Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer*

Draft review available for public comment from June 25, 2012, through July 23, 2012.

Research Review Citation: Havrilesky LJ, Gierisch JM, Moorman PG, Coeytaux RR, Peragallo Urrutia R, Lowery WJ, Dinan M, McBroom AJ, Wing L, Musty MD, Lallinger KR, Hasselblad V, Sanders GD, Myers ER. Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer. Evidence Report/Technology Assessment No. 212. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-E002-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Abstract	Based upon the overall findings in the conclusions, that there is uncertainty about the probability of a negative impact, I recommend that the order of the sentences be changed. The first sentence makes a statement about risk benefit that may be misleading.	We have revised this text.
Peer Reviewer 3	Executive Summary	Key Question 6, paragraph 1 (ES-19): "for stroke, projected mortality was actually decreased, likely due to a younger age distribution in OC users and subsequent higher post event survival". This casts serious doubt on the models the authors are using to calculate projected mortality – any adequate model will have built in the effect of age on post event survival. The authors need to check on why this is not taken into account in their calculations.	We agree that, ideally, we would have estimates on long-term cause-specific mortality for stroke, MI, PE, and VTE, stratified by age and race/ethnicity. However, the only population-level data we were able to identify for the US is in-hospital mortality, for these events, as described in the Appendix. Because age-specific in-hospital mortality for stroke is lower in younger women, use of OCs, by shifting the incidence to younger ages, results in overall decreased risk of in-hospital death, even with increased incidence. As we discuss, the potential implications for quality-of-life are unclear; we also note that this is one example of a bias in favor of OC use.
Peer Reviewer 3	Executive Summary	Key Question 7, paragraph 3 (ES-20): This is precisely what the Collaborative Group has already done. This should be stated.	We have added a discussion of the potential of pooled analyses such as the Collaborative Group: "Alternatively, pooled analyses of individual data collected across multiple studies offers an opportunity to address some of these shortcomings of reporting, but this approach is still dependent on consistency in how data is collected. Because the number of references is limited in the Executive Summary, we have not specifically cited the Collaborative Group here, but do discuss it more extensively in the revised Section 5.
Peer Reviewer 4	Executive Summary	(ES1) Page 12 Line 21 - define baby boom generation using years.	We have specified the generally acceptable definition of 1946-1964.
Peer Reviewer 4	Executive Summary	(ES2) Page 13 Lines 9 through 11. Unclear what this statement means.	We have deleted this statement.
Peer Reviewer 4	Executive Summary	(ES5) Page 16, Population, KQ3 and 6. Unclear what is meant by "strong family history."	We have clarified to indicate "family history…suggesting increased risk according to current recommendations."
Peer Reviewer 4	Executive Summary	(ES6) Page 17, Publications. Would suggest providing a date instead of "present."	We have revised the text in the Executive Summary and all Methods sections to clarify this inclusion criterion as "published on or after" the dates specified. Search end dates are provided in each Methods section in the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Executive Summary	(ES8 Line 18) "general population of reproductive aged women." Per statement above, would be helpful to provide a more informative definition i.e. age etc.	We have revised the statement to specify ages 15-44.
Peer Reviewer 4	Executive Summary	(ES10-11)Page 22. Table entries seem to be missing magnitude of effect and confidence intervals for some rows: incidence in women with family history and mortality from ovarian cancer.	The categories for which the magnitude of effect and 95% confidence intervals are missing are those for which the data available were not sufficient to perform a meta-analysis. We have added a footnote to the table and referred the reader to Section 2 of the main report.
Peer Reviewer 4	Executive Summary	(ES11) Page 22 line 51 Time since last use was not significantly associated with ovarian cancer." - may be helpful to define direction of expected association i.e. increased risk?? decreased risk??	Our updated analysis did find a significant decrease in protection with increasing time since last use, and we have revised accordingly.
Peer Reviewer 4	Executive Summary	(ES13) Page 24 - Table c. Duration of Use - is an effect measure missing?	The revised table now includes effect measures.
Peer Reviewer 4	Executive Summary	(ES14) Page 25. Table e - ever versus never. Isn't the lower bound 1 so is not significant. Would not include so many sig. digits.	Although not “significant” by traditional methods, a lower bound of 1.0 implies that there is approximately a 97.5% probability that the risk is greater than 1.0. We have restricted effect size values to 2 decimal places throughout the report.
Peer Reviewer 4	Executive Summary	(ES20) Page 31 - lines 17 to 22. These sentences are hard to follow without having read the last section of the report detailing the modeling. Can the authors expand?	We have revised this section to include more detail, in particular pertaining to Figures 51 and 52, which illustrate the expected absolute difference in age-specific incidence attributable to use of OCs.
Peer Reviewer 4	Executive Summary	(ES20) Page 31 - lines 32-33 - unclear how voi addresses limitations of observational studies etc.	This statement has been removed from the Executive Summary.
Peer Reviewer 4	Executive Summary	(ES21) Page 32 lines 24 - "net negative impact on mortality is low: ...did the authors mean morbidity instead? Sentence is somewhat confusing.	We have clarified the statement.
TEP Member 2	Executive Summary	page 23 (ES 12), line 8, I think "estrogen" should be "progestin" here.	We have made the correction.
TEP Member 2	Executive Summary	(ES 16-17) Table G last row is mortality from stroke--not mentioned in text but mentioned for Table H which does not include mortality and mentions 2 studies??	We have revised the table and text for both Tables G and H in the Executive Summary as well as their corresponding tables in the main report.
TEP Member 2	Executive Summary	Text for Table G should mention increasing risk for newer generations of progestin.	We have revised the text as suggested.
TEP Member 2	Executive Summary	Page ES20, line 2, typo: due "to"	We have corrected the text.
TEP Member 4	Executive Summary	The introduction is thorough and provides a basis for the manuscript	Thank you.
TEP Member 4	Executive Summary	The authors used appropriate inclusion/exclusion criteria and justified their approach.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Executive Summary	The search strategy is described in detail, however it is unclear what identified a review as "key" (p. ES4, lines 41-42). It would be useful to add references at this point in the manuscript that identify which reviews were manually searched. I see they are in the body of the paper. If references are not being included in the Executive summary, then this is OK.	Thank you; as noted, references for the manually searched articles are provided in the main body of the report. As the reviewer suggests, this was done to limit the total number of references required in the Executive Summary.
TEP Member 4	Executive Summary	Data extraction and synthesis are well described and appropriate.	Thank you.
TEP Member 4	Executive Summary	Appropriate use of the Methods Guide for evaluating the strength of the body of evidence and applicability.	Thank you.
TEP Member 4	Executive Summary	Outcome measures are well defined and appear appropriate, however on p. 52 where harms are discussed, it seems that pregnancy risks should also be considered as harms even though the focus of this is cancer.	Although we agree that the use of OCs clearly has benefits for reduction of unwanted pregnancies, as well as prevention of complications associated with their use, incorporating pregnancy as an outcome was (a) specifically outside of the scope of the requested review, (b) raises additional modeling issues ranging from how best to incorporate different timing of pregnancy, and (c) would necessitate a direct comparison with other contraceptive methods in terms of contraceptive efficacy and effects on other outcomes. While, ultimately, a comprehensive assessment of the global harms and benefits associated with OCs should incorporate all of these things, our task was to focus specifically on noncontraceptive effects.
