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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Author's response to reviews: see over
Reviewers report

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

Version: 5 Date: 27 October 2014

Reviewer: Marguerite Guiguet

Reviewers report:
The manuscript has been improved but a few clarifications are still needed.

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

1. Statistical analysis. I understand that you used an indirect standardization but the additional sentence explaining the calculations of the expected number of cancer is unintelligible. Please clarify.

Response: According to your suggestion, we revised the sentence “The expected number of cancer cases was obtained from the number of cancer cases that would occur in comparison group that corresponded to the age-, gender-, and year of enrollment of HIV-infected participants.” in the “Statistical analysis” paragraph, page 6, lines 1-2.

2. Results: As it is now clear that HIV diagnosis could have been before or after the diagnosis of cancer in the group of HIV-infected patients, the high percentage of HIV-infected patients receiving ART is misleading. To compare your numbers with others studies, you should present the percentage of cancer diagnosis that occurred among HIV-infected patients receiving ART at the time of cancer diagnosis. If this number is not available, this would be discussed in the limitations.
Response: According to your suggestion, we added the description in “limitation” paragraph: “The lastest limitation, although we obtained 99.28% of the enrolled 1,115 HIV-infected patients had received ART, the percentage of HIV-infected patients receiving ART at the time of cancer diagnosis can not be obtained in this database.” in the “Discussion” section, page 11, lines 22-25.

3. Table 3: As in the first manuscript you presented some expected number as low as 0.25, it was impossible to understand that your expectations of 0 was because the expected number was less than 0.5. Rather than the corrections you have done, it would be better to indicate “<0.5” with no calculation of SIR and to apply the same rule to all expected numbers <0.5. Statistical methods should be written accordingly. For Kaposi, it is curious that the expectation of 0 in the initial manuscript is now 1.36 – above your previous threshold of 0.5? For Kaposi, the expected number for “All” is clearly wrong.

Response:
(1) We apologize for the typing error in Table 4 (former Table 3). In order to correct the error and according to your suggestion, we revised the Table 4 (former Table 3). If the case number or expected number was less than 0.5, we indicated “<0.5” and “N/A” with no calculation of SIR in Table 4 (former Table 3). We added the sentence “We indicated “<0.5” if the case number or expected number was less than 0.5 and “N/A” with no calculation of SIR.” in the “Statistical analysis” paragraph, page 6, line 6-7.
(2) We revised the expected number and SIR of Kaposi in Table 4 (former Table 3).

4. Discussion: As indicated in the revised manuscript, median age of breast cancer is not different between HIV infected patients (median age 46 years) and general population (median age 45 years). It is therefore difficult to understand your conclusion that the age difference between the two groups may explain why your HIV infected patients had a higher incidence of breast cancer than those without HIV infection.

Response: We explained the reason of higher incidence of breast cancer than those without HIV infection and revised the sentence “A recent nested case-control study from the Women's Interagency HIV Study and HIV Epidemiology Research Study cohorts showed that a low risk of breast cancer may be linked to infection with CXCR-4 tropic virus [17]. This demonstrated lower risk was observed in the pre-cART era but not in the cART era [18]. It may explain why our HIV-infected patients, who decreasing CXCR-4 protective effect after using cART, had higher incidence of breast cancer. Future studies may be needed to explore it.” in the “Discussion” section, page 9, lines 5-11.
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: 5
Date: 30 October 2014
Reviewer: Suzanne Marie Ingle

Reviewer's report:

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

--Major Compulsory Revisions
1. I am still confused by how the matching of cases and controls was done according to year of enrolment. The authors have clarified that ‘year of enrolment’ was in fact year of HIV diagnosis. How then was ‘year of enrolment’ defined for the control, HIV-negative, population?
Response: When we identify a new HIV-diagnosis patient in some year, we randomly chose four HIV-negative subjects matched with the same sex and age appeared in the database in the same year.

2. In response to the comment from reviewer 2 about the timing of HIV infection and cancer diagnosis, the authors have said that the date of cancer diagnosis might have been before the date of HIV diagnosis. Therefore, it seems like a person could be diagnosed with cancer in the year 2000 and get infected with HIV in the year 2008, and they would be included in the group as HIV-positive instead of as a control. Is this the case, or have I misunderstood? If this is true, then I think there are some major issues with the design of the study. Can you please clarify the temporality of events?
Response: Yes, you are right. If a person could be diagnosed with cancer in the year 2000 and get infected with HIV in the year 2008, he/she would be included in the group as HIV-positive patient. In this study, we wanted to explore the risk of cancer among HIV-infected patients. However, because incubation period of HIV-infection is long, 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.

So, we used the odds ratio instead of hazard ratio to demonstrate the significant association of cancer with HIV-infection.

3. In response to my first comment about lack of information on follow-up time, the authors have provided some explanation. This explanation is critical and should certainly be included in the text of the manuscript and not just in the response to reviewers. In this explanation it sounds like only people diagnosed with HIV in the year 2000 were included, and it then seems like the mean follow-up time of 2.5 years is very short. Were people in fact diagnosed with HIV throughout the years 2000 to 2011? This seems more likely, but is unclear. I think that Table 1 should include information on year of enrolment.

