Reviewer's report

Title: The effect of menopause and hysterectomy on systemic Vascular Endothelial Growth Factor in women undergoing surgery for breast cancer.

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Reviewer: N Bundred

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Overview:
The authors aim to investigate circulating VEGF levels in breast cancer patients and assess the effects of the menopause or hysterectomy on systemic VEGF. This is an area that has been well published upon and there is extensive data for VEGF in breast cancer patients (see authors own reference 7). The effect of the menopause or hysterectomy on systemic VEGF has also been well investigated in the literature as far back as 2000 (Agarwal R et al. Fertil Steril. 2000. 1:56-60 and Byrne GJ et al. Anti Cancer Res. 2007. 3481-7).

This is a relatively small study, which is cross-sectional, that attempts to address the role of the menopause and hysterectomy on VEGF levels by looking at the effects of removing a tumour on VEGF levels in patients with breast cancer. The finding that VEGF is higher in breast cancer patients and particularly those who are post-menopausal is not new data (see authors own reference 7), nor is the finding that the highest systemic VEGF levels are in post-menopausal breast cancer patients. Previous authors have argued both that an intact uterus increases VEGF levels or lowers VEGF levels but these studies are not discussed appropriately in the discussion.

Specific points:
1. The introduction states there is little data on serum or uterine VEGF levels in post-menopausal women but as I have already pointed out there are multiple publications on this area.

2. The authors use a commercial assay but give no evidence for inter or intra assay variability and do not state whether all samples were measured on the same plate or paired samples were measured on different plates. If paired samples were measured on different plates with a 10% inter assay variability then levels could vary by as much as 20% which would remove any significance found in this study.

3. Not all patients had invasive breast cancer, in fact for some reason one patient had low grade DCIS and the group should be more homogenous, particularly since DCIS is known to have higher levels than invasive breast cancer.

4. The data is difficult to understand. It would appear that only post-menopausal breast cancers have higher levels of VEGF than control patients when platelets
are taken into account. If hysterectomy significantly affected levels then some sort of attempt to control for patients with hysterectomy who were post-menopausal would be appropriate.

5. It is noticeable that because this is a small series of breast cancers, no association was found between serum VEGFp and clinical pathological prognostic factors. Since VEGF levels do not relate to prognosis or prognostic factors, the argument that hysterectomy causes increased breast cancer metastasis is difficult to follow and, in any case, if a woman has already had a hysterectomy it is not possible to replace it to in some way protect her against breast cancer.

The conclusion is thus somewhat difficult to justify. I found it difficult to follow and it implies that all women with breast cancer should have a hysterectomy to protect them against breast cancer metastasis - is this really what the authors are proposing?