Reviewer's report

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

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Reviewer: Jack Youngren

Reviewer's report:

Dr. Tseng presents data concerning the insulin exposure of Taiwanese women with type 2 diabetes and subsequent risk of breast cancer.

The manuscript is concise and well written. The data are clean. However, the enterprise is ultimately limited by the strong association between the length and severity of the underlying disease (type 2 diabetes) and the requirement for exogenous insulin. The fact that every single comorbidity is increased in the ever-treated group suggests the significant toll that prolonged, severe diabetes takes on human health.

Major Compulsory Revisions:

1. This work represents the logical and appropriate interrogation of a rich dataset. However, this approach is also ultimately limited by inherent bias across the two groups that can be directly influencing breast cancer risk independent of exogenous insulin administration. As reported by Carstensen et al. (reference #21 in the manuscript), the cancer incidence increases with the presence of type 2 diabetes without insulin administration. It is easy to imagine that disease severity is a prime driver of risk, and the limitations of the present dataset involve the segregation of advanced v.s more benign disease neatly across the never-user vs. ever-user groups.

Central to the robustness of the data is the author's assertion that “we included most of the important comorbidities and medications that may be related to the exposure to human insulin as potential cofounders”. However, rather than the subject characteristics/medications/comorbidities that would be present at different frequencies across groups, severe diabetes is an underlying trait that specifically divides the two groups and will be innately intertwined with the administration of exogenous insulin. While the tertile analysis of dosage/exposure helps break this one to one relationship, both of these factors serve as specific surrogates for prolonged, severe type 2 diabetes. The author needs to address this specific limitation in the discussion, and, if possible more fully control for this cofounding issue statistically, with a discussion the approach taken and the effect on the results.

Minor Compulsory Revisions:

I would suggest, given the significant dose/exposure thresholds reported in the
data, that the authors change their wording of the findings from phrases in the
away from phrases such as “human insulin increases breast cancer risk” (title) or
“a significantly higher risk of breast cancer associated with the use of human insulin” (conclusion, line 233) to include a qualifier on the dose. Thus, the title
would be more accurate if it read “Prolonged use of human insulin increases…”

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.