Reviewer's report

Title: Gestational diabetes as a risk factor for pancreatic cancer: A prospective cohort study

Version: 1 Date: 9 January 2007

Reviewer: Dominique S Michaud

Reviewer's report:

General

This study examines the relation between gestational diabetes and subsequent risk of pancreatic cancer in a cohort of women who gave birth in 1964-76, in Jerusalem. This the first study on pancreatic cancer to address this particular relationship which may be of significance as diabetes types II and elevated glucose levels have been previously linked to pancreatic cancer risk. Women with a history of gestational diabetes had a statistically significant 7-fold increase in risk of pancreatic cancer. The major study limitations include a small number of cases (54 pancreatic cancers; 5 with gestational diabetes), and lack of data on other potential risk factors for pancreatic cancer, including smoking, family history of pancreatic cancer, and BMI. The authors argue that given the strength of the observed association, confounding by these risk factors (which individually have smaller effects) is unlikely. However, given that the confidence interval includes 2.8, this possibility cannot be completely ruled out (authors need to make that clear). Despite this, and other limitations that the authors should be able to address (see comments below), the study is unique as it is prospective in design, and raises the important possibility that gestational diabetes may contribute to pancreatic carcinogenesis.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Methods. The study description is confusing. Given that the Perinatal Study was of birth between 1964-67, it is unclear from where the "subset" of mothers came from who were interviewed between 1974-1976? Please clarify. Also it is not clear where the 84,781 number comes from; perhaps it would be easier to provide exclusions of women not eligible due to limited data availability?

How did 84,781 get down to 40,898? What happened to the other half? Why did they not get traced? How did these women differ from those who were traced?

How many women died? Could the cause of death be obtained for those women? (to confirm cancer registry cases or verify if any cases were missed).

Page 5. Was a covariate included for time period (calendar year)? This should be included in the models given that the baseline recruitment spans twelve years. Was the assumption of proportionality over time tested and does it hold?

It is not clear how gestational diabetes "exposure" was handled for women who entered the study during their first pregnancy, but only developed gestational diabetes during their second or third pregnancy? Please clarify how these time-varying exposures were handled.

Page 6. It is unclear what the relative risk of 0.2 is for? Please clarify.

Tables 2 and 3. Person-years should be presented, instead of numbers of individuals.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Page 5. The Cox proportional hazard models estimate the relative risk of pancreatic cancer in women with gestational diabetes – compared to women without gestational diabetes, as this is a relative risk.

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Discretionary Revisions (which the author can choose to ignore)
Background. Given the evidence, as presented by the authors, the “longstanding debate” is no longer really a debate; both “views” are likely to be true. In other words, diabetes type II is likely to be both a cause and a consequence of this cancer—one doesn’t exclude the other.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

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