Author's response to reviews

Title: Cancer risks among patients with type 2 diabetes: A 10-year follow-up study of a nationwide population-based cohort in Taiwan

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Version: 3
Date: 12 April 2014

Author's response to reviews: see over
Dear Editor:

Thank you very much for giving us the chance to reply the reviewers’ comments for our paper "Cancer risks among patients with type 2 diabetes: A 10-year follow-up study of a nationwide population-based cohort in Taiwan (MS: 1935894654112033) ". The authors would like to thank all of you for judicious reading our manuscript and valuable comments which greatly improved this manuscript. We have made revision and replied your comments point-by-point.

Your sincerely,

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**Reviewer's report**

**Title:** Cancer risks among patients with type 2 diabetes: A 10-year follow-up study of a nationwide population-based cohort in Taiwan

**Version:** 1  
**Date:** 6 March 2014  
**Reviewer:** Hung-Che Chiang

Reviewer's report:

In this study, the authors explored the cancer risks among patients with type 2 diabetes mellitus (T2DM) through a national population-based cohort study that included diabetic patients and the general population in Taiwan by using standardized incidence ratios (SIRs) and population attributable fractions (PAFs). The authors demonstrate that increased risks of cancer are observed in liver, colorectal, oral, pancreatic, and kidney cancers in men and in liver, colorectal, breast, pancreatic, endometrium, bladder, and kidney cancers in women. The finding indicates that unusual risks of cancer are associated with T2DM. This study is the largest study to examine the largest study to examine the SIRs and PAFs of diabetes on site-specific cancer incidence for the Taiwanese population. It was valuable to show the risks of site-specific cancer among men and women with DM in Taiwan. However, a few concerns should be addressed:

Reply:
The authors would like to thank you for judicious reading of the manuscript and
valuable comments which greatly improved this manuscript. We have made revision and replied your comments point-by-point.

Major Compulsory Revisions
1. Study subjects were selected by ICD-9-CM code 250 and A-code A181. Depending on these criteria, the study subjects included type 1 and type 2 DM patients. Owing to the different mechanism of type I and type II DM patients, it would be nice if only to screen specific type 2 DM patients in this study.

Reply: Thank you for your suggestion. We have followed your suggestion to exclude those individuals with type 1 diabetes by the following steps. First, we identify all individuals with type 1 diabetes from Registry for Catastrophic Illness database, which contains type 1 diabetes. Second, we excluded those individuals with type 1 diabetes in the first step from our study cohort with diabetes. We have added the above statements in our method second, re-perform the statistical analysis, make revision accordingly for the entire manuscript. The added statements and the modified flowchart for recruitment procedures for the current study are shown below.

The population with type 2 diabetes should have at least three ambulatory claims or at least one inpatient claim with diagnosis of ICD-9-CM code 250 or A-code A181 from 1997 to 1998. To exclude those individuals with type 1 diabetes, we have done two steps. First, we identify all individuals with type 1 diabetes from Registry for Catastrophic Illness database. Second, we excluded those individuals with type 1 diabetes identified in the first step from our study cohort with diabetes.
2. The residential area information should not use the variable in insured dataset directly because this area variable did not present where the man lives, it presented the area where his company was.

Reply: Thank you for your comment. Yes, the variable in insured dataset represents the area where an insurer’s company was located or the area where an insurer register NHI program. There is no residential area information in insured dataset. We followed your suggestion by changing “residential area” as “area registered for NIH program.”

3. Metformin is the most commonly prescribed drug for type II diabetes. Previous studies show that metformin is associated with decreased cancer risk. As I know, the prescription information was included in NHI database, please group study subject by different therapy in order to eliminate the effect of DM treatment.

