Reviewer’s report

Title: TGFB and TGFBR1 polymorphisms and breast cancer risk in the Nurses’ Health Study

Version: 1 Date: 25 May 2007

Reviewer: Boris Pasche

Reviewer’s report:

General

This is a well conducted study, which unfortunately does not bring any additional useful information to the field of low penetrance breast cancer susceptibility genes as it is markedly underpowered to assess the effects of low penetrance breast cancer susceptibility genes.

Recent reports (see below) suggest that only large collaborative groups (about 10,000 cases and controls) may provide useful information on this topic.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

It is incorrect to state that there is "no overall association between the L10P polymorphism and breast cancer". A recent report by Cox et al Nat Gen 2007, 39:352-358, demonstrates a weak but significant association between TGFB1 L10P and breast cancer. These findings are particularly important as they reconcile previous conflicting results. They also underscore the need to study very large populations to answer questions related to low penetrance susceptibility alleles. The authors genotyped 15,109 controls and 12,946 cases to reach their conclusion. This study now firmly established a small but significant association between TGFB1 L10P and breast cancer risk.

With respect to TGFBR16A and breast cancer, a meta-analysis of 13,000 cases and controls published by Zhang et al, J Clin Onc 2005, 23:7743-7743 showed a significant association between this allele and overall cancer risk. The authors also genotyped 2,422 breast cancer cases and 2,998 controls and showed a significant association with breast cancer. Since then, two small studies have reported the lack of an association between TGFBR16A and breast cancer: Chen et al, Clin Cancer Res 2006, 12:392-397 and Spencer et al CEBP 2006, 15:1236-1237. Both studies were underpowered but the first study showed a trend towards an association between TGFBR16A and breast cancer and the other did not. Overall, the association between this allele and breast cancer is very likely to persist when a new meta-analysis is conducted.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Title: TGFB1 should be used instead of TGFB in the title. TGFB is not a gene name. The authors correctly use TGFB1 throughout the remainder of the manuscript.

Abstract: TGFB1 forms a complex first with TGFBR2, then with TGBFR1, not only with TGFBR1 as incorrectly indicated in the abstract.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because scientifically unsound

Level of interest: An article of limited interest
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I have no competing interests.