Reviewer’s report

Title: Effect of genetic ancestry on leukocyte global DNA methylation in cancer patients

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Reviewer: Saraswati Sukumar

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The paper reports global DNA methylation data in 42 melanoma patients and 46 controls as well as 86 breast cancer patients and 92 unaffected controls. Subtle but significant differences were detected in global leukocyte DNA methylation between individuals with cancer and unaffected controls (p<0.001); the average methylation levels in melanoma and breast cancer patients were lower (2.54±0.37% and 2.33±0.48%, in each case) than the average level of 2.79±0.27 and 2.77±0.77% in unaffected controls, respectively. As shown in Fig S1 where the differences are measured in quartiles, were these values considered as continuous variables as well? Does the significance still hold?

Other than genetic ancestry as studied by analysis of 59 biallelic SNPs selected from the AIMS panel for Hispanic populations described by Fejerman et al., no other confounders, such as BMI, age, smoking status or common variants appeared to contribute to this difference in global methylation values. Here, Kendall rank correlation revealed a significant inverse association between the African ancestral component and the percentage of global DNA leukocyte methylation in breast cancer patients (#=-0.199, p<0.01), but no in melanoma patients. Considering all cancer patients together, according to the authors, the negative correlation with the African ancestral component became statistically stronger (# = -0.187 p<0.005). A significant positive correlation with the European component was also found (# = 0.169 p<0.01). As is evident from the r values, these are low to modest correlations, probably due to the small number of samples in the study.

In summary, while the findings are interesting and provide a clue regarding the contribution of ancestry to global hypomethylation in PBCs, the data are of borderline significance. These findings again suggest the importance of taking into account genetic ancestry when examining epigenetic data and that point is well taken. The conclusions over-interpret the data and the study does suffer from too few samples. As such, the authors are recommended to tone down their conclusions and present a cautious statements that the results and data are suggestive of the contribution of ancestry, which need to be substantiated in larger studies.

Editorial: Many spelling mistakes are present throughout the manuscript.

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

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'