Reviewer's report

Title: Novel polymorphisms in caspase-8 are associated with breast cancer risk in the California Teachers Study: a nested case control study

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Reviewer: David Goldgar

Reviewer's report:

The paper by Park et al. describes the results of an analysis of 12 SNPs in/near the CASP8 gene in terms of their role in breast cancer susceptibility using 1353 cases and 1384 controls from the large California Teachers Study cohort. Of course the main question regarding this paper is what it contributes to our knowledge of the relationship between CASP8 and breast cancer risk over and above the large iCOGS/GWAS analysis of a much larger set of SNPs in this region published early this year by Lin et al. Given that the iCOGS study had ~30 times the sample size, the major contribution of this paper to our understanding seems to be a finding of a significant effect of a single SNP (rs2293554) in HER2 positive breast cancer. This result is based on comparison of SNP genotypes between 159 HER2+ cases and the 1400 controls.

Major Compulsory Revisions

1. Interesting that the one SNP that in the present study that was not included in the BCAC/iCOGS study was the one which had the only significant finding (after correction for multiple comparisons). Presumably there is one in that study that is in strong LD with rs2293554; the authors should examine that in HER2 breast cancer in iCOGS as a replication (there are ~3400 HER2+ cases in the iCOGS study). The authors should request these data from the iCOGS. They might be able to be simply looked up on the BCAC website.

Minor Essential Revisions

1. Please report the unadjusted ORs, particularly for the one significant finding.

2. The OR of nearly 2 observed in this study for HER2 breast cancer seems a bit unbelievable given that it is larger than any existing SNPs even in subtypes. Even the lower 95% CI is higher than almost all effects defined in very large sample sizes. This should be commented on in the discussion.

Table 2: Please put the SNPs in chromosome order; it is not clear what order they are in now - random?)

3. It seems as if the CTS (at least in part) was included in the larger study. This should be noted in the manuscript and the overlap specified.

4. The Supp table should include genotype distributions by subtype.
Discretionary Revisions

1. Could HER2 status be imputed from ER status, age, etc. to improve the power of the analysis.

2. It is noteworthy that the SNP rs1861270 which is 5kb away from rs2293554 is not significant (and apparently not in LD according to the authors) - this seems strange to me. Is this a recombination hotspot between these two SNPs?

**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 declare that I have no competing interests'