Reviewer’s report

Title: Quantitative methylation profiling in tumour and matched morphologically normal tissues from breast cancer patients

Version: 1 Date: 9 November 2009

Reviewer: Seema Khan

Reviewer’s report:

Major Compulsory Revisions

The selection of tissue is a convenience sample which does not allow quantitation of the distance of the normal tissue from the cancer. It was not possible for the investigators to exclude DCIS from the normal tissue sample. Both of these are problematic when trying to reach conclusions about whether the methylation status of normal tissue can be used to identify women at high risk of breast cancer. For this reason, the presentation of data regarding the comparison of adjacent normal tissue from mastectomy and lumpectomy samples is over-interpreted, and does not contribute to the overall message of the paper.

The number of normal tissues from unaffected women is small, and this population is not described at all; the paper would be significantly improved by enlarging the number of samples and providing information as to how these samples were acquired; e.g. reduction mammoplasty, benign biopsies, if so what was the histology of the lesion being biopsied, etc.

None of the p values appear to be corrected for multiple comparisons.

Discretionary Revisions

Figure 1 does not show correlations as claimed by the authors, it merely shows that in the majority of cases the matched normal samples have lower methylation than the cancers. It does not add to the manuscript.

Table 4: the fraction of methylation negative tumors is surprisingly high: 73% for DAPK, 54% for TWIST, 41% for HIN-1, 71% for RARb2 and 44% for APC. How does this compare to reports from the literature? Which comparison is the kappa statistic describing?

The age results are surprising, since there are several reports (euhus, seewaldt) documenting increasing methylation in normal breast epithelium with increasing age. Here again, the ages of the unaffected women providing normal east tissue is important.

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