Reviewer's report

Title: Influence of family size and birth order on risk of cancer: a population-based study

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Reviewer: Yani Lu

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Summary:

Bevier et al. examined the association between family size, birth order and risk of cancer using the Swedish Family-Cancer Database. The authors proposed to check if the effects of family size and birth order on the risk of cancer were carried on from childhood to adulthood. They divided the age at diagnosis in two groups, below and over age 50 years. The authors observed that increasing birth order decrease the risk of endometrial, testicular, skin, thyroid and connective tissue cancers and melanoma, but increase the risk of lung, male and female genital cancers; moreover, family size was also associated with several types of cancers. The authors concluded that the effect of birth order decreases from childhood to adulthood for lung and endometrial cancer.

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

1. The authors proposed to check whether the effects of family size and birth order on the risk of cancer are carried on from childhood to adulthood. However, the authors divided the age at diagnosis into groups of below and over age 50. Both groups of cancer were adult-onset. If all the cancers before age 50 in this dataset were diagnosed after age 18, then, in fact, the authors checked the effects of family size and birth order on cancers of early age adult-onset (before age 50) and late age adult-onset (after age 50). The authors did not provide the basic information of age distribution; it is hard for readers to judge what age group the data can address.

2. The authors did not state any limitation of this study. Obviously, several limitations exist for this study. For example, the authors reported the association between birth order and lung cancer. However, smoking history was not taken into account in the analysis. Besides the adverse effect of active smoking, passive smoking has been found to increase the risk of lung cancer. The increased risk for increasing birth order may due to higher level of passive smoking during childhood (older brother or sister may smoke) and active smoking later in life.

3. Hemminki et al examined the same topic using the Family-Cancer Database 10 years ago. In that study, the authors found an increased risk for breast cancer by birth order and a decreased risk for melanoma by birth order. In this recent study, the authors did not find any association for breast cancer. The authors
need to address the potential reasons for the inconsistent results.

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

1. The authors grouped subjects into two groups: age at diagnosis below and over age 50 years old. Where are those subjects whose ages at diagnosis are equal to 50 years old?

2. In the first paragraph of introduction, the authors mentioned that higher parental age at conception has not been reported to be a risk factor. In fact, higher paternal age has been linked to prostate cancer, non-Hodgkin lymphoma and breast cancer; higher maternal age also has been linked to breast cancer.

3. In the methods part, the authors mentioned that individuals born after 1932 have been registered. The cancer registry covers all cancers from 1961 to 2006. What about subjects who were diagnosed between years 1932 to 1961. How did the authors treat these people? Were they excluded from the study?

4. In the methods part, “The family size (grouped 1, 2, 3-4, 5-17) is defined as the number of children per mother. What about those who had divorce?

5. In the methods part, “Individuals were categorized according to their age at diagnosis of cancer below age 50 years and above age 50 to distinguish between the effect of birth order and family size in childhood and adulthood.” The cut at age 50 is too high to address the different effect of exposures in childhood and adulthood. It may be more appropriate to check their effect on early age adult-onset cancer and late age adult-onset cancer.

6. In the methods part of the covariates: please list the detail categories in these variables. For example, “age” means “age at diagnosis” or “age at registry”? What is the age range? What means “period”? Calendar period? What are these 5 groups? What are the 4 groups of region? How socioeconomic status was defined? What are those 6 groups? Is there any subject with unknown values of these categories?

7. In the results part for Table 3: This paragraph is confusing regarding to results for which group of age at diagnosis. Please clarify the age group after describing the relative risk. The authors mentioned that “In a separate analysis for the age at diagnosis, the risk was increased for stomach cancer…….” It seems like that the authors were presenting the results in Table 3. It this is true, it is not appropriate to describe it as “a separate analysis”.

8. In the results part: “The risk for cancer of the thyroid gland was marginally significantly decreased for birth order…….” The authors did not report the results for specific birth order on the risk of other types of cancer. Does that mean the results for other types of cancer are null? Please clarify. Same to the next paragraph on family size, only testicular cancer was mentioned. What about other types of cancer?

9. In the discussion part: the authors drew the conclusion from the results of lung cancer, “The effect of birth order and family size decreased from childhood to adulthood.” However, this conclusion is not appropriate since we don’t know what their effect on cancer in childhood.
10. The results for family size and endometrial cancer (age at diagnosis below 50) is controversy between Table 3 and Figure 2. In figure 2, using family size of 5-17 as reference group, the relative risks for family size of 1, 2, 3-4 are 0.65, 0.64, and 0.72 separately for age at diagnosis below 50 years. In Table 3, using family size of 1 as the reference group, the relative risk was 0.72 (95% CI=0.64-0.81) for age at diagnosis below 50 years. Please check the analysis and corresponding results.

11. Table 3 presented the results for family size; the reference group should “first born child” or “family size of 1”? 

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore):

1. In the methods part for cancer sites grouping: “Cancer sties were grouped by ……” should be edited to emphasize that these are special cancer sites instead of all cancer sites. “Liver” should be “liver and gall bladder”?

2. In Table 3, the RR for Nervous system (age at diagnosis <50 years) is statistically significant (RR=1.16, 95% CI=1.05-1.29), but was not bolded.

3. The first word of the notes for Table 2 and Table 3 should be capitalized.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests