Reviewer's report

Title: Population Attributable Fraction of Modifiable Reproductive Factors for Breast and Ovarian Cancers in Korea

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Reviewer: Susan Jordan

Reviewer's report:

Thank you for asking me to review this interesting paper on the proportion of breast and ovarian cancers in Korea that can be attributed to potentially modifiable reproductive factors. I agree that making some estimation of the number of cases potentially preventable through avoidance to particular exposures is crucial for the development of appropriate public health policies. I have some questions and comments, mainly related to the methods used in the study.

Discretionary revisions

Background:

1. Is there a reason that breast and ovarian cancers were chosen for this analysis? Most of the factors investigated are of relevance to endometrial and cervical cancers as well. Did the authors consider including these cancers in their analyses?

2. Are the increases in incidence and mortality of breast and ovarian cancer age-standardized or are these increases due solely/mostly to the aging of the population?

Methods:

3. Analyses:

a. For many of the exposures included, the literature suggests there is a dose-response association with cancer (e.g. number of children, duration of breast feeding, duration of contraceptive use, etc). It seems that this issue has mostly not been considered in this analysis. Have the authors considered including dose-response effects in the analysis?

b. Was the breast feeding analysis only conducted for parous women? It is difficult to recommend to women that they breast feed (for long durations) if they never have a child.

c. Were the PAFs calculated for specific age groups and summed based on the age-specific prevalences?

4. Sensitivity analyses: given the uncertainty of some of the prevalence estimates (and indeed the RR estimates) had the authors considered conducting some sensitivity analyses around these using plausible estimates from other studies, etc?
Major Compulsory revisions

Methods:

5. Selection of risk factors: Given the key assumption around the calculation of PAFs is that the exposure of interest is causally related to the outcome, selecting risk factors for inclusion in this analysis by a process of backwards stepwise regression using data from one study seems inappropriate. Would it not be better to select particular factors that have been recognized in the broader literature as causal factors for these cancers? (for example, the conclusions from the IARC monographs, which take into consideration of a large body of work from both epidemiological and laboratory studies).

a. I think that it is challenging to argue that pregnancy (is this full-term or any pregnancy, including miscarriages or induced abortions? This should be defined) is a modifiable risk factor, especially given the way this analysis has, in essence, modeled parous versus non-parous. I suspect that relatively few women are childless by choice. Furthermore, age at first birth is something that many women may have relatively little choice about. It would be useful if the authors defined what they mean by ‘pregnancy/age at first birth’ in the methods section as this is does not become clear until the tables are read.

b. The reasons for inclusion or exclusion of particular risk factors are not congruent between the breast cancer and the ovarian cancer analyses. For example, breast feeding is included as never, < 6 months and >6 months for breast cancer, but only as ever/never in the ovarian cancer analyses. My understanding is that risk decreases with increasing duration of breast feeding for both cancers (although the evidence for an association with ovarian cancer is less well established). In addition, oral contraceptive use is included as a risk factor for breast cancer but is not included in the ovarian cancer analysis (which is odd given the profoundly protective association with ovarian cancer). Why was this decision made? I think it could be argued that the use of oral contraceptives is a more modifiable factor than childbirth.

6. Relative risk estimates: is there any evidence that risk factors for breast or ovarian cancer are different in Korean women compared to women from other parts of the world? It would appear not, given that the selected risk factors reflect findings from other international studies. If this is the case, then would it not be better to use relative risk estimates from large pooled or meta-analyses rather than using those derived from a single study or from meta-analysing results of a few selected studies? Quite a few of the RR estimates used do not achieve statistical significance so some might question the causal conclusions that have implicitly been made. I would argue that it is the use of Korean prevalence data (as has been done), rather than relative risk estimates derived from Korean studies, that is the key to making these results applicable to the Korean population.

7. Selection of the duration of the lag period: It would be useful if the reason for selecting a 20 year lag period was explained. I did not fully understand how this lag period was applied and this could also be clarified in the methods. I also think that it is unnecessary to even attempt to estimate prevalence of exposures in
1990 (if that is what has been done) because, for the exposures of interest, it is whether they have ever been experienced at all in a woman’s life that is important (compared to, say, smoking or alcohol consumption where applying a lag would be more important). You are most interested in the lifetime birth/breast feeding/contraceptive experiences of women in the population in 2010 (when the cancers are being diagnosed) so the prevalence of these factors in 2005 is generally much more relevant than in 1990 (and for many this will reflect the same thing – a 60 year old woman surveyed in 2005 who reported having one baby when she was 25 will have reported exactly the same thing in 1990; similarly the tubal ligation she reports in 2005 will be the same one she would have reported in 1990). Further to this, there is good evidence that for some factors it is recency of exposure that is critical. For example, for breast cancer and the oral contraceptive, it is current use that has the strongest association and this tends to wane over time so exposure to the OC in 1990 is probably less relevant. Women whose breast cancer was caused by OC use are likely to have used it in the 5 years prior to diagnosis, not 20 years prior. Similarly the size of association between HRT use and breast cancer tends to wane over time once HRT has ceased.

**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