Author's response to reviews

Title: A Novel Method for Studying the Temporal Relationship between Type 2 Diabetes Mellitus and Cancer using the Electronic Medical Record

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Arlene Pura
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Manuscript ID 9077846210323094: A novel method for studying the temporal relationship between type 2 diabetes mellitus and cancer using the electronic medical record

Authors: Adedayo A Onitilo, Rachel V Stankowski, Richard L Berg, Jessica M Engel, Gail M Williams and Suhail A Doi

Dear Ms. Pura:
Thank you for providing us with additional comments/suggestions from the reviewers. Our responses to these additional comments are below.

Reviewers’ Comments
Reviewer 1: Minor Essential Revision:
In the abstract, should this be "70%"? "Stringent requirements for laboratory values resulted in a decrease in the number of potential subjects by nearly 70."

Authors’ response: Yes, the Reviewer is correct, it should be 70%. We appreciate the Reviewer bringing this mistake to our attention. The oversight has been corrected.

Reviewer 2: Revisions to the manuscript are thorough and have generally strengthened it; however two compulsory revisions remain unaddressed.

Major Compulsory Revisions:
1. The first and most important is the lack of data on validation of the Type 2 diabetes algorithm. If the recently published algorithm referenced is the algorithm used, then the utility of the manuscript is significantly lowered as it becomes a description of a cohort detected. If it is not the algorithm used, the validation data for the diabetes detection algorithm employed in this work, specifically sensitivity, specificity, and positive and negative predictive value are strongly recommended

Authors’ response: Data regarding validation of the algorithm for differentiating between subjects with and without diabetes and for determining date of diabetes onset has been added to the results section, as requested.

Page 10: “In our final validation sample, we manually abstracted evidence of diabetes in 70 patient charts. If a diabetes diagnosis was present (N = 50), we verified the date with laboratory values for HbA1c and glucose, office notes, and medications listed. Prior records were checked to ensure that the diagnosis had not been mentioned previously, but not coded. In patients in whom no diagnosis of diabetes was evident (N = 20), we verified the absence of any diabetes diagnoses on problem lists, verified that there were no high HbA1c or glucose levels, verified that no diabetes medications were listed, and that diabetes was not mentioned in the notes for a recent office visit or history and physical. In this validation sample, the observed predictive value for control subjects (NPV) was 100% (20/20). It is important to note that cases can always become controls and this was observed in one subject who developed diabetes in 2011, 7 years after the assigned reference date in 2004, but this has no bearing on
algorithm validity. The predictive value for case status (PPV) was 96% (48/50), with two subjects appearing to be incorrectly identified. However, upon arbitration, one of the two subjects was found to have a diagnosis of diabetes during the study period, increasing the positive predictive value to 98%. Overall sensitivity of the algorithm for detecting type II diabetes was 96% (95% CI 86.3 – 99.4%) and overall specificity was 95% (95% CI 75.1 – 99.2%). The date of diabetes onset determined by manual chart review was within 6 months of the study-assigned date of onset in over 70% of subjects with diabetes.”

A note about the validation process was also added to the discussion on Page 13: “Validation of a similar Marshfield Clinic EMR-based algorithm for identification of patients with and without type 2 diabetes showed a 99% predictive value for type 2 cases and 98% for type 2 controls [30]. Results were similar using the algorithm described here with a 98% predictive value for type 2 cases and 100% for type 2 controls.”

2. The second is the continued overstatement of the ability of the algorithm to allow for detection of the hyperinsulinemic pre-diabetes onset stage. No data on insulin or c-peptide are given and there is again no validation that one is able to detect this stage. While it may be that the algorithm can facilitate detection of that stage, in the absence of data demonstrating that is speculation that goes in the discussion section, not as a primary conclusion about the work.

Authors’ response: We agree with the reviewer and recognize that the terminology we are using to define the period of time before clinical onset of diabetes is incorrect given the medical condition of pre-diabetes that can be defined by laboratory values. Because laboratory values indicative of hyperinsulinemia were not captured in the present study, we have removed the pre-diabetes terminology from the remainder of the manuscript where appropriate.

In the Conclusion section of the abstract, Page 2: “The cohort described here will be useful for the examination of the temporal relationship between diabetes and cancer and is unique in that it allows for determination of the date of diabetes onset with reasonable accuracy.”

In the Introduction section, Page 4: “The purpose of this paper is to describe a unique method for determining date of onset of type 2 diabetes, even when onset of disease occurs prior to clinical recognition.”

Minor Compulsory Revisions:

Methods:
1) Authors state they have removed the measure of “glucose control” to predict A1C based on glycemic values; however reference to it remains in the manuscript in the last paragraph of the results sections.

Authors’ response: We apologize that this was not deleted after the first round of revisions as was our intent. The paragraph in question has been deleted from the current version of the manuscript.

We again thank the reviewers for their insightful comments and have attempted to address their concerns as thoroughly as possible. We hope that our manuscript is now acceptable for publication, and we look forward to hearing from you.

Sincerely,

Adedayo A. Onitilo, MD, MSCR, FACP