PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence and relative risk for developing cancers in women with gestational diabetes mellitus: a nationwide cohort study in Taiwan
AUTHORS	Peng, Yun-Shing; Lin, Jr-Rung; Cheng, Bi-Hua; Ho, Cheng; Lin, Yung-Hsiang; Shen, Chien-Hen; Tsai, Ming-Hung

VERSION 1 – REVIEW

REVIEWER	Chuanbo Xie Sun Yat-sen University Cancer Center
REVIEW RETURNED	04-Jul-2018

GENERAL COMMENTS	In this study, the authors systematically examined the associations between gestational diabetes mellitus (GDM) and risk of various cancers. They found that GDM is a risk factor for cancers of nasopharynx, kidney, lung and bronchus, breast, and thyroid gland. This is an interesting epidemiological study based on a large and a representative sample of pregnant women lived in Taiwan. Below are my comments. Major comments: (1)The association between GDM and breast cancer is still inclusive and controversial. According to the estrogen receptor status, breast cancer can be divided into ER negative and ER positive types. According to the study by Park et al (Park YM, Gestational diabetes mellitus may be associated with increased risk of breast cancer. 2017), the effect of GDM on breast cancer might differ across the types of breast tumors. Therefore, it will be helpful for the authors to run subgroup analysis based on the ER status of the breast cancer. (2)It is also important to examine the effects of GDM on cancers by the numbers of GDM pregnancies, as previous studies showed that having GDM two or more times but not ever having GDM was associated with increased risk of breast cancer. It's possible that this phenomenon also applicable to other cancers. (3)In the inclusion and exclusion section, the authors stated that they excluded 422,568 patients with missing data. The women with missing data accounted for about 1/3 of the whole pregnant women in NHIRD. If the missing related to GDM or cancer diagnosis, selection bias is very likely to occur. The authors should compare the characteristics between the excluded pregnant women and the pregnant women included into analysis. The results of this comparison could be added as a supplemental table

	to help judging the potential selection bias. (4)The explanation for the association between GDM and NPC is weak. If the authors want to use the EBV reactivation to explain the association between GDM and NPC, more direct evidence related about pre-diabetic chronic hyperinsulinemia or insulin resistance and EBV reactivation was needed. From my point of view, focusing on the hyperinsulinemia related anti-apoptotic effects are more plausible. The association might be also explained by the shared environment or genetic factors? (5)The survival curves in Figure 2 is hard to read. Please use high resolution picture to replace. (6)Did the authors consider the potential confounding effects of primiparity or multiparity? Minor comments (1)In Page 1 Lines 54-55, the spelling “Taoyoun” should be “Taoyuan”? (2)In Page 2 Lines 54-55, the full name of T2DM should be type 2 diabetes mellitus. (3)In Page 4 Lines 37-38, add a comma between 31 and 2013. (4)In Page 10 Lines 11-12, the date was between Jan 1, 2002 and Dec 31, 2012 but in Figure 1 the date was 2000 to 2013. Could the authors explain the discrepancy? (5)In table 1, the percentage is a little bit confusing. For variable “age at pregnancy” the percentages were proportion but for variable “Comorbidity” the percentages were incidence. Please use footnotes to clarify. The full name of GDM should be added below table 1. (6)In table 2, how the authors adjust age when examine the association between age and cancer risk? Similar question for comorbidity. (7)In table 3, please replace “、” with “,” and add the full name of each abbreviation below the table. The confounding variables which were adjusted should be clarified below the table.

REVIEWER	Yong-Moon Park National Institute of Environmental Health Sciences, USA
REVIEW RETURNED	12-Aug-2018

GENERAL COMMENTS	In this study, the authors report that women with gestational diabetes mellitus (GDM) is associated with developing cancers using the nationwide health insurance research database in Taiwan. Although there are some limitations, this paper is overall well written and contributes to the field. I have a few suggestions to improve the manuscript. - The “non-exposed” or “comparison” group is appropriate rather than “control” group in the prospective cohort study setting. - Confounders should be associated with both GDM and risk of cancers. The authors should provide a brief rationale that each of co-morbidities can be a confounder. - Whether Cox proportional hazard assumption was satisfied or not should be mentioned. - P12: Relative risk should be hazard ratio. - In Table 3, cancer outcomes with a few number of events (e.g. <10) should be discouraged to present the association results.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Chuanbo Xie
Institution and Country: Sun Yat-sen University Cancer Center
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
In this study, the authors systematically examined the associations between gestational diabetes mellitus (GDM) and risk of various cancers. They found that GDM is a risk factor for cancers of nasopharynx, kidney, lung and bronchus, breast, and thyroid gland. This is an interesting epidemiological study based on a large and a representative sample of pregnant women lived in Taiwan. Below are my comments.

Response: We would like to thank Dr. Xie for valuable comments. We made point-by-point responses as follows.

Major comments:

Q1. The association between GDM and breast cancer is still inclusive and controversial. According to the estrogen receptor status, breast cancer can be divided into ER negative and ER positive types. According to the study by Park et al (Park YM, Gestational diabetes mellitus may be associated with increased risk of breast cancer. 2017), the effect of GDM on breast cancer might differ across the types of breast tumors. Therefore, it will be helpful for the authors to run subgroup analysis based on the ER status of the breast cancer.

Response: It is true that previous investigations on the association between GDM and breast cancer have produced mixed results. In our study, we have observed a clear association between breast cancer and GDM. It is also true that Dr. Park has shown a differential impact of GDM on subtypes of breast cancer stratified by ER status (1). However, our study was based on NHIRD (National Health Insurance Research Database), which lacks information about ER status. This limitation has been stated in the revised manuscript. Nevertheless, we agree that it is an interesting topic to pursue in the future.

Q2. It is also important to examine the effects of GDM on cancers by the numbers of GDM pregnancies, as previous studies showed that having GDM two or more times but not ever having GDM was associated with increased risk of breast cancer. It's possible that this phenomenon also applicable to other cancers.

Response: The major aim of our study was to determine the risk of developing cancers in women with prior GDM. Indeed, Dr. Park has shown an association between multiple GDM pregnancy and increased risk of breast cancer (1). It is plausible that repeated episodes of GDM may augment the mitogenic and anti-apoptotic effects of hyperinsulinemia and contribute to carcinogenesis in susceptible tissues other than breast. However, in our protocol, we analyzed the data within the time frame between 2002 and 2012. The impact of multiple GDM pregnancy may not be appropriately addressed if other episodes of GDM occurred beyond the time frame. We agree it is an important issue to pursue. However, it needs to be addressed in the future in an appropriate investigational setting. We have stated this limitation in the session of Discussion of revised manuscript.

Q3. In the inclusion and exclusion section, the authors stated that they excluded 422,568 patients with missing data. The women with missing data accounted for about 1/3 of the whole pregnant women in NHIRD. If the missing related to GDM or cancer diagnosis, selection bias is very likely to occur. The authors should compare the characteristics between the excluded pregnant women and the pregnant women included into analysis. The results of this comparison could be added as a supplemental table to help judging the potential selection bias.

Response: We would like to apologize for the typo and the misunderstanding incurred. In our protocol, subjects were traced back 2 years before delivery to identify if there was a past history of malignancy or diabetes and assess baseline comorbidities which may confound the association between GDM and malignancy. Also in our protocol, participants had to be followed for at least 1 year after delivery. In this context, women with admission for delivery between Jan 1, 2002 and Dec 31, 2012 were further analyzed to avoid pre-existing malignancy and ensure adequate period of time in follow-up. In other words, we excluded those women who were admitted for delivery between Jan 1, 2000 and Dec 31, 2001 and those who were delivered between Jan 1, 2013 and Dec 31, 2013 (n=422,568). We have corrected our manuscript accordingly (Session of Material and Methods and Figure 1).

Q4. The explanation for the association between GDM and NPC is weak. If the authors want to use the EBV reactivation to explain the association between GDM and NPC, more direct evidence related about pre-diabetic chronic hyperinsulinemia or insulin resistance and EBV reactivation was needed. From my point of view, focusing on the hyperinsulinemia related anti-apoptotic effects are more plausible. The association might be also explained by the shared environment or genetic factors?

Response: The association between GDM and NPC is a novel finding in our study. Although our explanation for the association between GDM and NPC through EBV infection remains speculative, EBV has been considered as the primary etiologic agent in the pathogenesis of NPC (2). Interestingly, other etiological factor like smoking has been shown to reactivate EBV infection and be involved in the pathogenesis of NPC (3, 4). Indeed, the risk of NPC in GDM appears to be due to an interplay among several etiological factors including EBV infection, hyperinsulinemia, environmental factors, smoking, genetic predisposition. We agree that hyperinsulinemia may play an important role in the pathophysiological mechanisms in GDM women with NPC and other cancers as well. In fact, relevant discussion has been addressed in the session of Discussion. We also agree that shared risk factors for GDM and NPC and genetic susceptibility can be other explanations. Revisions have been made in the session of Discussion of revised manuscript.

Q5. The survival curves in Figure 2 is hard to read. Please use high resolution picture to replace

Response: We have improved the resolution of Figure 2.

Q6. Did the authors consider the potential confounding effects of primiparity or multiparity?

Response: We agree that it is interesting to look at the impact of parity. However, this issue may not be properly addressed in this study. The reasons are as follows: We analyzed the data within the time frame between 2002 and 2012. The influence of parity may not be appropriately addressed if other episodes of pregnancy occurred beyond the time frame. We have stated this limitation in the session of Discussion of revised manuscript.

Minor comments

Q1. In Page 1 Lines 54-55, the spelling “Taoyoun” should be “Taoyuan”?

Response: We have made correction.

Q2. In Page 2 Lines 54-55, the full name of T2DM should be type 2 diabetes mellitus

Response: We have made corrections.

Q3. In Page 4 Lines 37-38, add a comma between 31 and 2013.

Response: We have made correction.

Q4. In Page 10 Lines 11-12, the date was between Jan 1, 2002 and Dec 31, 2012 but in Figure 1 the date was 2000 to 2013. Could the authors explain the discrepancy?

Response: In our protocol, subjects were traced back 2 years before delivery to identify if there was a past history of malignancy or diabetes and assess baseline comorbidities which may confound the association between GDM and malignancy. Also in our protocol, participants had to be followed for at least 1 year after delivery. In this context, women with admission for delivery between Jan 1, 2002 and Dec 31, 2012 were further analyzed to avoid pre-existing malignancy and ensure adequate period of time in follow-up. In other words, we excluded those women who were admitted for delivery between Jan 1, 2000 and Dec 31, 2001 and those who were delivered between Jan 1, 2013 and Dec 31, 2013. Clarifications have been made in the revised manuscript.

Q5. In table 1, the percentage is a little bit confusing. For variable “age at pregnancy” the percentages were proportion but for variable “Comorbidity” the percentages were incidence. Please use footnotes to clarify. The full name of GDM should be added below table 1.

Response: "Age at pregnancy, n (%)"and "Comorbidity, n (%)” the percentages were both proportions. We have corrected footnotes.

Q6. In table 2, how the authors adjust age when examine the association between age and cancer risk? Similar question for comorbidity.

Response: We have deleted typos.

Q7. In table 3, please replace “、” with “,” and add the full name of each abbreviation below the table. The confounding variables which were adjusted should be clarified below the table.

Response: We have made corrections in the revised manuscript.

Reviewer: 2
Reviewer Name: Yong-Moon Park
Institution and Country: National Institute of Environmental Health Sciences, USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
In this study, the authors report that women with gestational diabetes mellitus (GDM) is associated with developing cancers using the nationwide health insurance research database in Taiwan. Although there are some limitations, this paper is overall well written and contributes to the field. I have a few suggestions to improve the manuscript.

Response: We would like to thank Dr. Park for valuable comments. We made point-by-point responses as follows. .

Q1. The “non-exposed” or “comparison” group is appropriate rather than “control” group in the prospective cohort study setting.

Response: We have replaced ‘ control group” with “non-exposed group” in the revised manuscript.

Q2. Confounders should be associated with both GDM and risk of cancers. The authors should provide a brief rationale that each of co-morbidities can be a confounder.

Response: We have added references (5-14) which address the associations among co-morbidities, GDM and risk of cancers, justifying that all the co-morbidities can be confounders. Revisions have been made in the revised manuscript.

Q3. Whether Cox proportional hazard assumption was satisfied or not should be mentioned.

Response: The predictors satisfied the proportional hazard assumption in Cox model. This point has been mentioned in the session of Statistical analysis of revised manuscript.

Q4. P12: Relative risk should be hazard ratio.

Response: We have replaced “relative risk” with “hazard ratio” in the revised manuscript.

Q5. In Table 3, cancer outcomes with a few number of events (e.g. <10) should be discouraged to present the association results.

Response: We agree that cancer outcomes of too few events should be discouraged to present. However, one of our major aims was to determine the risk of developing site-specific cancers in women with prior GDM. To maintain our framework and reconcile our approach with Dr. Park’s suggestion, we chose not to specify the association results of those cancer outcomes of less than 5 events. In this regard, we also combine sub-classification of bone cancer and sarcoma in the classification of bone and connective tissue cancers.

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VERSION 2 – REVIEW

REVIEWER	Chuanbo Xie Sun Yat-sen University Cancer Center, China
REVIEW RETURNED	15-Oct-2018

GENERAL COMMENTS	The quality of this manuscript has been improved after revision. I have no further comments. Congratulations!

REVIEWER	Yong-Moon Park Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, USA
REVIEW RETURNED	30-Oct-2018

GENERAL COMMENTS	Thank you for your responses.