and Asian patients is not informative with small numbers. Finally, Denic and Al-Gazali raise the interesting question whether the degree of consanguinity could affect breast cancer incidence and the spread of BRCA1 and BRCA2 mutations in different populations. In fact, homozygosity for BRCA1 or BRCA2 mutations appears to confer early embryonic lethality although there are certain BRCA2 mutations that have recently been found to cause rare forms of Fanconi anemia in the homozygous state (Howlett et al[8]). It is tempting to speculate that a long history of consanguineous marriages may have resulted in a substantial reduction of lethal cancer mutations. On the other hand, BRCA1 and BRCA2 are very large genes that are targets not only for singular ancient founder mutations but also for de novo mutational events and for many mutations with a limited history. Furthermore, BRCA1 and BRCA2 mutations constitute only a minority of the total cancer mutation load in the general population and other predisposing alleles may not necessarily be homozygous lethal (Pharoah et al[9]). In addition, genetic modifiers may also be important in influencing the lifetime risk for breast cancer in mutation carriers. For example, recessive alleles could lead either to attenuation or to an elevation of the breast cancer risk in homozygotes, and accordingly there could be beneficial or adverse effects of consanguinity. We are just at the very beginning to understand the complex genetic and environmental interactions that can modulate the onset and progression of breast cancer. Certainly, a comparative analysis of populations with different degrees of consanguinity could become particularly instructive towards this goal.

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