TEP Member 4	Executive Summary	The concern about not including the potential benefit of pregnancy prevention remains for this reviewer, it seems that since the initial intention of this drug is pregnancy prevention, it should be included.	Although we agree that the use of OCs clearly has benefits for reduction of unwanted pregnancies, as well as prevention of complications associated with their use, incorporating pregnancy as an outcome was (a) specifically outside of the scope of the requested review, (b) raises additional modeling issues ranging from how best to incorporate different timing of pregnancy, and (c) would necessitate a direct comparison with other contraceptive methods in terms of contraceptive efficacy and effects on other outcomes. While, ultimately, a comprehensive assessment of the global harms and benefits associated with OCs should incorporate all of these things, our task was to focus specifically on noncontraceptive effects.

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TEP Member 4	Executive Summary	The description of the literature searches and the approach to describe the results is clearly stated and is appropriate	Thank you.
TEP Member 4	Executive Summary	(pgES8), lines 53-57 and 3-4--Because the decision for the domains was qualitative, it would be helpful to know if there were set criteria that were used in your discussion. It is difficult to determine how decisions were made.	Set criteria used in assigning ratings to the strength of evidence domains are described in the Methods of the full report (Section 1, Table 3).
TEP Member 4	Executive Summary	(Pg. ES10), line 4, it would be helpful to know why none of the studies met the criteria for inclusion in the meta-analysis (or state these are described in the full manuscript.)	The text has been revised as suggested by adding the following statement: “Criteria for inclusion of studies in the meta-analyses, and reasons for excluding any studies that were not incorporated, are described in the full report.”
TEP Member 4	Executive Summary	(pg. ES10), line 11. Can you change the use of "at best" to something more scientific? This makes your discussion sound like a guess, although it is accurate	We have revised this text.
TEP Member 4	Executive Summary	KQ2 and 3 are well described	Thank you.
TEP Member 4	Executive Summary	(Pg. ES13), line 43, it is not clear what is meant by there was a greater reduction in risk if it was not statistically significant. If it is not significant, then can you appropriately make that statement?	We have revised to indicate that there was a trend, but that it was not statistically significant.
TEP Member 4	Executive Summary	Same comment for ES 18 line 47	We have revised to indicate that there was a trend, but that it was not statistically significant.
TEP Member 4	Executive Summary	For KQ 6,(ES20) there is no table, it would be helpful to see numbers since you are now discussing benefits versus risks. Additionally, lines 13-22, this paragraph is very confusing to follow. Additionally, was there any consideration put to the harms of unwanted pregnancies? It seems that this should be included in the decision analysis as there is a risk of morbidity and mortality associated with unwanted pregnancy. It may be of interest to include analysis comparing those who are nullipara to those who have been pregnant. (I understand the focus is cancer prevention)	We have added figures showing the absolute change in age-specific incidence of the events of interest, and have revised the section for improved clarity. Although we agree that the use of OCs clearly has benefits for reduction of unwanted pregnancies, as well as prevention of complications associated with their use, incorporating pregnancy as an outcome was (a) specifically outside of the scope of the requested review, (b) raises additional modeling issues ranging from how best to incorporate different timing of pregnancy, and (c) would necessitate a direct comparison with other contraceptive methods in terms of contraceptive efficacy and effects on other outcomes. While, ultimately, a comprehensive assessment of the global harms and benefits associated with OCs should incorporate all of these things, our task was to focus specifically on noncontraceptive effects.

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Executive Summary	(ES21)p. 32, line 9, it would be helpful to reference the previous reviews you refer to (same comment as for other requests for references, if they are not to be in the executive summary, OK).	As discussed previously, the number of citations is limited in the Executive Summary; specific relevant reviews are cited in the main body of the text.
TEP Member 4	Executive Summary	(ES21)p. 32, line 11, the use of the word "somewhat" leaves the reader wondering as it is imprecise. Please reword to provide a more detailed description	We have revised the sentence to be more precise.
TEP Member 4	Executive Summary	(ES21)p. 32, line 23. This is the first reference to pregnancy prevention, it seems out of place without discussion or analysis prior to it	We have added a more detailed rationale for the exclusion of pregnancy prevention from consideration to the Scope section earlier in the Executive Summary.
TEP Member 4	Executive Summary	(ES21)p. 32, the paragraph beginning with line 19 seems to start out stating there is an increase in life expectancy and then ends with a discussion about the harms. As a reader, it is difficult to discern the message that is intended as these statements are contradictory	We have revised this section to help distinguish between harms and benefits when considered as cases vs. deaths.
TEP Member 4	Executive Summary	(ES21) p. 32, Line 48 is the first time there is a discussion of US versus OUS studies (or in my reading, I missed this statement), if you are making a point here, then it should be discussed in findings or elsewhere before this point. Your concern about the differences is valid. Additionally, you do conduct analyses in the body of the manuscript, but then do not discuss them in the executive summary	We have added results of sensitivity analyses for US vs non-US studies to the relevant sections of the Executive Summary. Length constraints for the Executive Summary make it difficult to include every finding from the main report in the Executive Summary.
TEP Member 5	Executive Summary	One edit you may want to make in the executive summary is to change the statement about not knowing how long it takes for a cancer to spread from the ovary to an advanced stage. We now believe that most of these cancers start from the fallopian tube (serous) or endometriosis (clear cell/endometrioid), not from the ovary.	We have made the suggested revision in both the Executive Summary and main report in Section 2.
Peer Reviewer 1	Section 1. Introduction/ Methods/ Literature Search Results	Well written, clear, appropriately detailed	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Section 1. Introduction/ Methods/ Literature Search Results	In general the methods are state of the art. I had only a few specific questions: 1) Often times non-English articles still have English abstracts (at least in PubMed), providing some information like sample size and effect size with confidence interval. Even though these articles cannot be checked completely (understandable limitation), providing a summary table of this information from the abstract (to get at the sample size lost and the types of unadjusted effect sizes and consistency with included articles would be reasonable). 2) Why not include observational studies of <100 people? What was the power calculation that justified this for all endpoints (KQs) equally? Presumably a higher number would be needed for deaths or for rarer cancers? 3) In the duration of use meta-analysis with studies of various durations how is censoring due to OC-related, cancer-related, or other cause-related mortality handled? Would this tend to introduce a bias into the duration effect observed?	(1) We agree that limiting the evidence to English-language articles is a limitation of our systematic review. Given our focus on the formulations of OCs readily available and used in the US, we did not feel that this restriction would negatively bias our findings or the applicability of our results. Exploring potential sample size and effect sizes from abstracts in the non-English literature (or translating non-English full-text articles for possible inclusion) would be an interesting analysis but was outside of the current scope and resources. (2) We did globally require >100 patients for an observational study to be included in our analysis. This limit is often used to ensure that the included study was not a pilot study and thereby increasing the likelihood of the methods and data to be high quality. Note that in our review only 2 studies (both assessing acute harms) were excluded specifically based on this sample size criterion. (3) If the cause of death is the same as the incidence being studied (i.e., evaluating ovarian cancer incidence and the cause of death is ovarian cancer-related), then there should not be any bias. If the cause of death is different, then the bias would depend on an unknown correlation. We did not perform any additional sensitivity analyses to explore the direction or impact of such bias.
