Article details: 2022-0230
Title: Comparing trends in infection-related and infection-unrelated cancer incidence among people with and without HIV: a population-based matched cohort study using administrative health data in Ontario, Canada, 1996–2020
Authors: Ioana A. Nicolau MSc, Rahim Moineddin PhD, Tony Antoniou PhD, Jennifer D. Brooks PhD, Jennifer L. Gillis PhD, Claire E. Kendall MD PhD, Curtis Cooper MD MSc, Michelle Cotterchio PhD, Kate Salters PhD, Marek Smieja MD PhD, Abigail E. Kroch PhD MPH, Joanne D. Lindsay MES, Colleen Price BA BSS, Anthony Mohamed MES, Ann N. Burchell PhD

Reviewer 1: Shannon Turvey
General comments (author response in bold)

1. Large sample size, matched cohort, well designed observational study. Additive to existing understanding of the cancer landscape among people living with HIV in a Canadian context. Clearly and comprehensively acknowledges limitations.
I agree with the authors that lack of access to data on confounding cancer risk factors is a major limitation – I would add that in addition to antiretroviral data and information on CD4 count/percentage data, data on HIV viral load which depending on adherence does not always track with antiretroviral prescription (and is also more objective than record of ART) would have been relevant. However, the included sensitivity analysis exploring the magnitude of confounder that would be required to explain the association between HIV status and infection-related cancers significantly strengthens the findings of this study.
Thank you for the comments that our study is a well-designed observational study that fills an important knowledge gap in the Canadian cancer landscape.
We appreciate knowing that exploring the magnitude of confounding in a sensitivity analysis significantly strengthened the findings. We noted lack of HIV viral data in our limitations. (Interpretation (p 10))

2. Page 13, Statistical analysis section in methods: "categorical" not "categorial"
We corrected this. (Statistical analysis (p 13))

Reviewer 2: Karena Volesky
Institution: McGill University
General comments (author response in bold)

3. I enjoyed reviewing this work and think it will be a valuable contribution to the literature on what we know about the risk of cancer in people with HIV. This study will be of interest to those researching infections as a cause of cancer.
Many of the suggestions I would have had dealt with adding some details as to why certain things were carried out the way they were, but the word limit is restrictive at 2,500 - overall I think you chose well what appears in the manuscript versus the supplement.
Thank you for taking the time to review our manuscript and provide comments which will enhance the quality of the manuscript.

4. First, the choice of cancer sites, infection-related and unrelated. The supplement lists them out, but how did you determine which sites were considered infection-related? Did you consider utilizing IARC monograph volume 100B, and then select those sites where IARC deemed there was 'sufficient' evidence?

Yes, we used IARC monograph volume 100B, and then selected those sites where IARC deemed there was sufficient epidemiological evidence in humans. We added the reference to Supp. Table A1. (Supp. Table A1)

5. Laryngeal cancer is generally considered an HPV-associated cancer (though a small fraction is attributed to HPV, 5-10%) but it was not classified as an HPV-associated cancer. Unspecified male genital organ (C63) which includes subsites such as the epididymis and scrotum NOS, are generally not infection-associated but classified as an HPV-associated cancer, why?
The IARC Working Group considered that the epidemiological evidence was inconclusive to confirm the role of HPV in cancer of the larynx (IARC Monograph Volume 100B. Biological Agents. 2012). We added this in the footnote for Supp. Table A1. In total, there were 17 cases of laryngeal cancer and <5 cases of unspecified male genital organ cancers which would not affect the conclusions of the manuscript. (Supp. Table A1)

6. Selecting the broader cancer site/not pairing with the histology associated with the infection could influence the cancer-specific HRs; for example, H. pylori and gastric cancer versus non-cardia gastric cancer, HBV and HCV and liver cancer versus hepatocellular carcinoma histology (C22.0, 8170-8175 – HCC is ~80% of liver cancer diagnoses but that leaves 20%), and HPV and pharynx versus oropharynx and tonsil. For the last one, you may have been constrained by what codes were available (pharynx vs oropharynx) but was it possible to include tonsil on its own? Were you constrained by the available cancer incidence data?
We agree with the reviewer that we selected the broader cancer sites due to constrains in data morphology codes/histology information and we noted this in the limitations. (Limitations (p 10))

