Reviewer's report

Title: Human insulin increases breast cancer risk in Taiwanese women with type 2 diabetes

Version: 4
Date: 22 April 2015
Reviewer: Juhua Luo

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Comments to the authors

Major compulsory revisions:
1. P5, lines 116-118, it is stated that “those who had ever been prescribed with insulin before entry date were defined as ever-users; and never-users were defined as those who had never been prescribed with insulin before entry date”. It is unclear the insulin here refers to human insulin or any types of insulin. If it refers to human insulin, where other types of insulin go? Regardless of how to define the ever-users, the reference group (never-users) are a mixture of women. It includes women with any oral anti-diabetic agents, may also include women with any types of insulin other than human insulin. It would be more informative to separate the exposure more than only two categories (ever or never use). In addition, for the ever-users, it may be also helpful to separate it into human insulin alone, or human insulin use plus others.

2. P5, line 120-121. It is unclear how the authors define and calculate the other exposures. Such as, time since starting insulin in months, how the authors know when women initiated insulin based on claims data, especially for those women who might be newly diagnosed with diabetes before 1996. In addition, how to calculate cumulative duration of therapy in months? What therapy here refers to, any anti-diabetic treatment or only human insulin? Similar question for cumulative dose.

3. P6, line 123-135, Why chose these comorbidities as potential confounders? Are all of them risk factors for breast cancer? How highly these comorbidities are related to each other?

4. In addition, in the discussion, the authors should further discuss how lack of important confounders, such as obesity, reproductive factors and hormone uses may influence the findings.

Minor Essential revisions:
1. Background: the rationale for this study needs to be strengthened.
2. P5, line 101 - It is unclear why selected entry date on 1 January 2004.
3. P5, line 112-113 – explain why excluded patients who had been prescribed with insulin only once.
4. P6, line 137-140. It states that “Chi-square test was used to compare … ”, I do not see any results match this analysis.
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