On the proposed association of the ATM variants 5557G>A and IVS38-8T>C and bilateral breast cancer

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Dear Sir,

In their mutation analysis of the ATM gene in patients from 121 Finnish breast or breast-ovarian cancer families, Heikkinen et al.1 reported that a haplotype composed of the alleles 5557G>A and IVS38-8T>C was statistically significantly associated with bilateral breast cancer. They observed 5 haplotype carriers among 16 (31.3%) bilateral breast cancer patients studied when compared to 7 carriers among 160 (4.4%) unilateral breast cancer patients (OR = 9.9). The observed frequency of the haplotype in a sample of cancer-free female blood donors from the same geographical area did not differ statistically from that observed among unilateral cases (4.2% vs. 4.4%, respectively). These findings led Heikkinen et al.1 to propose that the 5557G>A and IVS38-8T>C haplotype might have a significant effect on the risk for bilateral breast cancer, and to suggest that additional studies should be performed to confirm this finding.

The WECARE (Women’s Environment Cancer and Radiation Epidemiology) Study is a population-based, case-control study designed to examine the joint roles of ATM gene mutations, radiation exposure and breast cancer.2 The primary hypothesis of the WECARE Study is that women who carry a mutant ATM allele, and who received radiation therapy as treatment for their first primary breast cancer, have an increased risk of developing a second primary breast cancer. The study population, ascertained through the WECARE Study, consists of 708 women with asynchronous bilateral breast cancer and who serve as controls. Controls were individually matched to 1,397 women with unilateral breast cancer who serve as cases and 1,057 women with unilateral breast cancer patients (crude OR = 0.9; 95% CI = 0.6–1.5 for 5557G>A carriers among the cases compared with the controls; there were 36 haplotype carriers among the 708 (0.1%) cases and 69 carriers among the 1,397 (4.9%) controls (crude OR = 1.0; 95% CI = 0.7–1.6). Using conditional logistic regression analysis appropriate for the individually matched study design yields RR = 0.9; 95% CI = 0.6–1.5 for 5557G>A and IVS38-8T>C carriers, and RR = 1.0; 95% CI = 0.8–1.3 for 5557G>A and non-IVS38-8T>C subjects.

Our analysis of the WECARE Study population fails to provide any support for the proposal that the haplotype of 5557G>A and IVS38-8T>C in the ATM gene confers an increased risk among women with bilateral breast cancer when compared with women with unilateral breast cancer. There are several potential explanations for the discrepant findings between our study and that previously published.1 First, it is possible that the 5557G>A and IVS38-8T>C variants are not causative but instead are markers of a risk haplotype that carries other risk modifying alleles. Within the WECARE Study, there was no evidence for significant linkage disequilibrium between either of these variants and alleles at any flanking site detected by mutation screening that might be consistent with such a possibility. However, the patterns of linkage disequilibrium in the ATM gene within the Finnish population may well differ from those observed in the WECARE population and the 5557G>A and IVS38-8T>C haplotype might carry with it additional variants conferring risk that are unique to the Finnish population. Second, the nature of the populations are different; the WECARE Study is population-based and unscreened for family history, while the women studied by Heikkinen et al.,1 i.e. among 16 women with bilateral disease, were ascertained based on their membership in high risk breast cancer families. Therefore, differ-

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ence in background risk factors of the 2 populations may contribute to differing abilities to observe a risk-modifying effect of this ATM variant haplotype. Third, we cannot rule out the possibility that the large observed association between the 5557G>A and IVS38-8T>C haplotypes and bilateral breast cancer reported by Heikkinen et al. is a chance finding; the result of individually assessing the association of many possible allele combinations with bilateral breast cancer. Given that overall we observed no association with the 5557G>A allele, it would be useful to determine whether 5557G>A and non-IVS38-8 haplotypes in the Heikkinen study are negatively associated with bilateral breast cancer. No such effect is observed in the WECARE Study population.

In conclusion, we have examined the reported association between a haplotype containing the 5557G>A and IVS38-8T>C alleles of the ATM gene and bilateral breast cancer using the WECARE Study population. Our design and large number of cases and controls provided a considerably greater number of carriers for the haplotype of interest than the initial report. Despite having greater than 95% power to detect an OR as low as 2.0, we were unable to replicate the reported association with bilateral breast cancer.

Yours sincerely,

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References


Appendix

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