Author's response to reviews

Title: Association of vitamin D receptor polymorphisms with the risk of prostate cancer in the Han population of Southern China

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Author's response to reviews: see over
Dear Dr Edmunds:

Thank you very much for reviewing our manuscript entitled: “Association of vitamin D receptor polymorphisms with the risk of prostate cancer in the Han population of Southern China” (Manuscript ID 4910149112673367 ) for BMC Medical Genetics. We were pleased with the overall positive reviews of our paper. We are now able to respond to these major, as well as minor, but important issues brought up by the two reviewers. Enclosed please find our revised manuscript.

**Reviewer: Sonja Berndt**

We were pleased that the reviewer felt that our “findings are important to those with closely related research interests”. We have corrected both the major and minor points, and thank the reviewer for his careful notations on our manuscript.

**Major Compulsory Revisions**

1) **Results p.10:** The authors state that “Considering no association with the age distribution among different genotypes based on the Independent-sample test, we here hypothesized the Bsm1 ‘B’ allele might have a protective effect against tumorigenesis.” It is not clear why having no association with age would lead the investigators to hypothesize that the B allele is protective for prostate cancer.

**Answer:** Thank you for your comments about the sentence “Considering no association with the age distribution among different genotypes based on the Independent-sample test, we here hypothesized the Bsm1 ‘B’ allele might have a protective effect against tumorigenesis”. As you argued, it is not clear why having no association with age would lead the investigators to hypothesize that the B allele is protective for prostate cancer. Here, it is unfit to draw a cause-and-effect conclusion between age and hypothesis. Therefore, in the revised manuscript, this sentence should be replaced by “Due to the observation of the distribution difference of the Bsm1 ‘B’ allele between prostate cancer cases and controls, we here hypothesized the Bsm1 ‘B’ allele might have a protective effect against tumorigenesis”. What’s more, the data in the Table 3 are also revised.

2) **Results p.10:** Not all studies of Bsm1 have observed the same association with prostate cancer. The authors should mention studies that have not observed the same association to give a fair presentation of the literature.

**Answer:** Yes, as you stated, not all studies of Bsm1 have observed the same association with prostate cancer. That the B allele may be protective for prostate cancer may be limited in some areas or some
populations, such as Taiwanese, Japanese, and Chinese population. However, some studies obtained inconsistent results. Therefore, we should add to analyze the results of this difference. In the revised manuscript, we have added the following sentences “However, there are still some studies failed to show such a result. For example, studies such as Liu et al. in Beijing population and Ingles et al. in African-Americans. In addition to ethnic characteristics, geographical differences and living habits, the factors, including the study sample size, the choice of the control group (BPH or healthy people), might be the important reasons for these inconsistent results.” (Results p.11)

3) Table 3: The odds ratios for the association with prostate cancer should be given in Table 3 as this is the primary objective of the study. The mean age for each genotype is not needed. A sentence in the manuscript stating no association with age is sufficient.

Answer: Exactly. We accept the reviewer’s comment. It would be more useful to give the odds ratios (ORs) for the association with prostate cancer as this is the objective of the study. Thus, we revised them in Table 3, including supplementing the ORs and 95%CI values, and deleting the mean age data for each genotype.

4) Table 3: The nomenclature used in this table is inconsistent with the nomenclature in the manuscript (e.g., the alleles for BsmI are given as A and G, instead of B and b). Also, the labels for BsmI appear to be incorrect assuming A is rare in this population.

Answer: Thank you once again reminded. We had revised the A and G (BsmI) to B and b. Yes, as your stated, the frequency of the BsmI “B” allele is rare in this population, not “A”.

5) Table 6: The labels for the haplotypes do not appear to be correct as ‘B’ appears to be common based on the frequencies of the haplotypes, but it should be infrequent.

Answer: Yes, the haplotypes with ‘B’ are infrequent, particularly in the Asian population. In our study, we just want to show the possible role of these haplotypes. Maybe, in fact, due to the lower frequency of ‘B’ allele in Asians, this allele affected the incidence of prostate cancer in whole population is also limited.

6) Stratified results presented in Table 4. The number of cases with the variant allele for most of these strata is too small to draw meaningful conclusions. The manuscript should be revised accordingly. At most, the authors should only have one sentence regarding these results and should acknowledge that the numbers are too small to draw meaningful conclusions.
Answer: Yes, the number of cases with the variant allele for most of these strata is too small to draw meaningful conclusions. We accept the reviewer’s comment. Therefore, we added here a note (Discussion p.10) regarding these results and should acknowledge that the numbers are too small to draw meaningful conclusions.

Minor Essential Revisions
7) Table 1: Please indicate what the reference group is for the odds ratios given in the table.
Answer: Sorry, Table 1 showed the PCR-RFLP conditions for VDR gene polymorphisms. I guessed what you want to point out was the Table 3. In the revised manuscript, we had listed the odds ratios and deleted the mean age data. If what you want to point out was the Table 4 or 6, we had also revised them.

8) Table 6 and abstract. It is not clear what the reference group is for the haplotypes. Please indicate in the abstract that the comparison group for the association observed for the haplotypes. Please place a footnote in the table indicating what the comparison is.
Answer: Table 6 showed haplotype frequencies for VDR five polymorphisms between prostate cancer cases and controls. In the new manuscript, this part has been revised. See abstract and Discussion p.11. 12.).

Reviewer: Arslan Akhmedkhanov
We were pleased that the reviewer felt that our results are “interesting”, and “the strengths of the study include the well-defined study question and the appropriate methods that are well described”. We have corrected the major points, and thank the reviewer for his careful notations on our manuscript.

Major Compulsory Revisions
1. In the Methods section, please describe the eligibility and exclusion criteria for prostate cancer cases as well. Are these 122 prostate cancer cases represent all the cases seen in four hospitals during the recruitment period? Were there any exclusion of prostate cancer cases diagnosed in four hospitals in Southern China between March 2007 and August 2008? If yes, what criteria were used to select 122 cases for the study?
Answer: In our study, there are stringent scientific criteria for prostate cancer cases and controls. The eligibility criteria are (i) pathological diagnosis, (ii) high plasma PSA levels, and (iii) transrectal ultrasound. Other ancillary examinations including digital examination of rectum (DRE), magnetic resonance imaging (MRI) and emission computed tomography (ECT) are also performed. The controls
were individuals screened to ensure that there had never been diagnosed with cancer and had low plasma PSA levels (total PSA<4.00ng/ml). Based on these criteria, we believed that 122 prostate cancer cases can represent all the cases seen in four hospitals during the recruitment period.

Yes, as you stated, there are some prostate cancer cases excluded. The main reason is that the diagnosis of these cases is not clear, or depended solely on clinic manifestation and high PSA levels, not on pathological examinations (the golden criteria). However, the need to explain is that the number of cases excluded is very small. We think that these will not affect our representation of these groups.

2. In their response to the reviewer, the authors state that: “To match the age between cases and controls, we selected the elderly controls aged over 80 years, which are recruited from employees at the First Affiliated Hospital of Wenzhou Medical College.” Is it a common practice in China to have the hospital employees older than 80 years old? Please explain.

Answer: Actually the elderly controls we recruited were retired employees from the first affiliated hospital of Wenzhou Medical College. Of course it is not a common practice in China to have the hospital employees older than 80 years old. We did so because when we were working on recruitment for our project, just the hospital was doing the annual routine physical examination for these retired employees.