Author's response to reviews

Title: Risk of cancer among HIV-infected patients from a population-based retrospective cohort study: implications for cancer prevention

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Author's response to reviews: see over
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Version: 4 Date: 09 November 2014
Author's response to reviews: see over
Reviewer's report
Title: Risk of cancer among HIV-infected patients from a population-based retrospective cohort study: implications for cancer prevention
Version: 3 Date: 24 July 2014
Reviewer: Marguerite Guiguet

Reviewer's report:
This retrospective cohort study was performed using a national administrative database in Taiwan and was based more specifically on a random sample of 1 million people included in the Longitudinal Health Insurance Database 2000. HIV infection and cancer diagnosis were identified in the outpatients and inpatients claims recorded for 11 years (2000-2010). All people with HIV infection were included in the present analysis and four HIV-uninfected controls for each case matched on sex, age and year of enrolment. Logistic regression was used to estimate the risk of cancer associated with HIV infection after adjustment on confounding. SIRs for specific cancers were calculated. An increased risk for different cancers was observed and discussed.

The study is interesting but some additional information would help.

General
This is a useful contribution to the diagnostic literature. The following minor revisions might help improve the paper.
None

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
None

-Major comments
1. The timing of HIV infection and cancer diagnosis are confused and the figure 1 is clearly not the flow-chart of the present study. Did you select people with HIV infection at enrolment in LHID2000 or during the 11 years of follow-up. In the latter case, how did you classified people with a cancer revealing HIV infection.

Response:
(1) In this study, we wanted to explore the risk of cancer among HIV-infected patients. However, because most of the symptoms/signs of HIV infection tend to be evident late after
the initial infection, the date of the cancer diagnosis might have been before or after the date of HIV diagnosis.

(2) We selected people diagnosed with HIV infection during the 11 years of follow-up. And, we classified people with an HIV-associated cancer in HIV-infected patients with cancer occurrence.

2. How many people died or were lost of follow-up during the 11 years, and especially in the HIV infected group. The method of calculation of person-years at risk should be presented and the number of person-years should be added on Table 1.

Response: Because most of the symptoms/signs of HIV infection tend to be evident late after the initial infection, the date of the cancer diagnosis might have been before or after the date of HIV diagnosis. Otherwise, we added the mean follow-up time of the HIV-infected patients and controls (55.53 and 56.12 months, respectively) to represent the person-years to Table 1.

3. Table 3: Except for breast and cervical cancer which are clearly sex-associated, an expectation of 0 is surprising. The increased risk for some cancer with very low expected number and very large confidence interval (i.e. non-lung cancer) should be presented with more caution.

Response: In the original Table 3, the expectation of 0 for some types of cancer was because the expected number is less than 0.5. We replaced the “0” with the exact expected number for these types of cancer in the revised Table 3 on pages 22-23. We also revised the 95% confidence intervals in the revised Table 3.

4. Discussion: it was stated that “age and sex were still risk factors for the development of cancer in HIV-infected patients”. No data are presented to support this conclusion. The analysis only showed that age and sex were independent risk factors for cancer after adjustment on HIV infection.

Response: According to your suggestion, we revised the sentence

“our study also showed that age and sex were independent risk factors for cancer after adjustment for HIV infection.” in the Discussion section, page 7, lines 20-21.

5. Discussion: “Breast cancer occurred in HIV-infected patients at a mean age of 45.6 years”. Due to the very small number of breast cancer, the median would be more appropriate. The median age of breast cancer in the general population could be added to support your discussion.
Response:
(1) According to your suggestions, we revised the sentence as follows: “breast cancer occurred in HIV-infected patients at a **median age of 46 years**” in the Discussion section, page 8, line 23.

(2) According to your suggestions, we revised the sentence as follows: “Patients in Taiwan with breast cancer are younger (**median age of 45 years**) than those…” in the Discussion section, page 8, line 21 and added the reference as “Reference 19”.

6. **No data was presented according to HIV infection such as anti-retroviral therapy, CD4 cell count... If no such information was available in the database, this limitation should be discussed.**

Response:
(1) According to your suggestion, we add the percentage of diagnosed HIV-infected patients receiving anti-retroviral therapy and revised the sentence as follows: “**We finally enrolled 1,115 patients, of which 99.28% (1107) had received antiretroviral therapy.**” to the Results, page 6, lines 11-12.

(2) However, no CD4 cell count data were recorded in the National Health Insurance Research Database. So we added the sentence “**Third, there were no laboratory data on the CD4 cell counts recorded in the NHI Research Database. Therefore, we could not determine how severe the HIV infections were in our study patients.**” to the “Limitations” paragraph in the Discussion section, page 11, lines 8-10.

Minor comments
1. **Statistical analysis : the presentation of SIR calculation is difficult to understand. What would you say by “the cancer incidence of the control group in the general population”. What age strata were used for stratum-specific incidence rates of cancer for the entire population, and what was the corresponding age structure of the HIV population.**

Response:
(1) According to your suggestions, we revised the sentence as follows: “**The expected number of cancer cases was obtained from the number of cancer cases that would occur in groups from the general population that corresponded to the age-, gender-, and follow-up-year-specific groups of HIV-infected study participants.**” in the statistical analysis paragraph of the Methods, page 5, lines 21-24.

(2) The age stratum used for the stratum-specific incidence rates of cancer for the entire population and HIV population was 10 years, as in, 21-30 years of age, 31-40 years of age.
2. Table 1: the p-values for age and gender are clearly wrong as the distributions in the two groups are the same by construction. The p-values are 1.0 and not 0.5.
Response: According to your suggestion, we revised the p value for age and gender to “1.0” in Table 1.

3. Table 1/ Table 2: as only 3 HIV-infected and 3 HIV-uninfected individuals had a modified Charlson index >10, this category should be grouped with the 6-10 category.
Response: According to your suggestion, we reclassified the Charlson index into 3 groups (i.e., 0, 1-5, ≥ 6) and recalculated the percentages, odds ratios, and 95% confidence intervals in Table 1 and Table 2.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests
Reviewer's report

Title: Risk of cancer among HIV-infected patients from a population-based retrospective cohort study: implications for cancer prevention

Version: 3 Date: 5 September 2014

Reviewer: Suzanne Marie Ingle

Reviewer's report:
This is an interesting paper highlighting the increasing importance of cancer incidence among HIV-positive people and the need for screening procedures to try and tackle this. However, I do not feel that there is enough detail about the study design in this paper to be able to say this is publishable.

• Is the question posed by the authors well defined? Yes, this question is well defined.
• Are the methods appropriate and well described? The methods are not that well described – see my comments in ‘Major Compulsory Revision’
• Are the data sound? I am unable to tell.
• Does the manuscript adhere to the relevant standards for reporting and data deposition? I’m not sure.
• Are the discussion and conclusions well balanced and adequately supported by the data? Yes.
• Are limitations of the work clearly stated? There is some discussion of limitations, but I feel this could be expanded i.e. lack of data on smoking or HIV prognostic markers (CD4/Viral load etc) are not very clearly stated.
• Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? The authors say this has not been published elsewhere.
• Do the title and abstract accurately convey what has been found? Yes.
• Is the writing acceptable? Yes.

General
This is a useful contribution to the diagnostic literature. The following minor revisions might help improve the paper.

None

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Discretionary Revisions (which the author can choose to ignore)
None

- Major Compulsory Revisions

1. A major flaw in the reporting of this study is the lack of information on follow-up time. In the first paragraph of the Methods section it says that the database contains information for 11 years of follow-up, since the year 2000. I cannot find any information in the text though about whether all patients were followed up for 11 years or not. I would expect that some patients drop out of the study database before 11 years of follow-up either because they die or simply move out of the country. This could be introducing a serious amount of selection bias into the sample – a healthy cohort effect – if only those alive at the end of 11 years were included in the study. This issue should be clarified and commented on before on decision on publication can be made.

Response: This database was constructed with 1,000,000 persons derived (sampled) from Taiwan’s 27,000,000 citizens. The period of follow-up was from 2000 to 2011. Only the study participants alive at the start of follow up in 2000 were included in the study, and they were followed for 11 years. However, the study participants (including HIV patients and controls) were censored when cancer developed, death occurred, or retrieval from the National Health Insurance system.

We calculated the mean follow-up times of the study participants after enrollment. They were 55.53 months and 56.12 months, for the HIV-infected patients and controls, respectively. The results are shown in Table 1.

“Based on the similar follow-up times for the infected patients and controls, as well as the fact that only participants alive in 2000 were included in the study, we believe that there was minimal healthy cohort effect.

2. On a related note, the authors refer to ‘year of enrollment’ frequently. What is this enrolment into? Do they mean year of HIV diagnosis, or the year they first appear in the LHID database for any reason? As matching was based on year of enrolment, this really needs to be clarified.

Response: The “year of enrollment” means year of HIV diagnosis. We revised the sentence as follows: “year of enrollment (year of HIV diagnosis)” in the “Method” section, page 4, lines 23-24.

3. When looking at site-specific cancers, how were patients categorised if they had more than one cancer? Did they get counted under each type of cancer when calculating the SIRS? What happened if they had 2 occurrences of the
**Response:** A patient developing more than 1 type of cancer was categorized to each type of cancer. A patient with 2 occurrences of the same type of cancer during the follow-up period was calculated once in the SIRS.

4. **Why was matching required in this study design? Was it for practical reasons, i.e. did it cost more to obtain more records from the database? Couldn’t the authors have simply categorised everyone in the database as HIV positive/negative, and then included this as an explanatory variable in the logistic regression (outcome=cancer) and adjusted for age, sex, year of enrolment?**

*Please provide some more discussion on the choice of study design (see Greenland and Morgenstern 1990, AJE or Cummings et al Epi Reviews 2003).*

**Response:** Thank you for the study designs that you provided. I read them and arrived at the following conclusion: Matching is a common epidemiological statistical method in biostatistics that usually provided for the research group process the study of matching. “Matching is a design strategy to eliminate, or control for confounding” (from Greenland S, Morgenstern H, Matching and efficiency in cohort studies. Am J Epidemiol. 1990 Jan;131(1):151-9). However, the patients with HIV-infection were most likely to be male and young. Therefore, we used matching in our study and found a similar overall distribution, but some of the individual data have differences. This is the best way to adjust for differences via study design such as matching with the sex, age and regression for several confounders.

5. **The Figure 1 attached with the paper is clearly not correct as it refers to a study on glaucoma. The authors must present the correct figure. The correct figure would be very useful in determining whether the study sample is biased or not.**

**Response:** We apologize for including the wrong Figure 1. We deleted it and added the correct Figure 1, which shows the flowchart of this study.

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**Minor Essential Revisions**

6. **Abstract: Background. The first sentence makes it sound like ART causes cancer. Please rephrase. “The burden of cancer is likely to increase among the HIV positive population as it ages due to successful ART”**.

**Response:** According to your suggestion, we revised the sentence as follows: “**Because of effective antiretroviral therapy, the burden of cancer is likely to increase among the human immunodeficiency virus (HIV)-positive population as it ages due to successful ART.**” in the Abstract section, page 2, lines 2-4.

7. **Abstract: Methods, the word “was” is missing in the 2nd sentence. “It was**
performed using the National...”

**Response:** According to your suggestion, we added “was” to the Abstract section, page 2, line 6.

8. **Abstract:** Methods. Please specify in the abstract what the potential confounders were.

