Reviewer's report

Title: Environmental conditions correlate with estrogen receptor status

Version: 0 Date: 15 August 2013

Reviewer: Rachael Natrajan

Reviewer's report:

The manuscript by Lloyd et al correlates ER status with tumor vasculature given the working hypothesis that estrogen is carried to the tumors via blood and diffuses through the tumor. This is an interesting study attempting to address the issue of heterogeneity with ER staining vasculature, however a number of issues need to be addressed:

Major Compulsory Revisions

1. Are the authors sufficiently powered to detect significant differences with only 6 ER negative patients? Why did they only look at cases >90% ER+ cells if one of their aims was to assess the regional distribution of ER+ and ER- cells. Although the numbers are small, did the authors look at the tumors with heterogeneous ER staining and look at the vessel distribution? Did the ER+ cells congregate nearer to the vessels within the tumor?

2. Based on the findings the title would better be suited to being a little more specific. “Vessel size correlates with Estrogen receptor status” or something similar.

3. The authors hypothesize that ER will be expressed only if there is estrogen in the microenvironment. Is there a way to test this?

4. Is ER status correlated with the cellularity of the tumor? i.e. more densely packed the cells, perhaps the estrogen is more difficult to diffuse through the stroma to adjacent cells?

5. A number of times the authors quote p values >0.05 (page 9). P values >0.05 are NOT significant.

6. On page 9, the authors state that ‘Vessel size was surprisingly not found to be correlated with disease progression (p=0.295)’. Why was this surprising?

7. The authors conclude that ‘This suggests that as ductal carcinoma in situ progresses towards invasion, if necrosis does not increase with the cancer progression, then ER+ cells are more likely to dominate the population.’ Isn't it more plausible here that the blood vessel size means the larger they are the less necrosis you get? and is actually determined quite early on? Is there a difference between vasculature in the adjacent normal breast and whether the tumor/DCIS lesion is ER+ or ER-?
8. On page 15 the authors state “Furthermore, it may be possible that ER+ cells cluster around vasculature and effectively act as a barrier”. Did the authors see this?

Minor Essential Revisions

9. Throughout the manuscript, the authors quote R2 values as percentages. It would be better to quote these as fractions.

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