Reviewer's report

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

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Reviewer: Chi-Chen Hong

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This is a well-conducted study investigating the relationship between human insulin use and breast cancer risk among women with type 2 diabetes. A number of studies to date have focused on the relationship between insulin use and cancer risk in general, but studies of sufficient sample size are also needed to examine associations with risk of specific cancers in which insulin is postulated to play an etiologic role. Strengths of the study include the use of a population-based national health insurance database, and a large sample size of ~480,000 women with type 2 diabetes, which included almost 60,000 human insulin users. The study also was able to adjust for the effect of other medications used to treat diabetes and health outcomes related to diabetes severity. There were, however, several concerns, particularly with clarification of analytic approaches. Individual comments are provided below.

Major Compulsory Revisions

1. It is not clear why the authors chose not to look at the effects of insulin glargine and other analogs at the same time as human insulin to determine if glargine has a similar or greater effect on breast cancer risk compared to human insulin in an Asian population. If glargine were included as an exposure of interest it would help justify why the investigators chose to exclude patients with a diagnosis of breast cancer before 2004 (n=11,969).

2. The rationale for setting the entry date at 1 January 2004 should be provided given that data is available from 1996.

3. In the study, only women who had ever been prescribed with insulin before the entry date were defined as “ever users” and “never users” were defined as those who had never been prescribed insulin before entry date. To reduce misclassification of exposure, however, it would be better if insulin exposure post entry date, but prior to breast cancer diagnosis, were also considered in the analyses.

4. The analytic approach needs to be clarified. Cox proportional hazards with left truncation (delayed entry) might be more appropriate if data on time of diagnosis was determined retrospectively. It appears that many patients were not enrolled in the study (based on entry date) until months or years after their initial use of insulin. Since women who were diagnosed with breast cancer prior to 2004 were excluded, the women remaining at the time of entry may be “healthier” and
different from women who were prescribed insulin post entry date. Again, handling of women prescribed insulin post entry date needs to be clarified.

5. How were medications that were included as covariates in the analysis coded? Were these variables just entered as dichotomous yes/no variables or did they incorporate a measure of cumulative dose. Accounting for dose might be particularly important for medications that are hypothesized to reduce breast cancer risk such as metformin, statins, and ACE inhibitors, and may be a better approach than using a dichotomous variable given that human insulin when considered as dichotomous variable (yes/no) was not found to be associated with breast cancer risk. Examining potential effect modification by medications postulated to reduce breast cancer risk, such as metformin, may also be informative.

6. To reduce the amount of residual confounding potentially introduced by varying diabetes duration, it would be better if diabetes duration were entered as a continuous variable (possibly requiring transformation to normalized the data). Presently, as shown in Table 1, the majority of women included in the cohort have had diabetes longer than 5 years, particularly among ever users of insulin (88%).

Discretionary Revisions

7. Similar to point 6 above, potential residual confounding by age can also be minimized by modeling the variable as a continuous measure.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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

Declaration of competing interests:

I declare that I have no competing interests.