**Response:** According to your suggestion, we revised the sentence as follows: “potential confounders (income, urbanization, and Charrold index of comorbidity)” in the Abstract section, page 2, lines 9-10.

9. **Abstract:** Results. Please specify what the follow-up period was.

**Response:** According to your suggestion, we revised the sentence as follows: “during the **11-year** follow-up period” in the Abstract section, page 2, line 13.

10. **Abstract:** Results. Please define OR as odds ratio.

**Response:** According to your suggestion, we revised the sentence as follows: “adjusted odds ratio” in the Abstract section, page 2, lines 14-15.

11. **Table 1** contains percentages in the style “01.97%”. Please remove the leading 0 in these numbers.

**Response:** According to your suggestion, we removed the leading 0 and revised to “1.97” in Table 1.

12. **Methods** 1st paragraph: It would help to be more precise in the terminology of the study – rather than just having done a retrospective cohort study, you have done a matched retrospective cohort study.

**Response:** According to your suggestion, we revised the sentence as follows: “This **matched** retrospective cohort study” in the Methods section, page 4, line 3.

13. **Methods** 2nd paragraph: When you talk about including all people with HIV infection who ‘filed claims’ – what exactly does this mean? Did they pick up pharmacy prescriptions for antiretrovirals? Please clarify.

**Response:** The “filed claims” means the patients were confirmed to have HIV infection.

14. **Methods**, 3rd paragraph mentions “administrative chronic diseases”. Please remove the word administrative as this does not make sense.

**Response:** According to your suggestion, we removed the word administrative and revised the sentence as follows: “in **chronic diseases**” in the Methods section, page 5, line 6.
15. Discussion 8th paragraph – is “hospital shopping” a phenomenon or a typo?
Response: “Hospital shopping” is a Taiwanese phenomenon referring to the frequent visiting of different hospitals.

16. I think the reference list needs some work. For example, in the 2nd paragraph of the Background section, the authors say “NADCs are emerging as a significant source of mortality(6)”. However, reference 6 is a paper from 1998 – this is not very recent to talk about an emerging source of mortality in the year 2014. I think this is the wrong reference.

17. Reference 1 doesn’t seem very appropriate – it is a cancer paper being used to reference the success of antiretroviral therapy for HIV. Please find something more appropriate.

18. Throughout the manuscript the authors talk of “AIDS-defined” cancers. Please change this to “AIDS-defining”.
- Discretionary Revisions
Response: According to your suggestion, we revised all “AIDS-defined” cancers to “AIDS-defining” cancers or “ADCs” after spelling out the term, in the entire manuscript.

19. Is it possible to assess whether duration of HIV infection had an impact of incidence of different types of cancer?
Response: We could not assess the impact of the duration of HIV infection on incidence of different types of cancer, because most of the symptoms/signs of HIV infection tend to be evident late after the initial infection. Therefore, the diagnosis of HIV may have occurred late in the disease, and the duration of HIV infection could be underestimated.

20. Keywords: Nationwide population-based study. The word “nationwide” is not very helpful for people searching for papers from across the globe. I would suggest adding “Taiwan” as a keyword instead.
Response: According to your suggestion, we added “Taiwan” to the Keywords section, page
21. **Background 3rd paragraph:** Phrasing is a bit awkward in “recommendations of screen protocol for HIV-infected patients” – perhaps use “recommendations of a screening protocol for HIV-infected patients” instead.

**Response:** According to your suggestion, we revised the sentence as “the recommendations of a screening protocol for HIV-infected patients…” in the Background section, page 3, line 20.

22. **Results 1st paragraph:** change tenses “Fig 1 is a flow chart”, “Table 1 shows the…”.

**Response:** According to your suggestion, we revised the sentence as follows: “Fig. 1 is a flow chart of the subjects enrolled in the study, and Table 1 shows the….” in the Results, page 6, line 4.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests