

Reviewer comments

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Article title: Prostate cancer incidence among immigrant men in Ontario, Canada: a population-based retrospective cohort study

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Reviewer: 1

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Comments to the Author

Thank you for the opportunity to review your manuscript. I have no conflicts of interest to declare. The authors use ICES data to identify risk of prostate cancer incidence among immigrant and non-immigrant men in Ontario. I think this is a useful analysis and would be of interest to the readers of the CMAJ. I also think it is a superbly written manuscript.

1) However, I am concerned about the robustness of the data presented in the manuscript. In Table 1, the authors indicate that over 45 million men are included in the analysis as the denominator of the population. I find this implausible, as the population of Ontario in 2021 is approx 15 million and presumably only half are men. Therefore, I am concerned about the denominator for the general population (and possibly the immigrant population) used in this manuscript and cannot recommend it be accepted as-is without further explanation for this by the study authors.

The incidence of prostate cancer, however, is as I would expect based on other analyses of Ontario data.

We thank the reviewer for the positive comments. We apologize for our lack of clarity regarding our sample size. We created annual cohorts for the years 2008-2016. Thus, our sample size in the header of Table 1 and Table 3 reflect person-years, not unique individuals. The headers have been adjusted accordingly.

Other, minor points that I believe could be addressed upon resubmission

2) The conclusion statement in the abstract is not supported by any data in the abstract and I believe should be removed / rewritten. I agree with the conclusions in the body of the manuscript (which are not the same as in the abstract), and I believe a more generic conclusion would be appropriate in keeping with the results presented in the abstract.

We have re-written the conclusion statement of the abstract as suggested. It now reads: "Future research in Canada needs to focus on further understanding heterogeneity in prostate cancer risk and epidemiology, including stage of diagnosis and mortality, for immigrant men".

3) I believe the authors need to reference this landmark analysis of Black race in prostate cancer mortality in the United States (First author Dess, doi:10.1001/jamaoncol.2019.0826). This manuscript shows using multiple data sets that Black men do not inherently have higher risks of mortality, and shows that it is more so

social constructs that have led to previous conclusions of Black men having more aggressive prostate cancers. While not truly linked to incidence (as this manuscript is), I think it would provide strength to the discussion of the manuscript to reference this paper. Of note, I am not an author on that manuscript.

We thank the reviewer for this suggestion. However, as we have been asked by the editors to remove any inference about race in the paper, we have not delved deeper into the literature on race and prostate cancer.

4) I apologize if I missed it, but do you discuss the impact of immigrant admission category on prostate cancer incidence, particularly among those from West African / Caribbean locations? I am not sure why this was included in the analysis (first paragraph of the results) but not discussed elsewhere. If not relevant, it could be removed to save on word count.

We thank the reviewer for raising this point. We included immigration admission category as it can be reflective of socioeconomic status, at least at the time of arrival. This was stated on p. 5, but we have now moved it up to earlier in the manuscript (see Introduction, p. 4).

Thanks for the opportunity to review this manuscript, I'd be happy to review a revised version

We thank the reviewer for this positive feedback.

Reviewer: 2

[Name withheld] / Manitoba

Comments to the Author

This manuscript reads very well and has some notable positives including:

- 1) Good descriptive analysis of the variation of prostate cancer incidence by different subgroups of the Ontario population including 15 categories of immigrants divided by geographic region of origin in a contemporary time period (2008-2016).**
- 2) Methodologically sound use of linked administrative, population-based, healthcare and socio/demographic data.**
- 3) Sizable population sample.**
- 4) Excellent sources of data (IRCC-PR, OCR, etc)**
- 5) Very well written.**

We thank the reviewer for this positive feedback.

