Author’s response to reviews

Title: Risk of prostate cancer after isolated high-grade prostatic intraepithelial neoplasia (HGPIN) detected on extended core needle biopsy: a UK hospital experience

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Author’s response to reviews: see over
Dear Sir,

Thank you for considering our manuscript entitled “Risk of prostate cancer after isolated high-grade prostatic intraepithelial neoplasia (HGPIN) detected on extended core needle biopsy: a UK hospital experience” (MS: 176119029239237) by Singh et al. for publication in *BMC Urology*. In line with the comments from your Reviewers, we have amended the text of our manuscript. Taking account of these comments, we have undertaken the revisions/alterations. Below is a list of points of how we have responded to the reviewer’s suggestions. The changes to our revised manuscript are highlighted in red uploaded in this re-submission. I hope our manuscript might be re-considered for publication.

**Reviewer(s)’ comments to Author:**

**Reviewer: Kenneth Iczkowski**

1. Abstract:
   Don’t say HGPIN may be a precursor lesion. Say that it IS. There is enough evidence out there that such hesitation is not justified.
   In the Results section of the Abstract, spell out what the predictive values for each PSA value were, don’t just say the rate was low. That is, “PSA ranges and their associated predictive values for cancer were: 0-5, 11%, 5-10, 34%.....respectively.” This is a big enough finding to belong in the Abstract.
   **We attend to these relevant points as requested in the revised version of the manuscript.**

2. Background: 1st sentence: Again, avoid saying “may be….”
   For the sentence about a lowered rate of CaP, along with reference [5], the Cory Schlesinger et al. paper [8], from 2005 should be cited, since that study also suggested a lowered risk of CaP after HGPIN, in contrast to prior literature. In fact, Schlesinger et al. came out before [5].
   **We attend to these relevant points in the revised version of the manuscript.**

3. Results: I would like to know two additional facts. First, it is stated that the mean number of cores was 12 (range 8-14). Was there a statistically significant increase in CaP detection according to number of cores taken?
   It is also stated that 71% of the patients diagnosed with isolated HGPIN had it unifocally. That means it was multifocal in 29%. Did those 29% with multifocal HGPIN have significantly higher detection rate of cancer than the 71% with a unifocal finding?. This is an important consideration as the authors state in the Discussion [13,14]. It may also be of interest to determine whether the cancer was ipsilateral versus contralateral to the site of the HGPIN. When the authors complete this and discuss their findings, they should be aware of Kronz JD et al. Am J Surg Pathol 2001;25:1079-85 (which is referenced in Zynger et al—see below).
We have addressed the first two points in the revised manuscript. We feel we are not in the position to comment whether the cancer was ipsilateral or contralateral to the side of HGPIN in the current study. Part of the reason for this is the retrospective nature of the study and our method of data collection and partly due to the fact that initial HGPIN or subsequently diagnosed CaP was multifocal.

4. In the paragraph about Table 2, please present all the percent values for prediction of CaP according to PSA stratification. This finding in Table 2 is quite striking and the numbers deserve mention in the text. Saying it was “higher” in men with PSA over 10 is an understatement, especially since it was 88% when PSA was >20. So this needs to be highlighted in the text. We are very thankful to Dr Iczkowski for highlighting this. We have addressed it in the revised manuscript.

5. Discussion: Reference [8] should be mentioned alongside [5] as to the incidence of HGPIN and predictive value for cancer, as the numbers were quite similar between these two studies. The authors are referred to a recent HGPIN review in the International Journal of Clinical and Experimental Pathology, an online journal (Debra L Zynge and Ximing Yang: High-grade Prostatic Intraepithelial Neoplasia of the Prostate: The Precursor Lesion of Prostate Cancer. Int J Clin Exp Pathol 2(4), 327-338; 2009. (Abstract, full text PDF). ) in which the authors found a 4.26% incidence of HGPIN, identical to that in the current work. We have grouped the two references as suggested. Once again thank you for drawing our attention to this recent review on HGPIN.

6. Line 6, capitalize P (Capà CaP)
Thank you. This correction has been made in the revised manuscript.

7. Page 7. The authors found a 42% predictive value of HGPIN for cancer. This is higher than most contemporary US studies but if you compare it to mid-1990s U.S. studies, based on an era when there was less PSA screening and fewer cores were sampled (not 8-14 as nowadays) then the rate is quite comparable. I am specifically thinking of citing the Deborah Davidson J. Urol. 154:1791-94 paper of 1995 (with Bostwick) where she found a predictive value of 35% of HGPIN for subsequent cancer—not too far off from 42%. This paper was the very first to come out with a predictive value of HGPIN for cancer. This suggests that the different rates in PSA screening between UK and US are responsible for that difference in predictive values. Also, the Davidson paper found a significant interaction of HGPIN with PSA in predicting cancer. This is depicted in their Figure 2C. The authors should use their data to make a Kaplan-Meier plot like that of Figure 2C (although they won’t have an age-matched group without HGPIN). The benefit of doing this is that the x-axis depicts “Time from first biopsy,” providing a very clear picture of the time-dependence of the risk as stratified by PSA.
Thank you for highlighting this point and especially for pointing out one of the earlier studies on HGPIN which we have cited in the revised manuscript. However, we feel that depicting “CaP diagnosis and time from first biopsy” in Kaplan-Meier like plot might be inappropriate for a retrospective study like ours.

Reviewer: CRISTINA MAGI-GALLUZZI

The paper is well written and the findings are interesting. The conclusions are well balanced and adequately supported by the data. The limitations of the work are clearly stated.
Thank you.

We wish to assure the publishers of *BMC Urology* that the work contained within this manuscript has neither been published nor is being considered for publication elsewhere. Let me take this opportunity to thank you for the handling of our manuscript.

Yours sincerely,

Paras B Singh