Reviewer’s report

Title: Ovarian cancer risk and common variation in the sex hormone-binding globulin gene: a population-based case-control study

Version: 1 Date: 22 January 2007

Reviewer: Penelope Webb

Reviewer’s report:

General
The paper reports the results of a case-control analysis evaluating the association between polymorphisms in SHBG and ATP1B2 and ovarian cancer. The authors conclude that the data do not support a substantial association between these genotypes and ovarian cancer risk. This study appears to have been well conducted and the paper is well written. My only real criticism is its size – a sample of only 264 cases, particularly when this includes different subtypes of ovarian cancer that may differ in their hormonal aetiology, is not very large. And, although this may have provided sufficient power to detect an association of 1.5 or greater (or 0.7 or less), it does not provide sufficient power to detect more modest effects or, importantly, to clearly rule out quite large effects. The confidence limits are very wide and thus, while I suspect the authors' conclusion of no association is probably correct, the data do not actually rule out the possibility that there could be a strong association with risk. Studies of this size therefore provide very limited information regarding the existence or otherwise of an association between genotype and cancer.

Having said that, the literature is full of small studies reporting apparently significant associations between single SNPs and cancer risk and it is important that null studies are also published to balance this.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
None.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. Background para 3 and Discussion line 1 – the authors claim that this is a ‘comprehensive’ evaluation. While I accept that the approach to SNP selection may have been comprehensive, I do not think that this claim is warranted for the study overall given the relatively small sample size.

2. Methods para 1 – some additional information/clarification would help here. (i) Eligible cases were 437 women identified through hospitals and registries but it is unclear what proportion of ALL women diagnosed during the study period this represents. Would all women not identified through the participating hospitals have been identified through the registries? (ii) How complete are the population lists used to select controls? (iii) It would help to clarify that the numbers reported in the final sentence of this study were those that participated in the ‘main’ study (as opposed to the analyses reported here).

3. Results para 1 – I do not understand the comment that 0% of clear cell cancers were poorly differentiated. Clear cell cancers are not routinely graded and, by convention, are usually all considered high grade. NB the proportion of clear cell cancers (22%) is also unusually high, most studies report 5-10% clear cell cancers.

4. Results Table 1 – given the role of SHBG it would be helpful to know what proportion of women had taken hormone replacement therapy. (NB. it would also have been interesting to evaluate the associations separately for hormone users and non-users – although I note that the number of oral contraceptive users was too small to look at this).

5. Discussion paras 1 and/or 3 – as discussed above, I think some additional comment should be added regarding the lack of power to rule out even quite strong associations and, particularly, to look at interactions between genotype and environmental/behavioural factors.
6. There are a number of typographical errors that should be corrected (eg is the rs number for the D356N SNP rs6259 or rs6559? Spelling of differentiated (not differenciated), untranslated (not untraslated)

Discretionary Revisions (which the author can choose to ignore)
None.

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests