Reviewer's report

Title: Allelic variants of the transient receptor potential channel TRPV6 and risk of prostate cancer

Version: 2 Date: 17 August 2009

Reviewer: Arpad Szallasi

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Despite advances in its early diagnosis and treatment, prostate cancer remains the number two killer in men. It is a sad fact of life that if this referee lives long enough, his chance of developing prostate cancer approaches almost certainty. Most prostate cancers are, however, indolent and old guys die with, rather than because of, their prostatic adenocarcinoma. In the age of universal PSA screening, the "million $ question" is which carcinoma will behave aggressively (and thus need early medical intervention) and which can be managed safely by "watchful waiting".

Broadly speaking, TRPV6 is an endothelial calcium entry channel whose expression is markedly elevated in various adenocarcinomas, including breast and prostate. Interestingly, both carcinomas are hormone-sensitive. Indeed, the effect of tamoxifen on breast cancer cell viability was augmented when TRPV6 expression was silenced with SiRNA (Mol Cancer Ther, 7:271, 2008). The human TRPV6 gene has two allelic variants which are transcribed into two independent mRNAs designated TRPV6a and TRPV6b. Previously, a good correlation between TRPV6 expression and tumor grade (Gleason score) of prostatic carcinomas was reported. In this MS, authors tested the hypothesis that TRPV6 genotype may be predictive of the onset and clinical behaviour of prostate cancer. They find that the TRPV6b allele is present in 87% of the cancer samples with no correlation to Gleason score and tumor stage.

I think that the title of the MS is a bit misleading as it implies a link between allelic variants of TRPV6 and risk for prostate cancer. The running title ("TRPV6 alleles do not influence prostate cancer progression") appears to be more appropriate.

My specific comments mostly concern the prostate cancer patients in the study.

1) No such thing exists as "prostate cancer". I assume that authors mean "prostatic adenocarcinoma" (that is, acinar carcinoma) by this (as opposed to prostatic ductal carcinoma, transitional cell carcinoma, etc) - it needs to be spelled out as these cancers have origin in different cell populations and have distinct molecular signatures.

2) Were patients with high-grade prostatic intraepithelial neoplasia (PIN) included in these studies?

3) The way authors use the AJCC grading system in the text is a bit confusing. A T1c tumor implies that the tumor was identified by needle-biopsy and no residual
carcinoma was found in the subsequent prostatectomy specimen. T2 means that the tumor in confined to the prostate. In fact, these are invasive adenocarcinomas (as opposed to PIN which is an in-situ neoplasia). To designate only carcinomas with extraprostatic extension as "invasive" is incorrect. Furthermore, I don't think that a Gleason 3+3 = 6/10 score T2c (or T1c) carcinoma is biologically different from a similar score T3a carcinoma it was just discovered earlier. Also, the difference between T2c and T3a is often a sampling issue.

4) Authors define "low-grade tumors" as Gleason score 2 to 6. This is technically correct. Nonetheless, I don't know any pathologists who would make a diagnosis of Gleason 1+1 = score 2 adenocarcinoma.

Level of interest: An article whose findings are important to those with closely related research interests

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