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Reviewer A

The authors of this study attempted to examine the relationship between pubertal development and prostate cancer risk of diagnosis. More specifically they examine the relationship between age of onset of shaving, as well as current height and risk of PC diagnosis, using participants from a prostate biopsy registry. The topic is of identifying prostate cancer risk factors is important considering the only known risk factors are family history of prostate cancer, African ancestry, and age, the design of the current study has faults in the current state.

Major issues:
1. The authors used participants from a prostate biopsy registry. Although they claim that information was prospectively collected but the only information prospectively collected was the outcome of interest and that is prostate cancer (+/-). The exposures of interest were age of onset for shaving, which was retrospectively collected, and current height which was collected at time of biopsy. Nevertheless ~52% of participants were excluded due to missing data and this is unacceptable! This alone is a large number of participants to exclude which will definitely bias the result. Why did the authors not create a missing data category which will provide us information of potential bias of the missing group. It has to be noted that people who choose not to answer are a significant group and not to be excluded. A similar study on pubertal development by Nair-Shalliker et al that non-responders/missing data are a group of individuals with significant outcomes (PMID: 27741552). Especially in the current study when they form 50% of the study population, it violates the basic principles of epidemiology to exclude this group.

Reply 1: We thank the reviewer for emphasizing the importance of this epidemiologic principle. There was a significant proportion of patients for whom age of first shave was not available.

Accordingly, we have included all 2,456 patients with results of the prostate biopsy available (24 were excluded as results of the prostate biopsy were not available). We have performed all the analyses (Tables 1-2 and Supp Tables 1-6) again to include all these patients. The results were consistent with those obtained from the cohort of 1,176 patients with patients shaving at age >18 having increased odds of a positive prostate biopsy and those who were 175-180 cm having higher odds of high grade prostate cancer compared to those <175 cm. The aforementioned subcohort of 1,176 patients was included as a sensitivity analysis cohort to demonstrate that the results are consistent whether patients with missing data were included or not. Obviously, this factor is still a source of potential bias and cannot be ignored. However, by including both cohorts, we hope that this will, in part, assure the readers that the missing data was not a source of major bias in our cohort/results and missing data was missing at random hopefully.

Changes in the text: We have made changes to the abstract (page 1), methods (pages 2 and 7), results (pages 7-9), and discussion sections (page 11) to reflect the above changes. Furthermore, Tables 1-2 and Supplementary Tables1-6 have been modified extensively to reflect the above changes to the cohort. Supplementary Tables 7-13 have been added as the sensitivity analyses tables, referenced in the Results section. Figure 1 was also modified to reflect the changes to the cohort. We have also changed the phrasing on page 5 to a prospectively collected **outcomes** registry to reflect the fact that only the results of the prostate biopsy were prospectively collected. In addition to performing the sensitivity analyses, we have added the following to the limitations paragraph of the Discussion section: "Age of first shave was not available in 52.7% of patients, with missing data a known source of potential bias (22). However, sensitivity analyses of the subcohort of patients without missing data (n=1,176) demonstrated consistent results suggesting that the data may be missing at random."

2. If only 10 participants did not have information on height, then why not exclude only these 10 men in the analysis examining height and PC risk. Why exclude the other 1294 men for who this information is available. Exclusion of these men have compromised the validity of the study population.

Reply 2/ Changes in the text: *Please reference the above response, with appropriate changes made in conjunction with this comment.*

3. The authors have acknowledged in their discussion that the selection of men from a prostate biopsy registry may have biased the study selection in favour of men with elevated androgen levels, as a biopsy would only be requested for men with elevated PSA levels. Additionally excluding 50% of the cohort for reasons mentioned above, I fail to see what is being examined.

Reply 3: We thank the reviewer for this comment. Patients with missing data were included in the revisions as referenced in Reply 1. We hope that the reviewer finds these changes satisfactory and we are happy to make any further appropriate changes as deemed necessary by the reviewer.
Changes in the text: "Age of first shave was not available in 52.7% of patients, with missing data a known source of potential bias (22). However, sensitivity analyses of the subcohort of patients without missing data (n=1,176) demonstrated consistent results suggesting that the data may be missing at random."- Included in the Limitations paragraph of the Discussion section on page 11.

4. In the regression analysis for Height as the exposure, the authors have adjusted for BMI which is derived using weight and height. This would result in collinearity between exposure and the confounder especially since the BMI is emerging as an established PC risk factor for advanced OC cases, which may have contributed to the lack of significant outcome.

Reply 4: We thank the reviewer for making this excellent point. We agree that including both BMI and height may have introduced collinearity. We have acknowledged this issue in the

limitations section.

Changes in the text: "As a patient's BMI is derived from his height and weight, including both height and BMI variables in the multivariable models may have introduced collinearity, influencing the significance of the results."- Included in the Limitations paragraph of the Discussion section on pages 11-12.

