Reviewer’s report

**Title:** A genetic polymorphism of the osteoprotegerin gene is associated with an increased risk of advanced prostate cancer

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**Reviewer:** Yen Ching Chen

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Title: A genetic polymorphisms of the osteoprotegerin gene is associated with an increased risk of advanced prostate cancer

This is a case-control study that explored the association between the polymorphisms of the promoter region of OPG and the development and progression of prostate cancer. For 950 T/C polymorphisms, men with TC and TT genotypes had significantly higher risk of extraprostatic and metastatic prostate cancer as compared to those with CC genotype.

**BACKGROUND**

“The promoter region of human OPG contains various putative transcription factor binding sites that may…….The polymorphisms of OPG in this region may contribute to the genetic regulation of bone mass, .....” Why the authors believe that only two SNPs in the promoter region could explain the genetic regulation of bone mass? Has the LD structure been analyzed in this gene region? Are these two SNPs strongly linkage disequilibrium with other SNPs? If not, then these two SNPs may only explain part of the effect of this gene and the risk of prostate cancer.

**MATERIALS AND METHODS**

“The prostate specific antigen (PSA) levels of all the controls were measured and men with a PSA level of 4.0 ng/ml or more were omitted from the control group” Does this mean that the authors excluded controls without PSA information?

Page 11, “A recent report revealed that the OPG polymorphisms in the promoter region, 149 T/C, 209 G/A, and 245 T/G, show complete linkage [9]”. Does the linkage here actually mean “linkage disequilibrium”? Please clarify.

Page 11, “to evaluate the risk of PCa according to the OPG genotype, logistic regression analysis was conducted with an adjustment for age at the time of diagnosis (Table 1 A, B). No significant increased risk was observed among the different genotypes of patients with PCa and the controls (P=0.939 and 0.294 for 149 T/C and 950 T/C polymorphisms, respectively).” These results were from Table 2 instead of Table 1. In addition, the author only put the results of 950 T/C in Table 2 but lack of the results for 149 T/C. Because these are main results, it is weird only put the results of one SNP.
Page 14, please check the spelling of alkariphosphatase (ALP).

It is odd that the authors automatically delete all results for 149 T/C after Table 1 and in Discussion. The authors should explain why this is the case or they should drop out 149 T/C from the manuscript.

For figure 1, the author should calculate the p-value comparing survival between different genotyping groups.

Page 15, …"however, the age of the patients with PCa was also significantly higher than that of the healthy controls." Please give P-value for this result.

Page 19, the comparison between DNA (SNPs), serum (protein), and mRNA level are interesting. It will be better if the authors could find a reference for mRNA expression level in human instead of in mince.

The subtitles in RESULTS are too long and may not be necessary.