Author's response to reviews

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

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Author's response to reviews: see over
Thank you very much for your e-mail containing reviews of August 3, 2015. We are pleased to hear that our manuscript “Population Attributable Risks of Modifiable Reproductive Factors for Breast and Ovarian Cancers in Korea (MS: 2059584580158962)” could be accepted for publication if appropriately and extensively revised. We are submitting the revised manuscript, on which we indicated where we made changes in response to suggestions of two reviewers in yellow and a point-by-point response to reviewers’ comments.

I guarantee that this or similar material has not been and will not be submitted by me or my colleagues to any other publication prior to its appearance in the BMC Cancer, and that all of my co-authors have made a substantive and specific intellectual contribution to the article.

We wish to thank you and the reviewers for the valuable comments and helpful
suggestions which contributed significantly to the revision of our manuscript.

With regards,

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Responses to the Reviewers’ Comments

Thank you for the valuable comments.

We have revised the paper in accordance with the reviewers’ comments, and the revisions are summarized below and highlighted in the manuscript.

Reviewer 1

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?

Response:

According to prior studies, in Korea, cervical cancer is associated with sexual behavior (i.e., transmission of human papillomavirus (HPV)) and reproductive factors that affect sexual behavior (e.g., number of children, marriage, and age at menarche). In a study by Shin et al., they estimated that more than 99% of cervical cancer cases in Korea were attributed to HPV [1].

Endometrial cancer is a rare form of cancer in Korea. In 2010, the Korean Central Cancer Registry reported 3,956 cases of cervical cancer, 2,025 cases of ovarian cancer, 1,795 cases of corpus uteri cancer, and 14,544 cases of breast cancer [2]. To our knowledge, there are no published studies reporting an association between reproductive factors and endometrial cancer in Korea. Thus, we were unable to estimate a population attributable
risk (PAR) for endometrial cancer in Korea.

From 2011-2013, we had several discussions with International Agency for Research on Cancer (IARC) investigators on the topic of reproductive factors and their association with cervical and endometrial cancers. They also suggested that we not include these factors in our population attributable risk (PAR) estimates of reproductive factors in Korea.

We previously stated: “overall, 3.2 % of the total cancer cases and 2.2% of total cancer deaths in Korean women in 2010 were attributable to modifiable reproductive factors.”

However, for this calculation, we only used PAR of reproductive factors for breast and ovarian cancers. Although we could not estimate the PAR of endometrial cancer, due to the absence of published epidemiological data, the role of reproductive factors in endometrial cancer cannot be neglected. The reviewer’s concern is correct. Therefore, we removed the sentence regarding PARs of total cancer cases and deaths from the manuscript and only described the PARs of reproductive factors for breast and ovarian cancers.

Reference


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?

**Response:**

In this study, we used age-standardized rates. The increase observed was not solely due to an ageing population. As previously reported [3-5], an increase in breast and ovarian cancer may be due to several factors including changes in reproduction, westernized lifestyle, age of population, and increase in cancer screening.

We described this in the manuscript. Please refer to page 6-7, line 117-124.

**Reference**


**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?

Response:

To our knowledge, there have been no previously published studies representing risk changes in units. The majority of studies have categorized risk changes as ‘ever’ or ‘never’.

Using Seoul Breast Cancer Study (SeBCS) data, we estimated the risk change (in units) associated with breastfeeding (odds ratio [OR] = 0.995, 95% CI, 0.991-0.998) and OC use (OR = 1.001, 95% CI, 0.994-1.007) for risk of breast cancer. Using Ko-EVE data, we also estimated the risk change (in units) associated with number of children (OR = 1.001, 95% CI, 0.991-1.110) for risk of ovarian cancer. The strength in association for risk change was not significant due to the small sample size and insufficient power. Therefore, in our meta-analysis we used categorical variables to show the risk increase by category for dose-response relationships (i.e., ‘age at first birth’ and ‘breastfeeding duration’ for breast cancer risk).

In cases in which the risk change in units was very weak (i.e., OC and HRT use for breast cancer risk; pregnancy and breastfeeding for ovarian cancer risk), we used ‘ever’ and ‘never’ instead.

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.
Response:

Yes, we calculated PARs of breastfeeding only in parous women (97%). You are correct in that breastfeeding needs to be recommended to parous women only.

