Author’s response to reviews

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

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To: BMC Cancer Editor
From: Mary C Perrin, DrPH, MPH
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Comments of Feng Wang

1. The conversion (p.4, lines 9-15) of diabetic and pre-diabetic diagnoses to insulin dependent diabetes and gestational diabetes mellitus (GDM) needs more evidence-based support. The following statement: "In that era, pregnant women were screened for glycosuria...glucose tolerance test" sounds that all subjects involved in this study may not necessarily be handled by the screening strategy.

We mentioned this as one of the limitations of the study. SH an author on this paper has managed the Jerusalem Perinatal Study almost since it inception over 40 years ago. As stated in the text, all subjects were screened for glycosuria at each antenatal visit but only those who tested positive for glycosuria were then administered a glucose tolerance test. SH knows that at the time most women with a diagnosis of diabetes were being treated with insulin and those with abnormal glucose tolerance tests were diagnosed with pre-diabetes. Throughout the study period, the prevalence of Type 2 diabetes in this age group was extremely rare.

Otherwise, the glycouric and GTT results, if any, may be included to rationalize the conversion of diabetic diagnoses.

We do not have the actual results of the glycosuria or the glucose tolerance tests.

Incidentally, 13 patients excluded for having both GDM and insulin dependent diabetes (p.6, line 12) were conceivably diagnosed as being both pre-diabetic and diabetic. This is confusing and has to be clarified.

Women could have had more than one live birth in 1964 - 1976. The 13 women who were diagnosed with both gestational diabetes and insulin dependent diabetes were classified as such in different pregnancies. The sentence in the text now reads "...an additional 13 women (none with pancreas cancer) were diagnosed with gestational diabetes mellitus in one pregnancy and Type 1 diabetes mellitus in another pregnancy during the study period." We excluded them because of the inconsistency between the diagnoses.

2. As the authors have discussed in this paper, a link between gestational diabetes and pancreatic cancer may come from hyperglycaemia that lingers on following GDM. However, it is also possible that the 137 insulin-dependent diabetic women who were presumably put in the non-GDM control group had even more severe hyperglycaemia than GDM subjects. The authors may acknowledge this possibility.
We have amended the text accordingly to include this in the discussion.

3. Insulin dependent diabetes mellitus (IDDM)/non-insulin dependent diabetes mellitus (NIDDM) and type-1/type-2 diabetes are two sets of definitions for two types of diabetes. The authors used the former set in Methods and the latter in Background (e.g. Type II) and Discussion (e.g. type 2). Be consistent with one (and within one, e.g. type 2 or Type II).

We have amended the text accordingly.

4. The authors have not discussed possible involvement of changed circulating insulin levels associated hyperglycemia in pathogenesis of pancreatic cancer. This topic is optional for a similar study. As no pancreatic cancer was seen in subjects with IDDM (featuring beta-cell failure), the topic is more relevant in this study.

A paragraph was added on the mechanism by which hyperinsulemia might act to increase the risk of pancreatic cancer.

5. The sentence starting on Page 5, line 13 is unclear and grammatically demanding. The last line on Page 10 has a misprinting.

The sentence is clear to someone with a biostatistical background and is correct as written. Was unable to find the misprint on page 10.

Comments of Dominique Michaud

1. 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).

We have drawn attention to this in the text.

2. 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?

The Perinatal study was of births between 1964-1976. 1964-1967 was a typo. Thank you.

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?

As stated in the text there were 92,408 births in 1964-1976. Only 84,781 of those births occurred in hospitals in which maternal and obstetric conditions were recorded.

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?

Most women had more than one birth during the study period. As stated in the text, 84, 781 refers to the number of births delivered in hospitals during the study period in which maternal and obstetric conditions were recorded. 40,898 refers to the number of mothers. We discuss the differences between traced and untraced women in the section "Numbers and Exclusions" in the manuscript.

3. 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).

This is beyond the scope of this paper. The Israel Cancer Registry performs active surveillance of death certificate data for deaths from any cancer.

4. 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?

The reviewer is correctly states that you should consider the question of time period in a study in which the baseline measure occurs over a long period of time. We of course did do that, however the inclusion of the
term for year of first observed birth did not effect the estimate nor did it predict risk of pancreatic cancer. Thus, we did not include this term in the final model.

We did test the assumption of proportionality over time using a log negative log graph and the assumption was met.

We have included these discussions in the Methods and Results section.

5. 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.

As stated in the text, gestational diabetes "exposure" was defined as a diagnosis of gestational diabetes in any observed birth regardless of whether it was a first, second or third birth in the study. Of course we considered handling the exposure as a time-dependent variable but did not as the first case of pancreatic cancer occurred long after exposure (see text). We respectfully remind the reviewer that Cox does not begin calculating before the first case of the outcome variable is observed.

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

We have amended the sentence to read "Among women who were successfully traced, the incidence of pancreatic cancer was not significantly related to hospital of birth."

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

We believe it is inappropriate to use person-years when performing a Cox proportional hazards analysis.

9. 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.

We have amended the text.