Minor isuues:
1. The authors have defined High grade as Gleason 8 or worse. I find this to be a very sloppy definition.

Reply 5: High grade disease was defined in our cohort as Gleason 8 or worse in conjunction with the current NCCN definition of high risk prostate cancer with the biopsy grade criteria being Gleason Score 8 disease or worse. This is not to say that this is an absolute definition or that a PSA >20 or cT3 disease do not qualify a patient as having high risk disease. If the reviewer would like for us to change this definition we will be happy to modify as appropriate.

2. In the results section of the abstract, the authors have started sentences with a number which is not proper convention. They will need to spell out the number.
3. In the abstract the interquartile age range for shaving is 16.0-9.0. Is this correct?

Reply 6: We thank the reviewer for bringing these two points to our attention. We have made the appropriate changes as referenced below.

Changes in the text: "Our cohort included 2,456 patients. Biopsies were positive in 1,257 (51.2%) patients, of whom 293 (23.3%) and 407 (32.4%) had high grade and volume disease, respectively." Abstract page 1.

"Median age of first shave was 17.0 years (interquartile range 16.0-19.0) and height was 177.7 cm (172.8-182.9)." Abstract page 1.

4. The authors claim in Page 6 Lines 133-134 that age of first shave and height were categorised appropriately to ensure a correct balance of distribution between groups. The authors need to clearly define was this specifically done? Was it done statistically or was another methods used?

Reply 7: The reviewer makes an important point. We have clarified that the cutoffs were selected by a consensus of the authors.

Changes in the text: "Age of first shave and height were operationalized as categorical variables with cutoffs selected by an author consensus to ensure relatively balanced distributions of study patients in each of the age/height category groups."- Page 6

We have also added the following limitation to the Discussion section on page 12: "Furthermore, the cutoffs for the categorical variables of age of first shave and height were chosen by a consensus

of the authors with choice of cutoffs potentially influence the significance of the results obtained."

5. Although the hypothesis was that early onset of puberty may increase PC risk, the authors have not referenced any of the previous publications to support this (PMID: 27741552; PMID: 12455039). They have instead included a study Lope et al which had a biased control population with high attrition rate, and two others that showed no association.

Reply 8: We thank the reviewer for bringing to our attention these two relevant studies that we had not referenced. They have been referenced in the Discussion section on page 10.

Changes in the text: "Nair-Shalliker et al. demonstrated that both later (versus same as peers; OR=0.75, 95% CI: 0.59-0.97) and earlier (OR=0.85, 95% CI: 0.61-1.17) onsets of puberty were associated with risk of PCa (10). In a population-based, case-control study from Australia between 1994 and 1998, Giles et al. demonstrated that having a growth spurt later than friends reduced risk (OR 0.79, 95% CI: 0.63-0.97) of PCa (11)."- Page 10

Reviewer B

This study is based on well structured and clear study design to draw the conclusions.

However, there are 2 important opinions that cannot be ignored.

1. (Most important) The study outcome is derived from the biopsy results that had been performed from 1995 to 2016. This is a fairly long period of time and due to the advances in biopsy technique, there is a possibility that the accuracy of the biopsy results performed thought the study period may not be consistently same.

Reply 1: The reviewer makes an excellent point. There have been significant changes between 1995 and 2016, both in number of prostate biopsy cores taken and likely the providers performing the prostate biopsies at the facility, which may have impacted the accuracy of the biopsies.

Changes in the text: We have added the following to the limitations section on page 12: "Given that our study period spanned two decades, prostate biopsies were likely performed by different providers, which may have potentially temporally impacted the accuracy of the biopsy results.".

We also hope that these two sentences previously included help address this limitation further: "As patients in our cohort were recruited from 1995, a significant proportion (45.9%) did not undergo a twelve core prostate biopsy, which is the current standard of practice (24). No differences were seen however in baseline characteristics of patients undergoing a twelve versus non-twelve core biopsy

2. As the authors mentioned in the discussion section, another important point that needs to be explained is that "Can we really trust the patients' self-reported age of first shave?" If the age category is re adjusted into maybe 4 categories... (ex <15, 16-17, 18-19, 20<) and the analysis

show the consistent results, it will be a little more reliable. This can be showed in the discussion section along with limitation, instead of revising the whole result by changing the age category.

Reply 2: The reviewer is correct in his assessment that cutoff choice for age of first shave or height may have influenced the significance of the results.

Changes in the text: We have added the following to the limitations paragraph in the Discussion section on page 12: “Furthermore, the cutoffs for the categorical variables of age of first shave and height were chosen by a consensus of the authors with choice of cutoffs potentially influence the significance of the results obtained.”