Reviewer’s report

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

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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 (!).

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.

Information on number of mothers, pregnancies, children (singletons, 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.

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.

Reference number 10 seems to be incorrectly used for “A questionnaire-based study….” mentioned on page 11, line12.
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.

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 uterine 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?

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.

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

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.

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

• 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.