In addition, tubal ligation for ovarian cancer was only considered for parous women and hormone replacement therapy (HRT) was considered only for post-menopausal women. To clarify, we made changes to the Methods Section and footnote of Table 2. Please refer to the main body of the manuscript. (page 12, line 245-248 and Table 2)

c. Were the PARs calculated for specific age groups and summed based on the age-specific prevalence?

Response:

Yes, right. We estimated prevalence by applying an age-specific prevalence rate by 5-year age categories from the KNHANES 2005 or the Ko-EVE studies to the female populations in 2010 and summed up the totals to obtain standardized prevalence rates. Please refer to the main body of the manuscript. (page 10, line 203-206)

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.?

Response:

Previous studies regarding PARs have applied various methods for sensitivity analysis, such as applying prevalence in previous years as Li did [29]. In this study, we applied a method previously published by Park et al. [6-8], in which a sensitivity analysis was
performed under alternative scenarios using the lower and upper limits of the 95% confidence intervals (CI) of the relative risk (RR) estimates. In Table 2, we showed both point estimates for the PARs and the estimated numbers of breast cancer cases with 95% CIs.

Reference


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).

Response:

Previous reports have suggested that the incidence and distribution of breast cancer and various lifestyle and/or reproductive factors and their distribution in population differ markedly across ethnic groups [9]; therefore, we considered that identifying risk factors and their strength of association in a Korean population is important to estimate PAR in Korea.

Prior studies focused on breast cancer risk factors in Korea were based on a subset of data from SeBCS. SeBCS was initiated in 1993 and lasted until 2007. In our previous studies, we have identified various risk factors of breast cancer in Korea including early menarche, late menopause, nulliparity, later first full-term pregnancy, family history, postmenopausal obesity, breastfeeding, and OC use [10-15].

For PAR calculations, the OR estimation for the full data set from the SeBCS, not a subset, was needed to get a small range for the 95% confidence interval. Next, we performed a pooled data analysis and selected variables according to the results from the multiple logistic regression. As a result, age at menarche, age at menopause, pregnancy age at first birth, total period of breastfeeding, and OC use were selected as significant reproductive factors. Of them, we chose pregnancy/age at first birth, total period of breastfeeding, and OC use as modifiable reproductive factors. “HRT use” was not a significant variable according to our results. However, we chose to include it since the IARC has reported that HRT is a carcinogenic agent in humans. Although we selected
risk factors for our new analysis, the selected risk factors of breast cancer were the same as those previously recognized as risk factors in Korea.

Holschneider et al. reviewed the literature and proposed family history, genetic mutations, nulliparity, late menopause, and early menarche as risk factors for ovarian cancer. In addition, they suggested that multiparity, oral contraceptive use, and hysterectomy or tubal ligation were protective factors [16]. We selected reproductive factors that have previously been recognized as causal factors. We estimated Korean OR values using our ovarian cancer data from multiple logistic regression models (backward) adjusted for age, education, and alleged risk factors reported in the literature. In this process, family history of breast cancer, family history of ovarian cancer, age at menarche, age at menopause, pregnancy, breastfeeding, tubal ligation, and OC use were significant factors and were chosen. Afterwards, we selected pregnancy, breastfeeding, and tubal ligation, and OC use as modifiable factors.

Please refer to the main body of the manuscript. (page 8-9, line 144-185)

Reference

12. Kim, Y., et al., Dose-dependent protective effect of breast-feeding against breast


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.

Response:

We agreed with the reviewer’s comment that the pregnancy and age at the first full-term pregnancy would be difficult to modify. The variable “pregnancy” represented full-term pregnancy excluding miscarriages and induced abortion. Please refer to the main body of the manuscript. (page 10, line 186-188; page 16, line 331-341)
We included “full-term pregnancy” and “age at first full-term pregnancy” as modifiable variables for the reasons outlined below:

Korea has experienced a steadily declining fertility rate (6.0 births per woman in 1960, 1.08 in 2005, and 1.23 in 2010) due to the implementation of the national birth control program in 1958 to control population growth [30]. Although a decreasing fertility rate has become common worldwide, the rate of reduction has resulted in Korea having one of the lowest fertility rates in the world [30]. To address this concern, the Korean government changed their family planning policy to encourage childbirth by offering incentives in attempts to increase the birth rate across the country. Considering that the PAF can aid policy makers in determining appropriate public health interventions and plans to control the birth rate in Korea, including ‘pregnancy/age at first birth’ as a modifiable factor would be beneficial not only for policymakers in Korea but also for other countries that have family planning policies.

Please refer to the main body of the manuscript (page 9-10, line 186-188.)

Reference


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.

**Response:**

For breast cancer, several previous studies in Korea had been performed; we re-analyzed the full set of data from the SeBCS, and identified the cut-off point of breastfeeding for the Korean population. However, there was only one study regarding risk factors of ovarian cancer in Korea, and this used a small sample size (n = 231). Thus, we were unable to identify proper cut-off points with significance. In addition, for ovarian cancer, we applied ‘never/ever’ for convenience in our meta-analysis. Please refer to the main body of the manuscript (page 18, line 372-375).

We agreed with the reviewers’ comment that oral contraceptives are a more modifiable factor for ovarian cancer and revised this in the new version of the manuscript. In addition, we included OC therapy as a variable for ovarian cancer and truncated the upper limit to 100. The PAR of ovarian cancer was 53.3% (95% CI = 27.9-100%). The changes regarding OC therapy were added to Table 2 and within the main body of the manuscript. Please refer to the main body of the manuscript.

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-analyzing 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.

Response:

Yes. The risk factors appear to be heterogeneous across different ethnic populations. Therefore, we considered that using Korean prevalence data as well as risk estimates in the Korean population was important for estimating PAFs in the Korean population. The performance of the Gail model, a risk appraisal model using multiple risk factors of breast cancer, yields different results for different populations. For example, use of the Gail model in the United States was unable to discriminate breast cancer cases and controls accurately in Korean [Prior study of ours, Ref. 18], Czech, and Spanish populations [17-19]. Although the same risk factors were included, the use of each population’s epidemiological data with their own ORs was better than using the Gail model [17-19]. The reason for this result is likely to be due to the strength of association for each risk factor and its distribution being different, according to each population, suggesting the necessity for identifying risk factors specific to a population.

A second plausible reason for the differences observed among populations is that prior studies on PAR in Korea [6, 7] and other countries [20-24] applied their own relative risk estimates because meta-analysis estimates were found to be heterogeneous across
different populations. Please refer to the main body of the manuscript. (page 17-18, line 365-368).

**Reference**


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.

Response:

We agreed with the reviewer’s comment about lag period. Although several previous studies regarding PARs have suggested there is, approximately, a 20-year induction period, from exposure to risk to cancer development [1, 6-8], studies regarding PARs of reproductive factors often suggested no lag time as previous French [25] or Chinese report [29]. In addition, for OC, the increased breast cancer risk disappears approximately 10 years after cessation of use [26], and cancer risk decreases rapidly after cessation of HRT use. To address this in our revised manuscript, we did not consider the lag period similar to a previously published French report [25] or Chinese report [29] and, instead, we calculated the prevalence, PAR, and number of cases. The modifications were made to our Methods Section. (page 10, line 193-198; page 10, line 203-206)

Reference


7. Park, S., et al., Attributable fraction of alcohol consumption on cancer using population-based nationwide cancer incidence and mortality data in the Republic of


Reviewer 2

Major Compulsory Revisions

1. The authors calculated the PAR using risk estimates summarized from case control studies or cohort studies that examined the associations of reproductive factors with the risk of breast cancer/ovarian cancer, but not with breast cancer deaths/ovarian cancer deaths. Nonetheless, the authors used the PAR to estimate the number of breast cancer
deaths/ovarian cancer deaths. Risk factors for cancer development are not necessarily risk factors for cancer mortality, and the PAR of risk factors for cancer development and cancer mortality might differ. It might be important to include the rationale or justification for this or to briefly discuss these issues. If not, it would be better to exclude the estimated number of deaths and focus on cancer incidence.

Response:

Thank you for your valuable comments. As suggested by the reviewer, PARs of incidence and mortality need to be calculated separately using pooled RRs for cancer development and death. We tried to find relevant studies regarding reproductive factors and breast cancer mortality, but only studies focused on reproductive risk factors and breast cancer incidence have been published. Thus, we excluded the estimated number of deaths in Table 2 and revised the main body of the manuscript focusing, instead, on breast and ovarian cancer incidences. Please refer to the Table 2 and whole manuscript.