Response:

(1) According to your suggestion, we added the sentence “This database was constructed with 1,000,000 persons derived from Taiwan’s 23,753,407 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.” in “Study population/case definition” paragraph, page 4, lines 20-25. In addition, we added the sentence “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.” in “Result” section, page 6, lines 18-20.

(2) Yes, the HIV-infection patients were diagnosed with HIV throughout the years 2000 to 2011. According to your suggestion, we added the Table 2 to demonstrate the information on year of enrolment and added the sentence “The numbers of patients were diagnosed in each year of enrollment were shown in Table 2.” in “Result” section, page 6, lines 23-24.

4. I would be interested to know how many patients died (and therefore were censored in the analysis) before a cancer diagnosis. Is there a problem of competing risks? This is probably not a problem, but having some numbers
would help to assess this.

Response: After analysis, we found there were 11 patients died in the HIV-infection group and 10 patients died in the non-HIV group before a cancer diagnosed. They were 1.0% (11/1115) and 0.2% (10/4460) censored before outcome (cancer) measured in the two groups. However, this censoring resulted in underestimate of the risk of cancer among HIV-infected patients. So, this is not a problem of competing risk.

5. You have answered my query on “Is it possible to assess whether duration of HIV infection had an impact of incidence of different types of cancer?” You could look at the time from HIV diagnosis to cancer occurrence (or censoring) and acknowledge it is an underestimate of duration of infection. This could give some valuable insight to the reader about how many patients had HIV and cancer diagnoses at similar times (This would also speak to the comment from reviewer 2 about whether people had a cancer which revealed HIV infection).

Response: According to your suggestion, we added the sentence “The duration of infection (time from HIV diagnosis to cancer occurrence) of the HIV-infection group was 41.94 (SD=±35.53) months”. “Because the patients maybe censor before cancer occurrence, the duration of infection was underestimated” in section “Result”, page 6, lines 26 and page 7, lines 1-3 to address it.

--Minor Essential Revisions

1. The author's note the increased risk of AIDS-defining cancers (i.e. cervical cancer) among the HIV positive population. This is not surprising, but could the author’s comment in the Discussion whether these are more likely to be diagnosed in HIV+ compared to HIV-, simply because they are AIDS-defining? i.e. if a clinician knows a patient is HIV+, are they more likely to look for these cancers?

Response: According to your suggestion, we added the sentence “If a clinician knows a patient with HIV infection, he/she is more likely to look for AIDS-defining cancers according to the guidelines in 2014 [31].” in section “Discussion”, page 10, lines 12-14 and added the reference 31.

2. The author’s response to my original comment on site-specific cancers [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 same type of cancer in the follow-up period?] should be included in the manuscript text.
Also please include information on how many patients had multiple cancers.

Response:

(1) According to your suggestion, we revised the sentence “The patient developing more than one type of cancer was categorized to each type of cancer. The patient with two occurrences of the same type of cancer during the follow-up period was calculated only once in the SIR.” in section “Method”, page 6, lines 7-10.

(2) According to your suggestion, we revised the sentence “There were 25 and 35 patients had multiple cancers in the HIV-infection and non-HIV groups, respectively.” in section “Result”, page 7, lines 24-25.

3. In Table 1, mean follow-up time has been included. Please also include the standard deviation, or median and interquartile range if that is more appropriate.

Response: According to your suggestion, we added the standard deviation and interquartile range in Table 1.

4. Methods 2nd paragraph: Please include the definition of ‘filed claims’ into the text of the manuscript.

Response: As your suggestion, we revised the sentence “filed claims, means the patients were diagnosed to have HIV infection,” in section “Method”, page 4, line 19.

5. After the introduction of the nationwide screening protocol in 2010, did incidence of cancer increase in the population? This study has data up to 2011, so the effect of the screening programme may start to be evident here.

Response: Although the nationwide screening protocol started from 2010 including four types of cancers. They were colorectal, breast, oral, and cervical cancer. There were 1326, 1427, 1370 patients of the four cancers were found in the 2009, 2010, and 2011, respectively. However, the effect of the screening programme may not start to be evident here.

---Minor issues not for publication

1. Abstract: Background. The first sentence now says the same thing twice in mentioning effective ART. Could simply be rephrased as “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 “The burden of cancer is likely to increase among the human immunodeficiency virus (HIV)-positive population as it ages due to successful antiretroviral therapy (ART).” in section “Abstract”, page 2, lines 2-3.
2. Table 1 contains percentages in the style “01.97%”. Please remove the leading 0 in these numbers. You have done this. Please also change the other numbers of this style in the table. 01.75%, 03.14%, 02.83%, 03.68%, 02.77%.

Response: According to your suggestion, we deleted the leading 0 in Table 1.

3. Figure 1, the English reads strangely. I suggest changing the text in the bottom 4 boxes. For example, change “Occur cancer” to “Developed cancer” and change “Not occur cancer” to “Did not develop cancer”.

Response: According to your suggestion, we revised the “Occur cancer” to “Developed cancer” and changed “Not occur cancer” to “Did not develop cancer” in Figure 1.

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.