5 June 2017

To the Editor, New England Journal of Medicine

Re: Co-occurrence of COMT and BRCA1/2 Variants in a population.

Movassagh et al, report an association between the COMT rs165631 variant and reduced breast cancer risk in female BRCA1/2 pathogenic variant carriers. The result was reported to be based on an analysis of 40 carriers of truncating variants: 25 breast cancer patients identified in the Cancer Genome Atlas; 15 assumed unaffected women in the Exome Sequencing Project of the National Heart, Lung, and Blood Institute. Supplementary information provided indicates that analyses also included carriers of missense variants, but most troubling, the dataset included eight carriers of the common BRCA2 c.9976A>T p. Lys 3326Ter variant associated with only a modest ~1.3-fold risk for breast cancer and ovarian cancer, and four additional benign missense variants (brcaexchange.org) - none relevant to analyses of modifiers of the high-risk BRCA1/2 pathogenic variants used in clinical practice.

These observations, and the fact that rs165631 has not been revealed as a potential modifier by previous large-scale genome-wide association studies of BRCA1/2 carriers, indicate that it is premature to consider rs165631 as a potential modifier of cancer risk in such women.

Yours faithfully

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