2. In addition, the authors said, “overall, 3.2% of the total cancer cases and 2.2% of total cancer deaths in Korean women in 2010 were attributable to modifiable reproductive factors.” However, for this calculation, the authors have only used PAR of reproductive factors for breast cancer/ovarian cancer, not taking into account any PAR of reproductive factors for other cancers. Therefore, this sentence is misleading. In addition, this information appears a bit out of the scope of this manuscript, given that the primary aim of this study is to estimate the PAR for breast/ovarian cancer, but not to estimate the PAR for all cancer.

Response:
We agreed that the PARs of modifiable reproductive factors for breast and ovarian cancer cannot be directly applied for all cancers. In this study, we considered other cancers including endometrial and cervical cancer.

Shin et al. reported that the PAR of cervical cancer due to human papillomavirus is 100% in Korea [1]. However, with regard to endometrial cancer, no prior studies indicated an association of this cancer with reproductive factors. Thus, we could not estimate the RR for Korean-specific endometrial cancers. According to the reviewer’s comment, we removed the sentence regarding PAFs of total cancer cases and deaths from our manuscript. Please refer to the Table 2 and whole manuscript.

Reference


3. The authors calculated summary risk estimates of risk factors for breast cancer by using results from the Korean study only, whereas the authors calculated summary risk estimates of risk factors for ovarian cancer by conducting a meta-analysis of studies not only from Korea but also from the USA, the Netherlands, Sweden, and Norway. It seems the authors primarily aimed to estimate the PAR that is specific to the Korean population, but resorted to this inconsistent method due to the limited numbers of ovarian cancer cases in Korean studies. If this is right, the authors should clarify their primary aim of this study, to justify their inclusion of only Korean studies regarding breast cancer; that
is, the authors should state their primary aim for this study was to calculate the PAR for
cancers of their interest in the Korean population first in the methods section in addition
to the sample size justification that authors included in the method section.
Alternatively, if what the authors wanted to do was to calculate the PAR regardless of
nationality, then summary estimates should be recalculated by including all available
studies of breast cancer in the current literature that meet the inclusion criteria.

Response:

Previous studies investigating PARs using population-specific prevalence and risk
estimates also applied country-specific data. In cases when country-specific data were
sparse, studies used meta-analyses from other countries [1, 27].

For breast cancer, we had a large data set (SeBCS) and other published studies with data
specific for Korea. However, for ovarian cancer we used meta-analyses in addition to the
Ko-EVE data. Prior meta-analyses reported an ovarian cancer risk estimate, which we
used, as the number of ovarian cancer cases from the Ko-EVE study were sparse (n =
231). The modifications were made to our Methods and Discussion Section. Please refer
to the main body of the manuscript. (page 7, line 129-130; page 11, line 211-219; page
17-18, line 365-375)

Reference

1. Shin A, Park S, Shin HR, Park EH, Park SK, Oh JK, Lim MK, Choi BY, Boniol M,
Annals of oncology : official journal of the European Society for Medical Oncology /
ESMO 22 (6):1435-1442.

27. Wang, J.-B., et al., Attributable causes of esophageal cancer incidence and mortality
4. PAR is function between prevalence rates and risk estimates for exposures of interests. Thus, it is critical whether both individual components of PAR are validly estimated. In that regards, there are some concerns about the prevalence rates and risk estimates calculated for the selected risk factors and several things need to be clarified.

a. The authors need to estimate PAR separately for pre- and postmenopausal breast cancer. Risk factors vary and prevalence of HRT use is negligible before menopause. Also, because association of HRT use with breast cancer differs by type of estrogen therapy, estrogen plus progestin or estrogen alone, and prevalence of use of the different types varies, combining all HRT into a single exposure to estimate PAR is not appropriate.

Response:

During the 1990s, HRT was shifted to estrogen plus progesterone formulas because estrogen alone increased the risk of endometrial cancer [25]. Because we did not report a lag period for OC and HRT treatments, these therapies were considered to consist of estrogen plus progesterone.

