Reviewer's report

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

Version: 2 Date: 7 January 2015

Reviewer: Hannah Park

Reviewer's report:

Major Compulsory Revisions
1. A major flaw with this study is the inclusion of cancer patients with no information presented on stage of cancer, treatment type, how long ago they were diagnosed. It is not informative to compare leukocyte methylation levels between cases and controls if the cases have already gone through surgery or other treatment to remove the cancer. Authors may want to narrow the scope of the paper to examining the potential significance of admixture determination and leukocyte methylation in controls only.

2. Race/ethnicity is already known to be a confounder in methylation studies. Although the admixture in Uruguay may present a potential layer of complication, please explain: Did the genetic analysis result in findings that differ from those if race/ethnicity were self-reported? That is, what is the actual significance of the findings that readers can take away and apply to their studies on global methylation in leukocytes? Self-reported race/ethnicity should be included in the analysis.

3. The breast cohort started with 179 women with breast cancer and 209 controls. The analytic cohort only had 86 cases and 92 controls. An explanation of why so many were excluded (all because the measured differences in 5mdC levels between duplicates were >3%?) should be included.

4. I am not sure how analysis of AIMs in the Han Chinese is relevant to a study on Uruguayans, given the trihybrid parental contribution of European, African, and Native American.

Minor Essential Revisions:
1. Please indicate what is meant by "normal peripheral blood count" (Methods section)

2. Table 1 says there were 42 melanoma cases and 46 controls but Table S2 says there are 41 and 45, respectively.

3. Table S3 says "Differences in overall CpG sites methylation..." - should be "Differences in CpG methylation at sites..." There are other examples where language can be improved.

Discretionary Revisions:
1. Figures S1 and S2 may be considered for inclusion in main body instead of being supplemental.

2. Leukocyte subpopulation % could have been a confounder and should be included as a limitation.

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

**Declaration of competing interests:**

I declare that I have no competing interests