Reviewer's report

Title: A cross-sectional study of global DNA methylation and risk of colorectal adenoma

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Reviewer: Xavier Solé

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- Summary

In their cross-sectional study, King et al. assess the relationship between global DNA methylation levels in pathologically normal colon tissue and risk of colorectal adenoma, as a surrogate for colorectal cancer. To do so, they use a cohort of 317 subjects (209 with normal colonoscopy and 108 with adenomas). Authors assess the methylation status of LINE-1 (Long Interspersed Nuclear Element-1) sequences and use it as a surrogate for global methylation levels. Moreover, for a subset of 280 subjects (185 with normal colonoscopy and 95 with adenomas), authors also look at the methylation status in their blood tissue and try to correlate it both with the colon tissue methylation and also with the risk of developing adenomas. Although both the study design and the methodology used are technically sound, there are some issues that should be addressed before the article could be considered suitable for publication.

- Major Compulsory Revisions

1) Authors state throughout the article that there is an association between lower levels of LINE-1 DNA methylation in normal colon tissue and increased adenoma risk. However, according to the results they show, this could be considered as an overstatement. Despite authors find a significant relationship between the lowest methylation levels quartile and adenoma risk in men and both sexes together (not in women), the significance is too marginal to be considered clinically relevant. Authors categorize methylation levels in quartiles but show no evident reason to do that. Due to the marginal significance levels, it could be possible that other categorization of the variable may produce non-significant results. In order to avoid the need to define arbitrary groups, authors should consider using methylation levels as a quantitative variable in their logistic regression model. Moreover, this could also increase their statistical power.

2) Even if authors could show a stronger and more reliable association between low methylation levels and adenoma risk, they should prove that this global methylation marker is useful in terms of sensitivity and specificity compared to currently used early-diagnosis methods. Authors should also show ROC curves and AUC scores so that they could be compared to FOBT tests.

3) Authors find moderate correlation (r=0.36) between colon tissue methylation and leukocyte methylation. This is completely expected, since it is well known
that methylation status is highly cell type dependent. In any case, the lack of association between leukocyte methylation status and adenoma presence raises concerns in terms of the usefulness of this marker as a non-invasive screening tool.

- Minor Essential Revisions
4) Authors should state whether they have followed the STARD guidelines (STAndards for the Reporting of Diagnostic accuracy studies), which is a requirement for any diagnostic paper published by BMC Cancer.
5) Authors should show p-values in their result tables.

- Discretionary Revisions
None.

**Level of interest:** An article of limited interest

**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