In addition, HRT therapy was considered only for post-menopausal women (32% in 1990). According to reviewer’s comment, we added in the Method section and Table 2 more detail. Please refer to page 12, line 245-248 and Table 2.

b. It is unclear if risk estimates shown in Appendix 1 are adjusted. Also, some ORs shown do not appear correct. For example, tubal ligation protects against ovarian cancer but the authors report OR for tubal ligation = 5.7
Response:
Thank you for pointing out typo. We correct the typo regarding OR of tubal ligation and reviewed Appendix 1 again.

c. The prevalence of tubal ligation (20%) was estimated from controls in a hospital based case-control study. It is unclear how well this reflects population prevalence

Response:
Although Korea has a nationwide study named “National Survey on Fertility, Family Health & Welfare (NSFFHW)”, conducted by the Korea Institute for Health and Social Welfare, we could not use the prevalence data because the population was limited to married females between 15-44 years of age. Our study had a population with an age range of 20-89 years.

Similar to our results, the NSFFHW reported a prevalence of tubal ligation among married women who were between 15 and 44 years old of 18.3% [28]. Please refer to the main body of the manuscript. (page 17, line 358-363)

Reference
d. To calculate risk estimates for ovarian cancer, the authors said they restricted the study design of previous studies to cohort studies. Please confirm the following: Did the authors use summary estimates only from cohort studies in reference No. 30 (meta-analysis results of tubal ligation with ovarian cancer) or from both cohort studies and case-control studies?

Response:

When combining the results from the meta-analysis on tubal ligation and OC use for ovarian cancer with the Ko-EVE results, the results from both studies (cohort studies and case-control studies) were applied. Please refer to the main body of the manuscript. (page 12, line 233-235)

e. Adding information on SeBCS and Ko-EVE would be helpful, particularly given that breast cancer results are largely driven by SeBCS. Although details are described in previous studies brief information on how data on reproductive factors were collected would be important to include. In addition, it is not clear how the authors calculated associations of reproductive factors with breast cancer in SeBCS and those with ovarian cancer in Ko-EVE. What were the covariates included in the final model? If these risk estimates were not first calculated in this manuscript, but were already published results, the authors should cite that paper, please.

Response:

According to reviewer’s comment, we explained the study design of SeBCS and Ko-EVE
and the process of variable selection included in the final model in the Methods section. Please refer to the main body of the manuscript. (page 8-9, line 144-185)

f. It remains unclear in the text whether the Ko-EVE and SeBCS are a population case-control study or a hospital case-control study. Thus, if any case-control study is a hospital case-control study, it would be important to discuss how the selection of controls or recall bias of those studies might have affected the summary estimates that affect the PAR.

Response:
Both Ko-EVE and SeBCS are community-based case-control studies, with limitations. We clarified this in our Methods Section. Please refer to the main body of the manuscript. (page 8-9, line 144-185)

5. Finally, additional information needs to be clarified so that the process of selecting modifiable risk factors was not subjective. In the methods section, please add briefly how the initial pool of major risk factors was chosen a priori. In addition, what were the p-value criteria for risk factors examined to be remained in the backward regression model?

Response:
According to reviewer’s comment, we explained the process of variable selection included in the final model in the Method section. Please refer to the main body of the manuscript. (page 8-9, line 144-185)
Minor Essential Revisions

1. I suggest the authors change “population attributable factors” to “population attributable risks,” which is more commonly used term in the literature.

Response:

Thank you for your comment about the term. According to reviewer’s comment, we changed “population attributable factors” to “population attributable risks” in the whole manuscript.

2. Line 150: “alleged” risk factors – please change this to “potential risk factors.”

Response:

According to reviewer’s comment, we changed “alleged risk factors” to “potential risk factors” (line 158).

3. In Table 1 and Appendix Table 1, please include the unit (yrs.), and please change -23 to ≤23 for pregnancy categories. Moreover, please change -6months to ≤6 months for total periods of breast feeding. In addition, there are typos in Table 1 and Appendix Table 1: “nullipara” and “para” need to be corrected.

Response:

According to reviewer’s comment, we included the units (yrs) and inequality sign (≥ or ≤) and corrected typo in Table 1 and Appendix Table 1 (nullipara → nulliparous, para → parous).
4. Table 2 is confusing. The authors calculated the PAR first and then multiplied the PAR by the numbers of breast cancer/death or ovarian cancer/death in the National Cancer Center Registry. It would be helpful to include footnotes in Table 2, although the authors described those in the methods section.

Response:

According to reviewer’s comment, we included the way to calculate the attributable number of cases (Attributable number of cases = population attributable risk X numbers of breast or ovarian cancer incidence in the year 2010 from National Cancer Registry) in the footnote.