7. Non-Hodgkin lymphoma contains several histologies associated with HIV (or really EBV) to varying degrees. Did you consider examining major types of NHLs such as DLBCL?
Due to cancer morphology coding constrains as mentioned above we were unable to examine major types of NHL. (Limitations (p 10))

8. Second, most readers will not be familiar with the e-value. I have a basic understanding of what it is but was not able to follow the description in the results – consider moving content from the limitations section (which is a nice clear description of how the e-value applied here) to the results. Was the e-value necessary to include? I ask because heighten risk of infection-related cancer is well-established for people living with HIV, the topic is now at the stage where people are assessing the magnitude of those risks, how risk varies across characteristics of those with HIV (confounders like age), and cancer-specific risks which change with time – these three items were well executed in this manuscript - the e-value doesn't add much but takes several sentences to describe.
We moved the content from limitations to the results section. (Results (p 8))

9. Third, a limitation is missing people with HIV (undiagnosed infection), can you comment on what proportion of HIV+ would be missed in the Ontario context? Since HIV prevalence varies from region to region, readers might like some estimate of whether like 10% or like 40% of HIV infections were missed.

Thank you for this suggestion. In Ontario there were an estimated 11% people with undiagnosed HIV in 2020 (OHESI, 2020 Report. Available at: https://www.ohesi.ca/wp-content/uploads/2022/10/HIV-Care-Cascade-2020-final-1.pdf) We added this information in the limitations. (Limitations (p 10))

10. Fourth, in the abstract, it reads "These trends were consistent for males and females with HIV" not crystal clear what 'these' refers to. Could apply to all results described in abstract or just part of the sentence before. Please clarify.
We revised the abstract. (Abstract (p 3))

11. There is a push to move away from the terminology AIDS-defining cancers since it's no longer accurate to define those three cancers as AIDS-defining.
We agree with the reviewer that AIDS-defining cancers is no longer relevant in the contemporary ART era. Nevertheless, we included this category for three reasons: 1) to be consistent with our previous publication, 2) to compare trends with earlier publications, and 3) because our study spans multiple ART eras where ADC trends changed over time, we wanted to be able to show historical trends.

12. Under study design and setting, "….insights from Ontarians living with both HIV and cancer through a Community Advisory board" which insights? How did this influence the conduct of this study?
We explained in detail our community engagement initiative in the Methods section. (Methods (p 5))

13. Supplementary table 1 could benefit from listing out the cancers you considered infection associated then the ones you did not without overlap – I think this would be easier to follow. May want note in the table that while NHL is classified as an ADC, that many NHLs arising in people with HIV are EBV-related (like how you did with HPV and cervical cancer).
We revised Supplementary Table 1. (Supp. Table 1)

14. Is it also worth mentioning in main text or supplement that there are other rare infection-associated cancers such as cancer of conjunctiva (HIV), extranodal NK/T-cell lymphoma - nasal type (EBV), Cholangiocarcinoma (HBV, HCV, C. Sinensis, O. viverrini) not included in the analysis?
We have noted all incident cancers diagnosed in our cohort in Supplementary Table 2 with a footnote 2 to specify what was included in "all other sites". (Supp. Table 2)

15. Thousand separators could make it easier to read: 20,000 versus 20000.
We adhered to CMAJ Open manuscript formatting which do not allow for thousand separators. (N/A)

16. Now, it is Hodgkin lymphoma (not possessive) not Hodgkin's lymphoma.
Thank you. We made the correction. (Table 2)

17. For Tables 1 and 2, there is a missing space between the years covered and the comma that proceeds it. Table 4 has a period instead of comma before the dates.
We corrected this. (Tables 1, 2 and 4)

18. Flow chart: missing age and sex, or did you mean missing age, sex (like one or the other)?
Yes, we meant missing age or sex and revised the flow chart. (Figure 1)