Reply: Yes, the prescription information was included in NHI database. Our team did not apply for datasets of prescription information for two reasons. First, our objective
is to compare cancer risks between patients with type 2 diabetes and general population by using standardized incidence ratios (SIRs). This line of research question usually uses sociodemographic factors for standardization. When diabetes medication is considered, this type of study is more likely to belong to pharmacoepidemiological study. Thus, we did not apply for datasets of prescription information during design stage. Second, many cancer incidence rates are very low and it is required to have a large size of sample to provide reliable and powerful estimates of SIRs. Thus, we determined to use the datasets of entire diabetes population for the current study. Our study cannot afford to buy prescription dataset for the entire diabetes population. In addition, most of studies using NHI database to explore medication used datasets of a random sample of one million residents. To consider anti-diabetic medication for entire diabetes population, it is beyond what we can handle. Hope Reviewer can understand. We have one limitation to discuss this, which is shown below.

Second, diabetic patients may have taken medicine that affected cancer risks. Previous studies have also indicated that glucose-lowering medicines, such as metformin, may reduce risks of cancers in diabetic patients. On the contrary, sulfonylurea drugs or insulin are associated with increased cancer risks [46]. Thus the strength of association between type 2 diabetes and cancer estimated for different populations depend on prevalence of anti-diabetes medication in population with diabetes. Although we did not have information regarding glucose-lowering medications, it won’t confound our estimation for association between type 2 diabetes and cancer in our population.

4. The results showed some higher risks of site-specific cancers and some lower risks of other site-specific cancers. Please add and discuss the clinical implication of these results in this study.

Reply: Thank you for your suggestion. We have added one paragraph to discuss the clinical and public health implications of our study findings in the manuscript. The added paragraph is shown below.

Our study showed men with a diagnosis of type 2 DM were associated with increases in risks of liver, colorectal, oral, pancreatic, and kidney cancer incidences and women with a diagnosis of type 2 diabetes with increases in liver, colorectal, breast, pancreas, endometrium, bladder, and kidney cancers. These findings have important clinical implication: it is necessary to develop strategies of cancer-specific screening and prevention care in patients with type 2 diabetes for men and women. For future
studies, what factors are associated with increased or decreased risks of site-specific cancer in patients with type 2 diabetes needs further investigation. In term of public health implication, we estimate that number of incident cases of liver, colorectal, pancreatic, and kidney cancers for men that can be attributable to type 2 diabetes by 272, 50, 194, 28, and 8, respectively; number of incident cases of liver, colorectal, breast, pancreatic, bladder, and kidney cancers for women by 105, 21, 50, 11, 4, and 5, respectively, based on number of incident cases from Taiwan National Registry for Cancer in 2010 and SIRs and PAFs of type 2 diabetes indicated in our study. These findings provide information for health policy makers on evaluation of the cost-effectiveness of cancer screening and prevention program.

5. In discussion, page 12, section 2, the authors explained the possible situation for the inconsistency results analyzed from the Registry for Catastrophic Illness database “because catastrophic illness status is not compulsory”. But, in clinical practice these days, the cancer patients will get the catastrophic application form when he or she was diagnosed with catastrophic disease. And nurses or administrators will help them to apply the catastrophic status to free from copayment to NHI. Most of cancer patients get the catastrophic card. Also, the Taiwan Cancer Registry used the Catastrophic Illness database to double check the cancer patients. The result from Catastrophic Illness database was authentic.

Reply: Thank you for your comments. We have followed your suggestion to make revision. The revised sentence is underlined and shown below.

Our sensitivity analysis showed that estimated SIRs of many major cancers were similar to those from the analysis, in which cancer cases identified in 1999 were excluded as well as cancer cases obtained from Registry for Catastrophic Illness database, except for stomach cancer. These consistent findings showed that the results of our study were robust. For several cancers with lower incidence rates, such as nasopharyngeal, small intestine, and brain cancers, SIR estimates based on Registry for Catastrophic Illness database are not consistent with those in the other two methods. The possible explanation for this inconsistency is that our sample size is not large enough for such low incidence rates that SIR estimates are not reliable enough. To be conservative, we only discussed cancer types with SIRs that are consistent with main and sensitivity analyses.