However, I do have some reservations/questions regarding aspects of this study:

- 1) Is the multivariable model employed a realistic model for prostate cancer risk or incidence?**

No, the multivariable model used in this study is overly simplistic especially when considering the contemporary understanding of the multifactorial blend of known risk factors for the development of prostate cancer. A prostate cancer model including only 3 covariates (age, neighbourhood income, immigration status) is fraught with confounding variables which are not accounted for (for example: family history, inherited germline mutations, polygenic risk from common genetic variants, dietary exposures, obesity, hyperglycemia, testosterone exposures, endocrine disruptor exposures, to name a few). It is understandable that most of these variables cannot be easily sought out from

administrative healthcare databases, hence why they were not included in the model by the authors, but there is considerable risk here that this overly simplistic model inaccurately estimates the strength of association of the immigrant status variable. In my mind, after reading this manuscript, I wonder what impact immigrant status would have (if any) after accounting for polygenic risk.

We fully agree with the reviewer that it would be ideal to have access to data at the provincial level that include family history, inherited germline mutations, polygenic risk from common genetic variants, dietary exposures, obesity, etc. However, this is not feasible with current data sources and study constraints. We have now added this as a limitation, and direction of future research (see p. 10). Specifically, we have added this text:

“Finally, we were not able to account for important variables such as family history, dietary exposures, environmental exposures, et cetera that are not available in provincial databases. Future research that is able to ascertain these details on immigrant men from these world regions may make a substantial contribution to advancing our understanding of why differences in risk exist.”

2) Does this data suggest any sort of practical change in management for patients at risk for prostate cancer? No, it is unclear how the study findings impact our screening recommendations. Should immigrant men from the Caribbean or West Africa be screened earlier starting at a younger age? As it is written, this study does not seem to have much practical implications for our patient populations.

We believe that raising awareness about particular subgroups at higher risk of a condition does have very practical clinical implications, especially when there is no population-based screening for prostate cancer as is the case in Canada currently. Of note, the CMAJ editors did state that they appreciate that this paper reports population data on the incidence of prostate cancer by region of origin and felt that the paper might also have value and interest for government policymakers. In addition, refining clinical recommendations for prostate cancer screening may well be an eventual outcome of research stimulated by our paper, but we acknowledge that our findings require additional study before any sweeping changes to policy should be considered.

3) Are the study findings novel? No, the geographic heterogeneity of prostate cancer incidence is a well described phenomenon in the medical literature. Take for example this paper [Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020 Jan;77(1):38-52. doi: 10.1016/j.eururo.2019.08.005. Epub 2019 Sep 5. PMID: 31493960.}, which highlights regional variations in prostate cancer incidence with relative “hotspots” in the Caribbean and West Africa. This study's findings likely reflect these regional variations.

We agree that the geographic heterogeneity of prostate cancer incidence has been described in the medical literature, and we included several references in the previous version of the manuscript to this effect (Sung et al, Beiki et al). We have now added this reference by Culp et al (see Discussion, p. 9) and thank the reviewer for sharing this paper. However, we do not feel that geographic heterogeneity of prostate cancer incidence worldwide takes away from the novelty of our work, which is the first population-based study we are aware of to examine prostate cancer incidence for immigrant men by region of origin in our setting. Of note, our findings did not align with those of Culp et al, which we believe also exemplifies that we cannot assume findings from other countries or jurisdictions are true in the Canadian context, and that we need to produce Canada-specific research.

4) Where is the prostate treatment and mortality data? I think that this paper would be much more impactful if it were determined that patient subgroups identified in this analysis were also found to be underserved populations in terms of accessing

surgical/radiotherapy/chemotherapy treatments for prostate cancer in Ontario compared to long-term Ontario residents, and/or if these subgroups had worse mortality outcomes following treatment. If this were the case, then there would be a much stronger case to help these population subgroups in advocating for access to treatment, and/or more intensified treatments if mortality is found to be higher in amongst immigrant subgroups when compared to long-term Ontario residents.

We agree that data on treatment and mortality for prostate cancer for patient subgroups are important to investigate but beyond the scope of the present project. Our last sentence of the paper reads “Future research in Canada needs to recognize this difference and focus on further understanding prostate cancer risk and epidemiology, including stage of diagnosis, treatment patterns and mortality, for these men”. On p. 10 of the Discussion, we also say “Thus, future research should also explore differences between immigrants and long-term residents in use of prostate cancer screening, stage of diagnosis, treatment differences and importantly mortality in the Canadian context”.