Reviewer's report

Title: Association of Estrogen Receptor beta variants and Serum Levels of Estradiol with Risk of Colorectal Cancer: a Case Control Study

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Reviewer: Peizhong Wang

Reviewer's report:

The authors of this study intend to test their hypothesis that endogenous estrogen and ESR2 genetic variation are associated with colorectal cancer (CRC) through a case-control study in a Chinese male population. I read this manuscript with great interest. Overall, this work is of good quality with respect to study design, execution, and manuscript preparation.

General comments:

While the authors argued their justification for their male-only decision, I feel that had females been included, the overall quality and importance of this study would have been strengthened. For instance, possible differential effects (interaction) of estrogen between two sexes could be investigated. Likewise for endogenous and exogenous estrogen. Hope the authors will be able to address issues in their future research.

Major Compulsory: More detailed descriptions on how cases and controls were recruited are needed. This information will help readers understand how cases and controls represent their corresponding target population (CRC and non-CRC patients in general), for example, inclusion/exclusion criteria and response rates. Similarly, why this particular hospital was chosen. The authors stated that controls were volunteers from Tongji Hospital Physical Center during. Were they patients of other health problems? There was very limited information on controls.

Discretionary:

1. More information should be provided in Table 1, for example, BMI, level of education, mean age with s.e., which, I believe, was collected.
2. Age 48-years was used as a cut-point, which is very un-conventional. Why was this particular cut-point being used?
3. Berkson bias is well know when hospital based controls were used and may need to be discussed.
4. I noticed that only 36.4% controls were ever smokers, which seems to be lower than the general male population in China or Wuha. It is likely that the protective effect of smoking on CRC could be explained by bias. I think it is worth discussing.
5. As an epidemiologist (limited knowledge in basic science), I would like to ask
the authors the possibility that high Serum estradiol concentrations in cases is result of CRC rather than the cause.

**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.