Peer Reviewer 2	Section 1. Introduction/ Methods/ Literature Search Results	Superb	Thank you.
Peer Reviewer 2	Section 1. Introduction/ Methods/ Literature Search Results	Perfectly described and appropriate - all limitations acknowledged	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Section 1. Introduction/ Methods/ Literature Search Results	Biological Plausibility, paragraph 1 (page 6): “from what would be expected simply on the basis of the number of ovulatory cycles”. The paper referenced in defense of this statement failed to allow for the fact that ovarian cancer incidence does not increase linearly with age but rather as roughly the 4th power of time since menarche until menopause; when this is taken into account number of ovulatory cycles does provide an explanation of the protective effect (Oncogene 2004; 23:6379-6391).	The sentence in question has been deleted.
Peer Reviewer 3	Section 1. Introduction/ Methods/ Literature Search Results	Biological Plausibility, paragraph 3 (page 6): “the distal fallopian tube, which plays no role in ovulation”. But cell proliferation in the distal fallopian tube, like the endometrium, is maximal during 12530876_File000003_243351472.docx 3 7/20/2012 9:55 AM the follicular phase of the menstrual cycle and is much reduced after ovulation, so cell proliferation in the distal fallopian tube is likely to be reduced in women on OCs (Fertil Steril 1985; 43:554-559).	This paragraph has been modified and now reads: “Although there are some biologically plausible mechanisms for a protective effect of OCs on ovarian cancer risk, recent pathogenetic data now suggest that many high-grade serous epithelial ovarian cancers arise not from the ovarian epithelium but from the distal fallopian tube. (Levanon 2008) Consistent with the epidemiologic data regarding OC use, prior work suggests that the fallopian tube epithelium is influenced by ovulatory cycles, with ovulation exerting an inhibitory effect.”
Peer Reviewer 4	Section 1. Introduction/ Methods/ Literature Search Results	The general approach and methods for both the meta-analysis and modeling seem appropriate. It is reassuring to see that the authors redid the meta-analyses excluding poor quality studies, and stratifying by study type.	Thank you.
Peer Reviewer 4	Section 1. Introduction/ Methods/ Literature Search Results	The only big question from this reviewer is whether an OR was actually calculated for cohort studies or whether a relative risk/rate was calculated and used to approximate an OR for the meta-analysis. It's never explicitly state, and the tables in the body of the methods present data that could mean either. Would just be helpful to know how the authors proceeded with the calculation of ORs, especially from studies with person time.	We used ORs. Most studies that used person-years also reported the endpoint as a dichotomous variable, and so the use of odds ratios maximized the number of studies included.
Peer Reviewer 4	Section 1. Introduction/ Methods/ Literature Search Results	(pg. 3) Page 37 - lines 38 through 40. This sentence is unclear.	We have clarified this sentence to remove the text about improvement in mortality. The sentence now reads: “Despite the advances in primary treatment, the mortality rate for ovarian cancer remains the highest among the gynecologic malignancies.”

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Section 1. Introduction/ Methods/ Literature Search Results	(pg. 21) Figure 8 page 55. What does the * refer to? Also the total number of studies appears to be 159 (perhaps the asterisk should be here??)	The footnote marked with an asterisk refers to the box in the flow diagram that specifies the total number of articles and studies included in the report. The asterisk symbol was inadvertently left out of the figure; this has now been corrected. Since many studies provide data for more than one outcome, the total number of studies included in the review is smaller than the sum of the number of studies that provide data for each specified outcome groups.
TEP Member 1	Section 1. Introduction/ Methods/ Literature Search Results	Can the meta analyses of cervical cancer risk be better stratified histological type (squamous versus adeno carcinoma?)	We thank the reviewer for the excellent suggestion. Unfortunately, there were not enough studies with this level of specificity to conduct a stratified analysis by histological type.
TEP Member 2	Section 1. Introduction/ Methods/ Literature Search Results	Introduction: this section is excellent--comprehensive, clear, and well written.	Thank you.
TEP Member 2	Section 1. Introduction/ Methods/ Literature Search Results	Consider adding a sentence or 2 more on the PLCO and UK trials, e.g. expected release of findings from the UK trial and how it differs from PLCO. (top of page 4)	As suggested, we have added discussion of the PLCO and UK trials.
TEP Member 2	Section 1. Introduction/ Methods/ Literature Search Results	Yes to all of the above questions (note: I am not qualified to evaluate statistical methods)... inclusion/exclusion critera are appropriate as are search strateges. This entire section was well written and the methods used appropriate and consistent with other studies of this type.	Thank you.
TEP Member 3	Section 1. Introduction/ Methods/ Literature Search Results	It may be worth noting that most women can safely use COCs, including those with a family history of breast cancer/BRCA mutations, citing CDC guidelines on the safety of contraceptive methods for women with certain medical conditions/characteristics (Centers for Disease Control and Prevention. U S. Medical Eligibility Criteria for Contraceptive Use, 2010: adapted from the World Health Organization Medical Eligibility Criteria for Contraceptive Use, 4th edition. MMWR Recomm Rep 2010;59:1-86.)	We have added this citation.

Commentator & Affiliation	Section	Comment	Response
TEP Member 3	Section 1. Introduction/ Methods/ Literature Search Results	The methods are well-described. I found the justification to limit the search to non-ovarian cancer outcomes to fewer years a bit confusing, particularly the statement that "Because our primary focus was on the association between OC use and ovarian cancer, we chose a less restrictive year range to increase power. In order to assess the potential for this decision to differentially affect results for OCs compared to the other cancers of interest, we analyzed the results with both a more and less restrictive year range for ovarian cancer."	We understand that difference in cutoffs was confusing, and therefore we now use 2000 as a publication date cutoff for the ovarian cancer studies included in our main meta-analysis. We do, however, perform sensitivity analyses in these analyses that explore the impact of relaxing this cutoff and allowing studies published between 1990 and 1999 to be included in our quantitative synthesis.
TEP Member 3	Section 1. Introduction/ Methods/ Literature Search Results	Although it is good to point out that a sensitivity analysis was done with a more restrictive range for ovarian cancer, it would seem that given one of the main goals was to assess the harm/benefit ratio that one would strive for the same power/precision in estimates for all potential benefits/harms.	See above explanation.
TEP Member 3	Section 1. Introduction/ Methods/ Literature Search Results	The results are presented in an organized, clear manner. I did not note any studies that were missed or that should have been included. The point on formulations is a good one, but again it seems strange to have different years for the literature search for one outcome compared to the others.	See above explanation.
Peer Reviewer 4	Section 2. OCs and Ovarian Cancer	(pg 27) Temporal relationships. Sentences34 to 36. Not clear what the intent of these two last sentences is. Would help to state what was then done to address potential dilution of the dose response relationship?	Anytime you group the independent variable (such as age or years) into intervals, you create a small bias toward the null. Given that studies had already grouped their data, we minimized this by (1) including only studies that reported odds ratios for at least three different time intervals and (2) portioning the effect across intervals where the authors used different intervals from the ones we chose. In many cases, we found very strong dose response curves using this methodology, and the results in one case were very similar to Beral et al. (Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371(9609):303-14. PMID: 18294997), who used individual data.

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	Section 2. OCs and Ovarian Cancer	Page 27 Ever OC use: Was it necessary to exclude articles on BRCA+ women that did not also include general population? How many articles were excluded? I would think these studies might have provided usable information for subpopulations and perhaps could have been compared to accepted numbers (e.g. decreased risk) in the general population. Also, it is not clear if this in conflict with page 29--studies on BRCA were included if they compared OC use in affected vs unaffected carriers and not the general population. (e.g. Narod study--included in the table but excluded from meta analysis?)	We have added language to clarify that articles on BRCA+ women were excluded from the primary ever/never analyses, but a separate ever/never analysis was performed in this subpopulation.
TEP Member 2	Section 2. OCs and Ovarian Cancer	(pg. 67-69)Table 10-- a couple of the studies are shown with decreasing time since OC use whereas all the others show increasing time... this inconsistency is confusing.	We have fixed this inconsistency; intervals are shown with increasing time.
TEP Member 2	Section 2. OCs and Ovarian Cancer	This section had the appropriate amount of detail, clearly described study characteristics, appropriate key messages, and excellent figures and tables. Just one question/area of confusion noted in methods section re whether/when studies were included or excluded for BRCA population.	We have added language to clarify that articles on BRCA+ women were excluded from the primary ever/never analyses, but a separate ever/never analysis was performed in this subpopulation.
TEP Member 2	Section 2. OCs and Ovarian Cancer	(Page 93 last line), does "high risk women" refer to women with a family history (i.e. that paragraph only) or also to women with a BRCA mutation (i.e. the entire section)? It seems that the former may not benefit from OC risk reduction but the latter (BRCA) group may.	This refers to both groups. We have clarified this statement.
TEP Member 2	Section 2. OCs and Ovarian Cancer	Implications and limitations are clearly described; no important literature was omitted. The future research section is very good.	Thank you.
TEP Member 2	Section 2. OCs and Ovarian Cancer	I found it confusing that in the results section it says risk decreases with time since OC use, then it says this finding had a low strength of evidence, and here it implies the finding is valid and consistent with previous studies.	The results of these analyses were statistically significant and reported as such in the Results section. However, the overall strength of the evidence for this outcome was deemed low as we reported significant heterogeneity between studies and future studies may influence the strength of the effects reported here.
TEP Member 4	Section 2. OCs and Ovarian Cancer	(p. 41), figure 10 would be more informative if you had the N for each study in the plot. Same comment for all figures following that have forest plot	In terms of a study's impact on a meta-analysis, we feel that sample sizes (Ns) can be very misleading. The key information is the uncertainty of the estimate and this is contained entirely in the width of the confidence interval. Sample sizes for the specific studies are included in the study characteristic tables.

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Section 2. OCs and Ovarian Cancer	(pg. 95)p. 129, line 5--what does "almost no evidence" mean? Please be more specific.	The sentence in question has been modified to read: "Even if the magnitude of the observed protective association is accurate, our analysis demonstrates that there is insufficient evidence to guide more specific recommendations regarding the preferred OC formulation and dose, the optimal time period of use for ovarian cancer prevention, and the benefits in certain high-risk women."
TEP Member 1	Section 3. OCs and Other Cancers	(pg. 159?)Page 194. The comment on indication to alter cervical cancer screening for women using OCs is not justified based on available data.	We have revised the sentence to clarify that there is no evidence to support different strategies.
TEP Member 1	Section 3. OCs and Other Cancers	(pg. 123) page 257: Line 5 should instead refer to the page/section where the modeling data are presented.	The results referenced on line 5 are for the duration of OC use presented in Table 20.
TEP Member 2	Section 3. OCs and Other Cancers	(Page 123) and corresponding methods section: My understanding is that risk of breast cancer returns to baseline after 5 years of ceasing OC use. Would it be possible/helpful to stratify the 0-10 year interval into 2 intervals?	Per the reviewer's suggestion, we now stratify time since last use for breast cancer as 0-5 and 5-10 years for the previously categorized 0-10 interval in Table 21.
TEP Member 2	Section 3. OCs and Other Cancers	(Page 124), line 48-49 there seems to be a typo here: "comparing BRCA1/2 carriers with BRCA1/2 carriers and" (I think the second carriers should be noncarriers?)	We compared carriers with carriers in our meta-analysis in order to assess the impact of OC use among BRCA1/2 carriers.
TEP Member 2	Section 3. OCs and Other Cancers	(Page 138), line 21: I found it confusing that previously the report stated that HPV+ women were the only relevant population but here studies were excluded if they focused on this subpopulation.	We agree that women who are HPV+ are the most relevant population, but only three included papers specifically addressed this population. We highlight the findings of these studies but do not include them in meta-analysis with other studies that did not select women based on HPV+ status because we deemed these populations too heterogeneous for inclusion. We also comment in the Results section that inclusion of these studies may be negligible because two prior reviews that were able to control for HPV status found similar patterns reported here.
TEP Member 2	Section 3. OCs and Other Cancers	I found it confusing that in the results section it says risk decreases with time since OC use, then it says this finding had a low strength of evidence, and here it implies the finding is valid and consistent with previous studies.	The results of these analyses were statistically significant and reported as such in the Results section. However, the overall strength of the evidence for this outcome was deemed low as we reported significant heterogeneity between studies and future studies may influence the strength of the effects reported here.

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	Section 3. OCs and Other Cancers	(Top of page 159): an additional possibility (?) is that OC use only increases ER+ breast cancers which have higher survival.	This is a possibility, and we have added text to this section.
TEP Member 2	Section 3. OCs and Other Cancers	Page 159 line 22: should it be endometrial here or cervical?	Yes. We have changed in this in the text.
TEP Member 2	Section 3. OCs and Other Cancers	(Page 160 line 16): see comment in results section for page 138... how is this different than Page 159 line 17 where it says the report only looked at studies of HPV+?	Please refer to our response to the similar comment about HPV+.
TEP Member 4	Section 3. OCs and Other Cancers	(p. 131),Table 25? Pg.166 line 26--it is not clear how you can call this an increased risk when the confidence interval crosses 1	The lower bound of the confidence interval is 1.00, which is consistent with a p-value of 0.05. We have added a discussion in the text about using a more Bayesian approach to considering the likelihood that risk is elevated—for example, if the lower 95% CI is 1.0, there is a 97.5% probability that the risk is increased.
Peer Reviewer 4	Section 4. OCs and Vascular Events	(pg. 176) Figure 36 - needs to be fixed.	We have corrected this figure.
Peer Reviewer 4	Section 4. OCs and Vascular Events	(pg. 177) Page 211 - lines43 and 44. Do the authors mean RR for the cohort study or is the OR correct?	We have corrected this text to say “risk ratio.”
Peer Reviewer 4	Section 4. OCs and Vascular Events	(pg. 188) Page 222 - move para on hemo. stroke. to page with Figure 39.	We have relocated the text to the same page as the figure.
Peer Reviewer 4	Section 4. OCs and Vascular Events	(pg. 190) Page 224. lines 54-57. Unclear why 2nd generation users are the baseline.	Most of the papers that reported direct comparisons between progestin generations used levonorgestrel, a second-generation progestin, as the referent and therefore this was used as the baseline in our analyses
Peer Reviewer 4	Section 4. OCs and Vascular Events	(pg. 191) Page 225. Lines24 to 25. Would be good to define "greater than multiplicative effects" for a non-technical reader. Same issue throughout results for example page 234 line 50.	We have modified the text to define “multiplicative effects.”
Peer Reviewer 1	Section 5. Overall Benefits and Harms of OCs	The discussion and conclusions are exceptional. The limitations are well documented and appropriate. The future research section clear and easily translated into new research	Thank you.
Peer Reviewer 2	Section 5. Overall Benefits and Harms of OCs	discussions and conclusions very clear and well-written FRN segments are complete	Thank you. No response necessary.
Peer Reviewer 2	Section 5. Overall Benefits and Harms of OCs	tables and figures are great: especially Fig 51/52 and Table 62/63 - which could be promoted to the Exec Summary	Thank you—we have incorporated Figures 50 and 51 (new numbers) to the Executive Summary (Figure B and Figure C).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Section 5. Overall Benefits and Harms of OCs	(pg.211) Page 245. Table 59. Would be helpful to indicate baseline comparator as a footnote.	We have clarified the referent groups in the table.
Peer Reviewer 4	Section 5. Overall Benefits and Harms of OCs	(pg.215) Page 249. Assumption of continuous use. This assumption may actually bias in favor of OC use? May be what's driving some of the results shown (refer to Figure 79 and 80)....	This is an excellent point. Ideally, we would have sufficient data to incorporate interval pregnancies, or interval use of alternative methods, into the model. There is certainly potential for bias in both directions. In the case of breast cancer and vascular events, where incidence increases with age, an assumption of continuous use may underestimate the upper tail of the age distribution of current OC users, and therefore underestimate the potential increased risk associated with OC use. On the other hand, to the extent time since last use potentially decreases protection for ovarian, colorectal, and endometrial cancers, underestimating the upper tail may lead to underestimating the protective effect, since the continuous use assumption results in longer average duration between last use and the time of highest cancer risk. We have added this discussion.
Peer Reviewer 4	Section 5. Overall Benefits and Harms of OCs	(pg. 229) Figure 52 - Y axis is unclear.	We have corrected the legibility of this figure.
Peer Reviewer 4	Section 5. Overall Benefits and Harms of OCs	(pg. 230, table 62?) Page 62 - given the number of simulations, why not include credible intervals around the estimates especially since the differences are small.	For purposes of clarity, we have not shown confidence intervals, but have noted that they are wide and overlap between models.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Section 5. Overall Benefits and Harms of OCs	(pg. 236-248) Figures 53 to 77. Needs labels for z axis. Also, a footnote that explains y axis would be helpful.	We state in the beginning of the presentation of the acceptability curves (in the Harm/Benefit Acceptability section p. 286) that "we present the results as acceptability curves—the y-axis represents the proportion of simulations where a given scenario was optimal at a given 'willingness-to-pay' (WTP) in terms of harms incurred versus benefits gained; in other words, the sum of all adverse outcomes divided by the sum of all desired outcomes." We have also added this statement (on p. 273) prior to the presentation of the age/duration figures (beginning with Figure 53): "Note that for each figure, the different shapes 15, 20, 25, 30, 35, and 40 represent the age of starting OC use, while the y-axis represents the absolute change in lifetime incidence or mortality due to the estimated association between OC use and the outcome."
Peer Reviewer 4	Section 5. Overall Benefits and Harms of OCs	(pg. 251-253) Figure 81-84. All combined group is not clear. Does this mean including cancers and vascular events for figure 81 and so on.	We have added explanatory text that all combined harms include incident cases and mortality from breast and cervical cancer, DVT, PE, stroke and MI. All combined benefits include prevented incident cases and deaths from ovarian, colorectal and endometrial cancers.
Peer Reviewer 4	Section 5. Overall Benefits and Harms of OCs	The discussion section and conclusions are appropriate and address the range of issues for both the meta-analysis and modeling. That said, not sure if the potential overestimation of benefit as a result of modeling OC duration as continuous is addressed.	This is an excellent point. Ideally, we would have sufficient data to incorporate interval pregnancies, or interval use of alternative methods, into the model. There is certainly potential for bias in both directions. In the case of breast cancer and vascular events, where incidence increases with age, an assumption of continuous use may underestimate the upper tail of the age distribution of current OC users, and therefore underestimate the potential increased risk associated with OC use. On the other hand, to the extent time since last use potentially decreases protection for ovarian, colorectal, and endometrial cancers, underestimating the upper tail may lead to underestimating the protective effect, since the continuous use assumption results in longer average duration between last use and the time of highest cancer risk. We have added this discussion.

Commentator & Affiliation	Section	Comment	Response
TEP Member 1	Section 5. Overall Benefits and Harms of OCs	Figures 53-77 are difficult to understand. Is there a better way to present these data.	The acceptability curves are a standard way to present uncertainty in cost-effectiveness analysis; although our use of harms as "willingness-to-pay" is somewhat novel, the graphic approach is consistent. The data on the effects of age and duration are indeed difficult to present, especially given the degree of uncertainty surrounding the estimates, and we experimented with different formats before reaching the conclusion that these were the most reasonable way to present the data. From the comments of other reviewers, we believe that the majority of readers were able to interpret the figures, and we have not radically changed the format; we would be happy to consider alternative.
TEP Member 2	Section 5. Overall Benefits and Harms of OCs	(Page 255), bullet 1: something is missing (a verb)... differences "were observed"?? Bullet 2 as well.	We have revised to clarify—the bullets should have been indented.
TEP Member 2	Section 5. Overall Benefits and Harms of OCs	(Pages 259-260): This is an excellent discussion of the characteristics and challenges of a potential randomized trial. It would be helpful to mention the sample size needed for a BRCA1+ population, which would be smaller given the higher incidence/risk of OC (and BC, and at a younger age). This population would be more willing to participate as well, and more motivated to adhere to the trial regimen.	We have added a brief discussion of this possibility, along with some of the challenges that might arise in this specific population, such as the choice of appropriate comparison interventions.
TEP Member 2	Section 5. Overall Benefits and Harms of OCs	(Page 265 line 28): is "available" supposed to be "unavailable?" I would think that cervical cancer mortality would be more of a factor where there is no screening (unless the early detection is more than offset by prevention perhaps)	We have corrected the text.