Minor Essential Revisions
1. Authors used “Chinese” and “Taiwanese” to describe study subjects. All of the insured in NHIRD (National Health Insurance Research Database) were Taiwan
people. If “Chinese” and “Taiwanese” used together, that will confuse audience. Please correct all the “Chinese” to “patients in Taiwan” or “population in Taiwan”.

Reply: Thank you for your suggestion. We have followed your suggestion by correct all the “Chinese” to “Taiwan”.

2. Due to Human subject protection statement, all of the studies use NHI database must receive approval from institutional review board (IRB), please provide clarifying information.

Reply:
[1] In response to your question regarding ethical review, we have provided a letter from the Research Ethics Committee about our ethical review board deemed that formal consent was not required for our study.

[2] In the end of the second paragraph of Method section, we have added one sentence to address the ethical issue. The added sentence is as follows: …Our study using these data was exempted from institutional review board approval of Public Health, Social and Behavioral Science Committee Research Ethics Committee, China Medical University and Hospital.
3. In methodology, Page 6, section 2, the authors identify lots of site-specific cancers but without showing ICD-9-CM code. Please show the ICD-9-CM codes that used to identify the outcome cancer you observed in the manuscript or in Table 2.

Reply: We have followed your suggestion by adding the ICD-9-CM and A-codes in the method section. The added sentences are as follows:

*Cancer cases were identified from ambulatory and inpatient care claims of NHIRD from 1999 to 2007. Incidence rates of lung cancer (ICD-9 code 162; A-code A101), liver cancer (ICD-9 codes 155; A-code A095), colorectal cancer (ICD-9 codes 153, 154; A-code A093, A094), breast cancer (ICD-9 code 174; A-code*
gastric cancer (ICD-9 code 151; A-code A091), oral cancer (ICD-9 codes 140 to 141, 143 to 146, 148 to 149; A-code A08), prostate cancer (ICD-9 code 185; A-code A124), esophageal cancer (ICD-9 code 150; A-code A090), pancreatic cancer (ICD-9 code 157; A-code A096), cervical cancer (ICD-9 codes 179, 180; A-code A120), nasopharyngeal cancer (ICD-9 code 147; A-code A08-01), small intestine, including duodenum cancer (ICD-9 code 152; A-code A092), gallbladder cancer (ICD-9 code 156; A-code A099-02), retroperitoneum and peritoneum cancers (ICD-9 code 158; A-code A099), laryngeal cancer (ICD-9 code 161; A-code A100), respiratory and intrathoratic organ cancers (ICD-9 codes 160, 163 to 165; A-code A109), bone cancer (ICD-9 code 170; A-code A110), connective and other soft tissue cancers (ICD-9 code 171; A-code A114), skin cancer (ICD-9 code 172; A-code A111), placenta cancer (ICD-9 code 181; A-code A121), endometrial cancer (ICD-9 code 182; A-code A122-01), ovarian cancer (ICD-9 code 183; A-code A123), testicular cancer (ICD-9 code 186; A-code A125), penile cancer (ICD-9 code 187; A-code A129-02), bladder cancer (ICD-9 code 188; A-code A126), kidney cancer (ICD-9 code 189; A-code A129-04), brain cancer (ICD-9 code 191; A-code A130), Hodgkin’s disease (ICD-9 code 201; A-code A140), leukemia (ICD-9 codes 204 to 208; A-code A141), and carcinoma in situ (ICD-9 codes 230 to 234; A-code A16) were estimated for type 2 diabetes group and general population.

4. Please check carefully for grammar, syntax, and usage. Some examples stated below:
   a. Page 14, this study was supported ….., this sentence was not complete, please delete.
      
      Reply: Thank you for pointing out our mistake. I have deleted the incomplete sentence.

   b. In Table 1, column 2 showed “general population” and column 4 showed “no diabetes”, please be consistent.
      
