Reviewer's report

Title: Is Prior Oral Contraceptive Use Associated with Improved Survival in Ovarian Cancer Patients?

Version: 2  Date: 26 March 2015

Reviewer: Patricia Moorman

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Major Compulsory Revisions
1. Lines 66-67 - This statement is contradictory and doesn’t make sense as written “…previous OC use was associated with a lower risk of death within three years of cancer diagnosis (five-year increase in relative risk 0.69…”

2. The description of the previous studies on oral contraceptive use and ovarian cancer mortality needs to make a distinction between the study designs used and hence the interpretation of the findings. For example, Hannaford, et al. and Vessey et al. used a cohort design of OC users and non-users and then looked at the outcome of death from ovarian cancer. In contrast, the Nagle study was a cohort of women with ovarian cancer and looked at the survival experience of cancer patients who were OC users and cancer patients who were OC non-users. In the former study design, the lower ovarian cancer mortality among OC users could reflect both lower incidence of ovarian cancer and improved survival after diagnosis, whereas the latter study design only addresses survival after diagnosis. The statement made in line 75 that these studies (Hannaford, Vessey, Collaborative Group) reported “decreased overall mortality among ovarian cancer patients who had used oral contraceptives prior to their cancer diagnosis” implies the comparison group is ovarian cancer patients who had not used oral contraceptives and does not accurately reflect the study design used. The discussion of the studies of ovarian cancer mortality related to OC use needs to more precisely describe the findings taking into account the different study designs used and acknowledge that the inconsistency in findings between the Nagle study and the other studies could be due to the study designs addressing slightly different research questions. Finally, the Hannaford paper that is referenced (ref 5) addresses ovarian cancer risk, not mortality. The more appropriate reference would be Hannaford’s 2010 BMJ paper “Mortality among contraceptive pill users…”

3. The rationale for censoring follow-up at five years for those with unknown vital status (line 119) needs to be described. If vital status was known at some point beyond 5 years, why would that patient be censored at 5 years?

4. Related to comment 3 above regarding censoring at five years, line 174 describes the number of deaths and recurrences that had occurred to date. Follow-up time for the cohort apparently ranged from 1 to 14 years, yet the survival curves only depict outcomes through 60 months. This needs to be explained.
5. Although the statement in lines 201-202 that the protective association was observed in univariate analysis is true, it is misleading because the univariate analysis does not take into account the obvious confounding by age and possibly other factors such as debulking status and receipt of chemotherapy.

6. Another limitation of the study that should be mentioned is that there apparently was no information regarding what age or how recently OCs were used. If there is in fact an association between OC use and ovarian cancer survival, the timing of OC use would likely have an important impact on the strength of the association.

7. The figure legends report large differences in the number of OC users (793 in Figure 1 and 700 in Figure 2) suggesting that different populations were used in these univariate analyses. An explanation should be included of why some women were excluded from the univariate progression-free survival analyses as compared to the overall survival group.

Minor Essential Revisions

1. References are needed for several statements made in the introduction including line 49 (effect of OCs in BRCA carriers) and lines 49-52 (mechanisms related to continuous ovulation).

2. The statement in lines 52-54 about numbers of ovarian cancer cases and deaths that could be prevented is not accurate – the numbers are not for the US, but for the world.

3. It would be useful to describe the completeness of vital status ascertainment.

4. What was the rationale for using 48 months as the cutpoint for OC use categories?

5. Please clarify if the 656 recurrences include some or all of the deceased patients.

6. Statements such as “the more numerous the DNA mutations, the more aggressive the cancer” need to be supported with appropriate references.

7. The figures should include a legend that indicates that the solid lines are OC users and the dotted lines are OC non-users.

Level of interest: An article of importance in its field

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.