TEP Member 2	Section 5. Overall Benefits and Harms of OCs	(Page 265 line 45) mentions that smoking prevalence may impact findings (in the context of non US studies) yet there is only one short paragraph in this entire report on smoking. I expected to see a little more, and perhaps a mention as a research need (i.e. to stratify results by current? smokers vs nonsmokers or ever vs never smoker)	We have added a discussion of the potential impact of smoking and obesity

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	Section 5. Overall Benefits and Harms of OCs	Another possible suggestion for future research (perhaps included in the more general "new formulations") is the newer practice of taking OCs continuously for 3 months without the usual 1 week break for menstruation, and also the newer or increased referrals for women to take OCs during peri menopause which may have a different impact on risks and/or benefits.	We have added these suggestions.
TEP Member 2	Section 5. Overall Benefits and Harms of OCs	Overall the discussion sections, including limitations and future research, were excellent and clearly written.	Thank you.
TEP Member 3	Section 5. Overall Benefits and Harms of OCs	The authors should be commended for thoroughly describing the limitations of the body of evidence. The implications are stated clearly and reflect the uncertainty based on the available evidence.	Thank you.
TEP Member 3	Section 5. Overall Benefits and Harms of OCs	The future research sections are clear. Some suggestions such as the standardization of categories might be difficult to implement. Do the authors have any suggestions how to encourage this? How would the categories be decided and by whom?	We have added the suggestion that this could most plausibly be accomplished through development of consensus-reporting standards.
TEP Member 4	Section 5. Overall Benefits and Harms of OCs	The conclusion section is weak and contradictory and leaves the reader with a lack of clarity about the message that is intended. This section needs additional work to give more information to the reader. This applies to the full document and the abstract.	We have revised the discussion/conclusion section to try to clarify as much as possible, but some of the lack of “clarity of message” is due to uncertainty about the evidence. We have focused our discussion on the sources of this uncertainty, recommendations for resolving it, and, to the best of our ability, the clinical and public health implications of the current state of the evidence, especially for women who might potentially take OCs primarily for ovarian cancer prevention—unfortunately, there is no clear message beyond “we’re not sure.”
TEP Member 4	Section 5. Overall Benefits and Harms of OCs	This concern pops up in several places as there are a number of discussions about the reduced risk of ovarian cancer from OC use (i.e. p. 128), but then this conclusion gives an opposite finding. It is difficult as a reader to understand.	We have revised the discussion/conclusion section to try to clarify as much as possible, but some of the lack of “clarity of message” is due to uncertainty about the evidence. We have focused our discussion on the sources of this uncertainty, recommendations for resolving it, and, to the best of our ability, the clinical and public health implications of the current state of the evidence, especially for women who might potentially take OCs primarily for ovarian cancer prevention—unfortunately, there is no clear message beyond “we’re not sure.”

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Section 5. Overall Benefits and Harms of OCs	(pg. 254) p. 289, line 12, this bullet is not written in the form of a sentence, it would read better if it started with "There is a..."	We have reorganized these bullet points.
TEP Member 4	Section 5. Overall Benefits and Harms of OCs	(pg. 254) p. 289, line 47, need to insert "in" before breast cancer.	We have revised.
Peer Reviewer 1	Appendix E: Modeling methods	1) How were ORs converted for simulation (were they applied as RRs to probabilities or HRs to rates or some other way)? While a JAMA article was published on how to "convert" these, other major epidemiologists have subsequently published substantial critiques -- hence documenting and justifying this would be important.	We converted age-specific incidences (rates) to probabilities, then, assuming that the odds ratios were estimates of relative risks, applied the OR to the probabilities. We have clarified this in the Appendix.
Peer Reviewer 1	Appendix E: Modeling methods	More detail on the relationship of smoking and obesity to outcomes and the potential for modeling these should be provided -- presumably there are strong non-linear effects that the mean rates within age/race/ethinicity groups do not capture (see Kuntz MDM on biases due to omitted risk factors, especially when time varying)	We agree that this would be a valuable exercise, but the available data to allow modeling of these effects are limited, both in terms of patterns of smoking and obesity among OC users, and in terms of potential interactions between OC use, smoking, obesity, and outcomes.
Peer Reviewer 1	Appendix E: Modeling methods	“The model is run as a microsimulation. During each iteration of the simulation, individual “subject” characteristics, including race/ethnicity, BRCA status, and age- and race-specific probabilities of events are drawn from the distributions described in Table 60.” I am confused by this b/c it seems like probabilities are drawn per individual but it seems like the way probabilities are estimated is more of a second-order Monte Carlo phenomenon?	We have clarified that the model is run as a two-dimensional simulation. Individual subject characteristics (age, race, and BRCA status, OC use) are drawn as a 1st order Monte Carlo, with the associations between OC use and outcomes as second order.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Appendix E: Modeling methods	"The use of microsimulation has two advantages. First, it allows the model to incorporate both the range of uncertainty in parameter estimates (e.g., the width of a 95% confidence interval) as well as the distribution of that uncertainty. For example, for a given mean parameter value with a normal distribution around that mean, the model can be run multiple times, drawing from the distribution with most of the values lying close to the mean value, but 2.5 percent would be drawn from below the lower 95-percent confidence bound and 2.5 percent from above the upper 95-percent confidence bound). Second, it allows the model to have "memory" so that the probability of the outcomes of interests can be conditioned not only on the current state but also on past events, such as past use of OCs or duration of OCs" It seems like only the second is b/c of the microsimulation. The first is more a function of PSA which can be done with a Markov cohort model.	The reviewer is correct, and we have revised this description to clarify that probabilistic analysis and microsimulation are two separate considerations, and describe our rationale for this approach.
Peer Reviewer 1	Appendix E: Modeling methods	Instead of making assumptions about OC use, age at start and duration especially for those over 45 due to data limitations, could one note obtain OC use by age >45 and duration (starting etc) from NHIS 1987 and then impute based on individual-level characteristics shared in common with NHIS and NFGS? This seems like a reasonable exploratory analysis potentially?	This is an excellent suggestion but requires additional resources beyond the scope of the current report.
Peer Reviewer 1	Appendix E: Modeling methods	It seems like no correlation is assumed between distribtuions in the second-order analyses. For various realizations of combinations of parameters, it would be important to check for epidemiological plausibility in terms of consistency with age-/race-specific observed outcomes; was this done? Perhaps a few paragraphs and graphs in the Appendix would be a good idea in this regard?	We did assume no correlation between distributions in the second order analyses; we have provided a table in the Appendix comparing model-predicted lifetime risks of cancer outcomes to estimates from SEER, which show good agreement. We agree that a graphical depiction of age- and race-specific outcomes would be very helpful, but this requires computational time and resources beyond those available for completing the report.
Peer Reviewer 1	Appendix E: Modeling methods	Minor: I am not able to read Figures 51 and 52 y-axis labels as they are garbled in the electronic version.	We have corrected these figures.
Peer Reviewer 1	General	Quality of Report: Superior	No response necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General	This report on evidence on the health benefits and harms of oral contraceptive use and potential use as a cancer prevention strategy is exceptionally well done. The structure and rationale are appropriate; the systematic reviews and meta-analyses are thorough and transparent and conservative in their assessment of potential bias; the modeling is very impressive; and the overall message is appropriately conservative	Thank you.
Peer Reviewer 1	General	The results are clear and well-articulated. No major comments.	Thank you.
Peer Reviewer 1	General	Clarity/usability: The use of graphical elements to layout the analytic structure and the use of tables and figures make this simple and easy.	Thank you.
Peer Reviewer 2	General	Quality of Report: Superior	No response necessary.
Peer Reviewer 2	General	this report is very clinically meaningful, relevant, and newsworthy all aspects are explicitly defined	Thank you.
Peer Reviewer 2	General	I know why the authors used OR (and occas RR) throughout the ExecSummary and the majority of the report - but many readers will be wanting to know the absolute risks - which are given in the modeling segments toward the end of the report - I suggest that you put some of these summary estimates in the Exec Summary under KQ6 (from p218, 223)	We have added Figures 50 and 51 (new numbers) from the main report, which depict the results.
Peer Reviewer 2	General	recognizing that most readers will only read the Exec Summary and not the report, and that this is especially true for the Primary Care audience, I suggest putting as much as you can from the modeling key points summary on pages 289-290 up into the Exec Summary	As suggested, we have added a condensed summary of the modeling key points.
Peer Reviewer 2	General	details are superb all messages clear	Thank you.
Peer Reviewer 2	General	not aware of any publications that were overlooked	No response necessary.
Peer Reviewer 2	General	Clarity/usability: superbly organized and structured all key points clear	Thank you.
Peer Reviewer 3	General	Quality of Report: Poor	No response necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General	Use of Ever/Never use to describe the effect of OC use: In the Results section the authors state "Ovarian cancer incidence was significantly reduced in OC users (OR 0.71, 95% CI 0.64-0.79), with greater reductions seen with longer duration of use." What is the value of the statement that (to be more precise) Ever Users of OCs had an OR of 0.71? This could be read to imply that using OCs for 1 month would reduce the user's risk of ovarian cancer by 29%, which is clearly not true. Is this the risk in current users? How does it change with time since stopping? These issues were considered in the Collaborative Group on Epidemiological Studies of Ovarian Cancer Overview (Lancet 2008; 371:303-314) and there is no reason this more sophisticated and more useful approach could not have been presented here.	We reported an ever/never OC use odds ratio since this is a very standard measure that allows us to be inclusive in performing the meta-analysis. The OR for ever use should not be interpreted as the risk in current users, because ever users is a combined group of both current and past users. Most epidemiologic studies, including the pooled analysis by the Collaborative Group, report an OR for ever use as a summary of the effect of OCs, followed by more detailed analyses by duration or timing of use. We also examined temporal relationships such as duration of OC use, age at first use, and time since last use in our analysis. Many of the methods in the Beral 2008 paper referenced by the reviewer are beyond the scope of our project in that they include analyses of data that were not part of our key questions. However, it is interesting to note that the results of relative risk by duration of oral contraceptive use (Beral et al., Figure 2) are almost identical with the results we reported based on just the observed trial results.
Peer Reviewer 3	General	These remarks apply with even more force to the statement concerning breast cancer. The overview essentially found that the risk was maximal in current users with no duration of use effect and with no risk 10 years after stopping. Similar descriptions should be made for colorectal and endometrial cancer, and some attempt should be made to describe the likely effects on cervical cancer. Similar descriptions should be given for "vascular" events. Some comparison of the absolute risks of these conditions needs to be given so that the reader is not left to compare ORs without any context. This level of understanding and description should be demanded even in an Abstract since this may be all that many readers will read. All these issues need of course to be built into their models. Conclusions (ES-22): My earlier remarks regarding the Structured Abstract also apply to this paragraph.	We have added a sensitivity analysis to the model using the cited article's joint estimates of the effect of duration and time since last use and present these results, along with a discussion, in Section 5. We have attempted to address these concerns in both the abstract and executive summary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General	Stating that the "The overall strength of evidence for ovarian cancer was moderate to low, primarily because of the lack of randomized trials and inconsistent reporting of important characteristics of use such as duration" is very misleading. The epidemiological evidence for a reduction in risk of ovarian cancer with OC use is very consistent. If one is to state that the evidence is at best moderate, the authors need to describe what biases could be producing the results and discuss the evidence for these biases operating. If all epidemiological evidence is to be regarded as at best moderate without a randomized trial then one would have to conclude, for example, that the overall strength of evidence for the causal connection between cigarette smoking and lung cancer was moderate to low because of a "lack of randomized trials"? Similar remarks apply to the effects of "inconsistent reporting".	We agree with the reviewer that the evidence on the effects of OCs on ovarian cancer risk is remarkably consistent. We exercised what we consider to be appropriate caution in characterizing the evidence as "moderate" because of the lack of randomized controlled trials. We believe this characterization was appropriate for two reasons: (1) The experience with menopausal hormone therapy and cardiovascular disease demonstrated that even very consistent data from observational studies can lead to conclusions that are not corroborated by randomized controlled trials. (2) If the conclusions of the analysis could lead to the use of OCs for ovarian cancer prevention in women who would otherwise not be using them, it is important to be prudent and not overstate the strength of the evidence.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General	The sentence “Overall, the model predicted that the harm/benefit ratio in terms of incident cases is likely to be unfavorable when only ovarian cancer prevention is considered, although there is a favorable balance of benefits and harms in terms of overall mortality, resulting in a net gain in life expectancy” is most confusing. The incident cases of what diseases are counted to make the comparison “unfavorable” yet lead to a net mortality benefit? As the authors note in the body of their report, OC use reduces the incidence of unwanted pregnancies with their increased risk of untoward events, this also needs to be taken into account in calculating the benefit/harm ratio.	It is entirely possible to have more harms than benefits in terms of incident cases, yet have a net benefit in terms of mortality, especially when the mortality rates for the different diseases vary (and when changing age distribution patterns may affect mortality). Although the model results presented in this section did specify which harms and which benefits, and indeed presented alternatives using different definitions, we have revised this section to clarify which harms (breast and cervical cancer, stroke, MI, PE, VTE) and benefits (ovarian, colorectal, and endometrial cancer) are considered, and extended our discussion. Although we agree that the use of OCs clearly has benefits for reduction of unwanted pregnancies, as well as prevention of complications associated with their use, incorporating pregnancy as an outcome was (a) specifically outside of the scope of the requested review, (b) raises additional modeling issues ranging from how best to incorporate different timing of pregnancy, and (c) would necessitate a direct comparison with other contraceptive methods in terms of contraceptive efficacy and effects on other outcomes. While, ultimately, a comprehensive assessment of the global harms and benefits associated with OCs should incorporate all of these things, our task was to focus specifically on noncontraceptive effects.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General	The Collaborative Group (Lancet 2008; 371:303-314) collected individual data on 23,257 ovarian cancer cases and 87,303 controls from 45 epidemiological studies. This data was collated centrally to permit analysis across studies while avoiding the problems with "inconsistent reporting" that the authors of this report rightly complain of. The Collaborative Group analysis showed that "reduction in risk persisted for more than 30 years after oral contraceptive use had ceased … Use during the 1960s, 1970s, and 1980s was associated with similar proportional risk reductions." A critique of the Collaborative Group's findings could have provided the basis of the EHC Report instead of which the authors abstracted the published reports from individual studies and restricted attention to articles published subsequent to January 1990 – the latter despite the findings from the Collaborative Group. Similar remarks apply to any discussion of the effects of oral contraceptives on breast cancer.	Our systematic review incorporates a meta-analysis of published data rather than a pooled analysis or individual patient-level meta-analysis. We acknowledge the limitations of using only the analyses presented in published papers, but a pooled analysis was beyond the scope of this project. We have included additional analyses and discussion specifically addressing the Collaborative Group's findings.
Peer Reviewer 3	General	Endometrial cancer (ES-13): There are many more studies of the relationship between OC use and endometrial cancer than the authors considered (see, for example, Mueck A et al. Endocrine- Related Cancer 2010; 17:R263 for a list). I am not sure why they were excluded, but presumably it is because they were published before 1990 – not a satisfactory reason for exclusion. Two studies were excluded "for not reporting point estimates for ever/never use" – but ever/never use is a most uninformative risk estimate, this is no reason for exclusion. The authors again draw attention to the "risk of bias in observational studies" but omit any mention of the vast amount of evidence linking 'unopposed' estrogen with endometrial cancer risk and how this provides strong biological support for the reduction in risk with OC use.	The reviewer is correct that many of the studies in the Mueck et al. review were conducted prior to 2000 and, thus, were excluded from our review. In collaboration with our stakeholders and our Technical Expert Panel, we make a decision to exclude studies published prior to 2000 in order to (1) minimize the influence of OC formulations no longer available on the U.S. market and (2) increase generalizability to current clinical practice. Studies were excluded from our meta-analysis of ever versus never use of OCs if they did not supply that effect estimate; however, they were not excluded from the overall systematic review. That is, if they met eligibility criteria and provided other estimates of the effects of OC use on cancer risk (e.g., recency, duration), they were included in the review even if there was no estimate for ever versus never OC use. We agree that the evidence on unopposed estrogen and endometrial cancer risk provides additional biological plausibility and have added this point.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	General	This is an extremely well written, important report that combines meta-analytic techniques with decision modeling to clarify the potential role of OCs in reducing ovarian cancer. The approach and the modeling include novel methods for incorporating the data from the analysis, for examining uncertainty and for quantifying benefits and harms. The authors should be commended for the insight and innovation used to address the key questions.	Thank you.
Peer Reviewer 4	General	The target population is hinted at throughout the document, but an explicit definition up front would be helpful. In particular, how does one define a "general population of reproductive age women" for this study? What age range does this group of women refer to?	We have clarified that “general population” refers to all women, including BRCA carriers, ages 15-44.
Peer Reviewer 4	General	The key questions are appropriate and explicitly stated.	Thank you.
Peer Reviewer 4	General	Clarity/usability: This is a well written and clearly presented report. Edits as suggested above would improve clarity, especially adding footnotes that aide in interpreting modeling results.	Thank you.
TEP Member 1	General	Quality of Report: Good	No response necessary.
TEP Member 1	General	Clarity/usability: The main points are clearly presented.	Thank you.
TEP Member 2	General	Quality of Report: Superior	No response necessary.
TEP Member 2	General	Clarity/usability: The report is easy to follow although the organization resulted in some repetitiveness of information. The main points are very clearly presented and summarized. The conclusions will inform practice (i.e. too soon to make recommendations although some may be made on an individual level based on informed decision making and patient preferences) and policy (hopefully to fund additional research).	Thank you.
TEP Member 2	General	This is an excellent, well written, and helpful report. It is clinically meaningful in summarizing the available evidence, with relevant analyses and recommendations for future research. As stated in the limitations sections, the available evidence and study characteristics did not allow for a more conclusive recommendation for or against use of OCs to prevent ovarian cancer. The key questions were appropriate and clearly stated at multiple places in the report.	Thank you.
TEP Member 3	General	Quality of Report: Superior	No response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP Member 3	General	Clarity/usability: The report is well structured and fairly easy to follow, given its complexity. The conclusions do not indicate a change in practice, but are nonetheless useful in addressing the question of the utility of OCs for primary ovarian cancer prevention.	Thank you.
TEP Member 3	General	This a carefully written, impressively detailed and thoughtful report. The key questions are appropriate and clear, as it the target population. The clinical utility of the report might be somewhat limited, but as a reflection of the limitations of the evidence, not the report itself.	Thank you.
TEP Member 4	General	Quality of Report: Good	No response necessary.
TEP Member 4	General	The report is clinically meaningful and well described.	Thank you.
TEP Member 4	General	The key questions are well stated.	Thank you.
TEP Member 4	General	Clarity/usability: Although the way the report is structured does make logical sense, it made reading cumbersome and difficult as the methods were similar in the various areas and it felt like you were re-reading parts of the report	We thank the reviewer for their comment and hope that our revisions help clarify the report and its methods and findings. The structure of the report was designed to allow the separate sections on the different outcomes to stand alone if needed while also providing global sections on the background, methods, and modeling components.
TEP Member 4	General	Clarity/usability: The main points are clearly presented, however the conclusion falls short of providing information that a reader could use for decision-making, and do not offer sufficient new information to change policy or practice.	The purpose of the report was to provide a systematic review of the literature; summarize the available evidence and the remaining uncertainties; and highlight areas of future needed research. We then look to the stakeholders to use this report as one piece of the information needed for decisionmaking or changing policy or practice.

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	General	Clarity/usability: The statistical methods were unique, but in some areas, it felt as though they were not comprehensive such as the complete elimination of pregnancy as a potential harm.	Although we agree that the use of OCs clearly has benefits for reduction of unwanted pregnancies, as well as prevention of complications associated with their use, incorporating pregnancy as an outcome was (a) specifically outside of the scope of the requested review, (b) raises additional modeling issues ranging from how best to incorporate different timing of pregnancy, and (c) would necessitate a direct comparison with other contraceptive methods in terms of contraceptive efficacy and effects on other outcomes. While, ultimately, a comprehensive assessment of the global harms and benefits associated with OCs should incorporate all of these things, our task was to focus specifically on noncontraceptive effects.
TEP Member 5	General	Looks great. Very interesting results. This is a wonderful contribution to our knowledge	Thank you.
Ovarian Cancer National Alliance	General	As a patient advocacy organization dedicated to promoting the interests of women with ovarian cancer, the Ovarian Cancer National Alliance is pleased to provide comments on the Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer report. We commend the Agency for Health Quality and Research for reviewing the available evidence on the impact of oral contraceptives on ovarian cancer. Overall, the panel was excellent and the findings appear to be sound. The Alliance is glad to see confirmation that the use of oral contraceptives reduces the risk of ovarian cancer. As with most medications, there are risks that come with the use of oral contraceptives. Patients and providers need to weigh the risks and benefits before deciding on a course of action. For those at high risk of developing ovarian cancer, use of oral contraceptives as a prevention strategy may be recommended. Unfortunately, this analysis leaves us uncertain as to the magnitude of benefit provided by the use of oral contraceptives. We look forward to further studies measuring said benefit.	Thank you.