      Reply: Thank you for pointing out our inconsistency. I have changed ‘no diabetes’ as ‘general population’.

   c. In Table 1, column 1, age “ $90\leq$ ” please be consistent with insurance premium “ $\geq 19200$ ”, change $\leq$ to $\geq$.
      
      Reply: Thank you for pointing out our mistake. I have made correction.

   d. In Table 2, annotation (b) and (c) were not note in the table.
      
      Reply: Thank you for pointing out our mistake. Annotation (b) and (c) have been added in the headers of columns 5 and 6.
e. In Table 2, column 3 and 5, there was an annotation “#” next to the incidence density, but without explain below the table.

**Reply:** Thank you for pointing out our mistake. We have added “#: per 1000 person-years;” in the last line of Table 2.

f. The number of study subject in Figure 1 and Page 7 was inconsistent. Page 7, line 9, with type 2 diabetes aged <20 years (N=19986). In Figure 1, the number was 19098.

**Reply:** Thank you for pointing out our mistake. We have made correction. Due to excluding individuals with type 1 diabetes from Registry for Catastrophic Illness database, the numbers are different. After revision, the numbers in Figure 1 are consistent with those in manuscript.

g. The number of subjects were eligible on the left side in Figure 1 was wrong, the 478,910 should be 478,022.

**Reply:** Thank you for pointing out our mistake. We have made correction. Due to excluding individuals with type 1 diabetes from Registry for Catastrophic Illness database, the numbers are different. We have double checked those numbers, they should be correct now.

h. The number of subjects without diabetes were eligible on the right side in Figure 1 was wrong, the 16,535,274 should be 9,478,609, please correct it.

**Reply:** Thank you for pointing out our mistake. We have made correction. Due to excluding individuals with type 1 diabetes from Registry for Catastrophic Illness database, the numbers are different. We have double checked those numbers, they should be correct now.

i. In Figure 2, the bar charts of “pancreas in woman” and “bladder in woman” were absent. Please provide these 2 bars.

**Reply:** Thank you for pointing out our mistake. We have added the bar charts of “pancreas in woman” and “bladder in woman” in Figure 2.

5. Finally, in Figure 1, the included participants were 474686. It was not consistent with the number of patients with type2 diabetes in 1997-1998 minus subjects that was excluded or without information for gender and residential area. That might due to the overlapping of those excluding criteria, please clarify.

**Reply:** Thank you for pointing out our mistake. We have made correction. Due to excluding individuals with type 1 diabetes from Registry for Catastrophic Illness database, the numbers are different. We have double checked those numbers, they should be correct now.
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.

Reviewer's report
Title: Cancer risks among patients with type 2 diabetes: A 10-year follow-up study of a nationwide population-based cohort in Taiwan
Version: 1 Date: 7 March 2014
Reviewer: Fu-Min Fang
Reviewers report:
This manuscript was well organized and addressed.
Some minor critiques:
1. In page 7, paragraph 2. The sentence "We initially excluded subjects with any cancer type at baseline (N = 135,672) from the 633,680 patients with type 2 diabetes aged < 20 years (N = 19,986)". Should it be aged > 20 years?
Reply: Thank you for pointing out our mistake. We have made correction. The sentences were revised as follows:

....We initially excluded subjects with type 1 diabetes (N = 3,750), any cancer type (N = 135,060), and those aged <20 years (N=17,679) at baseline from 633,680 patients with type 2 diabetes aged ≥ 20 years.....

2. It seems not matched for the number in the figure with those in the text.
Reply: Thank you for pointing out our mistake. We have made correction. Due to excluding individuals with type 1 diabetes from Registry for Catastrophic Illness database, the numbers are different. We have double checked those numbers, they should be correct now.

3. Could the variable of Insurance premium and Urbanization degree shown in the Table 1 also be adjusted in the Poisson regression?
Reply: We have followed your suggestion by including insurance premium and urbanization degree of area registered for National Health Insurance program in multiple Poisson regression models.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests