Author's response to reviews

Title: Cancer incidence in registered nurses potentially exposed to antineoplastic drugs and adverse pregnancy outcome incidence in their offspring

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Author's response to reviews: see over
To the Editor:

Many thanks for the reviewers’ constructive comments about our paper. We have made several revisions to the original manuscript in light of the reviewers’ suggestions and believe the paper to be much stronger as a result. Our responses to the specific concerns and suggestions are detailed below.

Reviewer: Wouter Fransman

Reviewer’s report: This is a well written and clearly understandable manuscript which describes the results of a survey to study the cancer incidence and adverse pregnancy outcomes of registered nurses potentially exposure to antineoplastic drugs. I do, however, think that there are major flaws in the exposure assessment procedures. This makes the exposure assessment very imprecise, which together with the lack of adjustment for potential confounding factors makes your results very hard to believe.

Thank you for the request for more detail about the exposure assessment. We appreciate the opportunity to describe it at greater length; the specific revisions are outlined below.

Major compulsory revisions:

1. Methods, page 4: It was assumed that antineoplastic drugs are mainly used in oncology departments. It is well known that antineoplastic drugs are used in many other departments outside the oncology department. Were these other departments excluded from the reference group of RNs?

   Thank you for pointing out that our description of the exposure assessment was not very clear. First, we have clarified that two different methods of exposure assessment were employed. Method 1 was restricted to oncology departments and the provincial cancer agency, and method 2, the survey-based exposure assessment, included any nursing department where antineoplastic agents were reported to be used (including oncology and the provincial cancer agency). We have removed the following phrase near the beginning of the exposure assessment section to try to mitigate any confusion: “Given that exposure to antineoplastic drugs occurred primarily within the oncology field.”

   We also have changed the beginning of the Results to highlight the difference in the numbers assessed as exposed via the two methods: “Of the 56,213 female RNs who had a work history between 1974 and 2000, 905 (1.6%) RNs were identified as ever having been exposed to antineoplastic drugs according to method 1, based on their employment in oncology nursing units or at a cancer center, and 7,635 (13.6%) of the 56,213 RNs were assigned at least 15 days
weighted duration of exposure to antineoplastic drugs according to method 2, based on information acquired through the hospital-based survey.

For Method 1, the unexposed reference group comprised any nurses not defined as exposed by that method, so yes it includes nurses in departments considered exposed in Method 2. Thus, if the exposures outside oncology units are important, Method 1 would provide a conservative (lower) estimate of effect. Alternatively, if those in oncology units are truly exposed and those in the other departments less so, then exposures assessed by Method 1 will be more specific, and therefore should result in stronger risk estimates. The latter was the case for both cancer and congenital anomalies. We believe that it is useful to be able to compare the results of the two assessment approaches given that each has strengths and limitations.

2. Methods, page 5: I really doubt the level of accuracy of the classification of exposure in unlikely, possible or probable. Who performed this classification? Was this the interviewed senior departmental representative or the investigator? How can one accurately retrospectively estimate the average number of patients per week, the type of ppe used and the use of any special handling procedures up to 30 years back in time? I think this exposure classification is very arbitrary and will distort the results of your research.

The exposure assessment approach used in Method 2 was not clearly explained in the initial submission. The assessment relied on answers to the survey questions for each department, nursing position, and year in an algorithm designed by the study hygiene team, based on their review of the literature about factors that are related to antineoplastic drug exposures. This section has been rewritten as follows to help clarify what information came from the survey responses and how that information was used in the algorithm.

“A second method of ascertaining exposure to antineoplastic drugs (method 2) was based on telephone interviews with pharmacists and with senior nurses in nursing departments from all 94 general hospitals (357 departments) and 19 diagnostic and treatment centers in BC. Pharmacists were asked about the periods of time antineoplastic drugs were used at the facility and about the frequency of use of up to 74 individual antineoplastic drugs. Senior nurses were asked whether any nurses in the department had administered or mixed antineoplastic drugs or cared for patients who received the drugs. Positive responses were followed by further questions about the probability of exposure (no exposure, possible exposure, or probable exposure) by nursing position (supervisor/ coordinator, clinical nurse specialist, head nurse/unit manager, charge nurse, staff nurse) and year. For all positions and years with possible and probable exposures, these senior nurses were asked whether specific personal protective equipment was used, and whether waste disposal, spill, and patient care guidelines were in place and followed. Finally, if nurses in the department were involved in the mixing of antineoplastic drugs, the location of the procedure was queried (e.g., bio-safety cabinet, laminar flow hood, desk/nursing station, or medication room). Exposure to antineoplastic drugs was then classified as no, unlikely, possible, or probable using an algorithm created by the study hygiene team. It used the available published evidence about factors influencing exposures, applied to the following departmental survey data elements for each nursing position and year: probability that the job involved antineoplastic drug administration; the number of times per week the drugs were administered; whether the mixing of antineoplastic drugs was performed; whether gloves and long-sleeved gowns were used; and
whether special handling procedures were followed for waste disposal, patient handling, and spill cleanup.”

Although we agree that exposure assessment almost 30 years back in time is not easy, we interviewed senior nurses who had worked in the department over the full period. Although we requested information on an annual basis, many things stayed relatively stable throughout the period (e.g., nursing positions involved in administering the drugs), and other elements were marked by single changes in policy (e.g., elimination of manual mixing of the drugs or adoption of personal protective equipment) at a point in time, making the reporting less daunting than might be imagined.

One of the benefits of the approach taken was that the nurses interviewed were asked about the department as a whole, so exposures were assessed independently of outcomes and were not limited to oncology units – the concern raised in comment #1.

3. Methods, page 6: How were the exponential weightings derived (0, 0.04, 0.16, and 0.64)? Were they based on exposure measurement results?

Thank you for raising this issue – it helped us identify errors/omissions in the reporting, both of the weightings used and the resulting weighted durations in Tables 3 and 5. The rationale for the weighting scheme is now explained in the methods as follows:

“A weighted exposure duration was calculated for each nurse’s working history during the cohort period. To acknowledge the skewed distributions of exposures of nurses to antineoplastic agents [17], and to ensure that only those with reasonable possibilities of exposure were attributed exposure-time, a multiplicative weighting (0.00, 0.0625, 0.25, and 1) was assigned to the exposure probabilities from the algorithm (none, unlikely, possible, and probable exposure, respectively). In addition, part-time employment was assigned a weight of 0.5 and full-time employment a weight of 1.0. Weighted exposure durations were cumulated over the person’s full job history, as follows:” The new reference [Fransman, 2007] was inserted as a source for the exposure weighting.

4. The results were not adjusted for possible confounding factors (not for cancers and not for adverse pregnancy outcomes), which probably would have great impact on the results. The reported elevated risks of breast and rectal cancer could well have been caused by many other risk factors or exposures which occur in or outside a hospital.

Adjustment was made for the important variables sex, year of birth, and maternal age for the birth outcomes analysis, and age and calendar period for the cancer incidence analysis. We lacked information on smoking and drinking behavior and other potential covariates, however all comparisons were made within the nurses cohort, which should have diminished differential impacts of these unavailable risk factors. There is evidence that smoking among US nurses has dramatically declined over the period of the study, and it is possible that this decline is correlated with exposures, which might affect the results. We have attempted to clarify this with the following change in the discussion:
“As is common in historical cohort studies, we had no information about potential confounding factors related to lifestyle; however, all comparisons were within the nursing profession, a narrow, well educated, socioeconomic stratum. Nurses have been documented to have healthier habits than the population as a whole, but there have been temporal patterns, for example strong declines in smoking rates among US nurses in the last 30 years (33% smokers in 1976 vs. 8.4% in 2002/2003 [29]). There were also temporal patterns in antineoplastic drug use in the British Columbia hospitals during the study period (e.g., hand mixing of the drugs was completed in 45% of the facilities in the 1970s and 1980s, but only 8% in the 1990s and later). If smoking and antineoplastic drug exposures were correlated and both related to the outcomes of interest, there could be uncontrolled confounding in the study results. In a recent study of 1,147 live births among nurses, controlling for parity, smoking, alcohol, coffee, multivitamin, and folic acid intake did not materially change effect estimates for congenital anomalies [15].” A new reference [Sarna et al., 2008] on smoking rates within the nursing profession was inserted.

Minor essential revisions:

5. Introduction, Page 3: The authors state that little research has been conducted on exposure to antineoplastic drugs of nurses. I disagree with this. There have been numerous papers published in the peer reviewed literature that have clearly studied occupational exposure to antineoplastic drugs.

   We concur, and have removed the statement implying there is little published on exposures to antineoplastic drugs.

6. Methods, page 5: What were these special handling procedures, which are mentioned in the exposure assessment classification?

   We hope this is now clarified in the revised section quoted above. The actual phrasing in the survey was, “What special procedures were followed?” The response categories were: waste disposal; patient handling, spill cleanup; and other.
Reviewer: Kristina Kjaerheim
Reviewer's report: Overall, this is a well designed, well performed and well written paper. I have some comments that I believe the authors should consider, however.

Minor Essential Revisions:
First, I would suggest changing the title to “Cancer incidence and adverse pregnancy outcome in registered nurses potentially exposed to antineoplastic drugs”. The adverse pregnancy outcome is in the nurses, and not in the offspring. The ‘pregnancy outcome of the offspring’ would be the grandchildren of the nurses (!).

You are correct. We have replaced the previous title with this one. Thank you.

The study population should be described more precisely, perhaps in a table. As it is, some details are given under Methods, some under Results. I will mention some of the mistakes and/or logical inconsistencies. In the Results section it is stated that 22,491 of the nurses gave birth during the period 1986-2000, surprisingly “constituting the RN offspring cohort”. This seems to imply that each nurse giving birth had only one child, which is not likely to be correct. Number of nurses giving birth (=mothers) cannot be the same as number of children.

We have included a clearer statement about the offspring cohort at the beginning of the results section:

“Of the 56,213 female RNs who had a work history between 1974 and 2000, 905 (1.6%) RNs were identified as ever having been exposed to antineoplastic drugs according to method 1, based on their employment in oncology nursing units or at a cancer center, and 7,635 (13.6%) of the 56,213 RNs were assigned at least 15 days weighted duration of exposure to antineoplastic drugs according to method 2, based on information acquired through the hospital-based survey.

During the 1986-2000 time period, 12,741 RNs gave birth to 22,491 live and singleton offspring, which defined the offspring cohort (see Table 1). Sixty nine RNs were identified as having worked in oncology for the time period it was available as a field code (1996-2000), of which 20 (29.0%) were also identified as having worked in a cancer center during pregnancy. A total of 141 were identified as having worked in a cancer center during pregnancy.”

We have also included data on the total # of births (and total # of including still births), the # of multiple births, the # of of still births, the frequency of sibling counts, and the # of mothers in a new table (Table 1). A statement on the exclusion of still births and twins/triplets was inserted: “Cases were limited to live, singleton offspring to prevent potential confounding from the adverse effects associated with still births and multiple-birth pregnancies.”

Information on number of mothers, pregnancies, children (singleton, siblings, multiple births, etc) should be given.
Period of inclusion should be given for all cohorts and sub-cohorts, and period of follow-up for all analyses. On page 9, line 2, is stated that stillbirth (n=115) was an infrequent outcome for the offspring cohort, but according to page 8, line 11, the offspring cohort comprises only live births (n=22,491). Moreover, according to the last line on page 3 the number of stillbirths was 120.

This is an important observation and we have now included a descriptive table with this information, described above. There were 115 still births. The size of the cohort, when including the still births (excluding multiple births and missing / incomplete congenital anomaly diagnosis data), is 22,606. Included in the results section quoted above and in the title of the tables are the periods of follow-up for each of the given analyses.

Regarding censoring, it seems sufficient to state that those who left Canada (and were no longer at risk) were censored (page3, under Study population). The sentence “Cancer causes that were incident within a 10-year lag following determined exposure were categorized by cancer site..” is unclear. Was cancer occurring 10 years after first exposure (or last exposure?) included?? I cannot find any statements on how person years were counted in this situation. As mentioned previously, a more precise description of follow-up period in the different analyses would solve this problem.

The calculation of estimates of exposure for the cancer incidence analysis excluded exposures that occurred within 10 years prior to cancer diagnosis. This has been reworded to: “The exposure period was lagged 10 years prior to the incident cancer cases to allow for a minimum latency period of 10 years.”

Reference number 10 seems to be incorrectly used for “A questionnaire-based study…. ” mentioned on page 11, line 12. Regarding the analyses, two questions should be considered: to do analyses based on the first birth only, to avoid ties between siblings, and to consider including stillbirths in the analyses of the offspring cohort. If this is not done, it must be discussed.

Reference “10” was a mistype; it should be “20.” Thank you for your attention to detail, it is much appreciated. The analysis of firstborn offspring resulted in much lower power to evaluate the risk, although the trends were similar (see tables with results at end of this document). Because exposures during each pregnancy can differ, we chose to include all births. The firstborns may not have necessarily been the first birth for each mother because the cohort consisted of live births born only in the province of BC and between 1986 and 2000 (the mothers may have delivered babies in other locations and before 1986). Still births were not included in the analysis of risks of congenital anomalies because of the greater probability of incomplete ascertainment both of still births and congenital anomalies in still births.

The discrepant results for the different types of exposure indicators (employment in oncology department or cancer center vs the probability of exposure) are difficult to understand and deserves some explanation in the Discussion. For uterus cancer, for instance, employment in oncology/cancer center gives an RR of 2.58 based on 4 cases, while possible or probable exposure to antineoplastic drugs gives an RR of 0.95 based on 16 cases. Is this due to the exposure variables themselves or to different periods of follow-up?
Both assessment methods are imperfect measures of exposure to antineoplastics drugs and each has its individual strengths. The survey exposure-based assessment had broader inclusion criteria in the exposed group (i.e., non-oncology employment) and therefore more cases, allowing greater stability of risk estimates. The years of employment in oncology or a cancer agency was a more specific measure, but excluded other nurses potentially exposed to antineoplastic drugs. This is outlined in the discussion session. “The exposure assessment methods used in the study were crude and may have resulted in misclassification of exposure. For example, most nurses working in oncology departments were outside of the cancer centers and were not identifiable in the registry, prior to 1996. The survey identified relevant departments in general hospitals and treatment centers that administered antineoplastic drugs and ascribed individual nurses therein with a probability of exposure. Within these departments, some nurses ascribed a probability of exposure may not have been exposed and other departments may have been missed due to poor information recall. These limitations to the assessment of exposure may affect their accuracy and could possibly result in an underestimation of the risks associated with exposure to antineoplastic drugs or distort the shape of the dose-response relationship.”

Discretionary Revisions:

In Abstract, line 2, I suggest to change ‘retrospective cohort study’ to ‘historical prospective cohort study’, to underline the fact that exposure has been assessed independently from outcome measures. This is an important strength of the study.

Thank you for suggesting this. The sentence has been rephrased accordingly and the following was included in the discussion: “Furthermore, the historical prospective design of the study meant that exposure variables were assessed independently from health outcomes.”

In Background, line 3, change ‘secondary malignancies’ to ‘second malignancies’.

This has been done.

In Results, page 8, line 9, it is stated that three cases of leukemia were observed. This is not correct, 61 cases of leukemia occurred, three of them in exposed nurses.

This was reworded to: “Three cases of leukemia were observed among those in the top exposure categories.”

Table headings should be more instructive, including information on N, follow-up period, etc.

The table headings and footnotes were expanded. For example, the title for Table 2 is now: “Relative risk of selected cancer incidence of female registered nurses according to cumulative years worked in oncology or a cancer center (method 1), 1996-2000 (N = 56,213)\(^{1,2,3}\)”

Based on the above comments I would advice the journal to accept the paper after minor essential revisions.
I find the paper being of clear interest to those in the same research field.

The quality of the written English is acceptable, although some clarifications are needed, as pointed out above.

I do not believe it to be essential that a statistician reviews the manuscript.

I declare that I have no competing interests.
Table 4: Risk of congenital anomalies among the firstborn offspring of RNs employed in oncology nursing units or a cancer center during pregnancy (method 1), 1996-2000 (N = 12,741)\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Congenital anomaly category (ICD9 code)</th>
<th>Employed</th>
<th>cases</th>
<th>OR\textsuperscript{2}</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CA (740-759)</td>
<td>never</td>
<td>794</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ever</td>
<td>8</td>
<td>1.15</td>
<td>(0.56-2.39)</td>
</tr>
<tr>
<td>Eye (743)</td>
<td>never</td>
<td>49</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ever</td>
<td>1</td>
<td>2.13</td>
<td>(0.29-15.71)</td>
</tr>
<tr>
<td>Circulatory system (747)</td>
<td>none</td>
<td>78</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ever</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal system (754-756)</td>
<td>never</td>
<td>276</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ever</td>
<td>3</td>
<td>1.20</td>
<td>(0.38-3.82)</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Congenital anomaly types with an incidence of less than 3 cases were excluded.
\textsuperscript{2} N for ever employed in oncology or cancer center = 190.
\textsuperscript{2} Adjusted for sex, year of birth, and age of mother.
Table 5: Risk of congenital anomalies among the firstborn offspring of RNs exposed to antineoplastic drugs (method 2), 1986-2000 (N = 12,741)\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Congenital Anomaly category (ICD9 code)</th>
<th>Probability of exposure</th>
<th>Exposure during first trimester of pregnancy</th>
<th>Exposure during 10 years preceding pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cases</td>
<td>OR\textsuperscript{3}</td>
<td>CI (95%)</td>
</tr>
<tr>
<td>All congenital anomalies (740-759)</td>
<td>766</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Nervous (740-742)</td>
<td>36</td>
<td>0.90</td>
<td>(0.63-1.27)</td>
</tr>
<tr>
<td>Eye (743)</td>
<td>48</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Ear, face, neck (744)</td>
<td>58</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Heart (745-746)</td>
<td>74</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Circulatory system (747)</td>
<td>74</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Cleft palate / lip (749)</td>
<td>15</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Alimentary system (750)</td>
<td>51</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Other digestive sys. (751)</td>
<td>19</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Genitals (752)</td>
<td>123</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Urinary (753)</td>
<td>58</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Musculoskeletal sys. (754-756)</td>
<td>268</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Integument (228, 757)</td>
<td>50</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Chromosomal anomalies. (758)</td>
<td>38</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Multiple anomalies (759.7-759.8)</td>
<td>8</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Congenital anomalies with an incidence of less than 3 cases were excluded.
\textsuperscript{2} N for possible or probable antineoplastic drug exposure during first trimester of pregnancy = 1,062; during 10 years preceding pregnancy = 2,650.
\textsuperscript{3} Adjusted for sex, year of birth, and age of mother.