Author's response to reviews

Title: Recent alcohol consumption and risk of incident ovarian carcinoma: a pooled analysis of 5,342 cases and 10,358 controls from the Ovarian Cancer Association Consortium

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Author's response to reviews: see over
Dr Christina Chap, Executive Editor  
*BMC Cancer*  

Oct 17, 2012  

Dear Dr Chap,  

On behalf of my colleagues, I am pleased to submit our revised manuscript entitled “Recent alcohol consumption and risk of incident ovarian carcinoma: a pooled analysis of 5,342 cases and 10,358 controls from the Ovarian Cancer Association Consortium” for consideration for publication as a Research Article in BMC Cancer.  

On the following pages, we have addressed each of the Reviewer’s queries, and have referenced the location of the changes made in the manuscript and tables. We appreciate the opportunity to improve the quality and presentation of our manuscript for the Journal and thank the Reviewers for their thoughtful comments.  

We look forward to the Journal’s decision.  

With Warmest Regards,  

\[Signature\]  

Linda E Kelemen, MSc, ScD
Response to Reviewers

Reviewer 1.

1. … From Supplementary Table 1 it emerges that the distribution of alcohol drinking of the HAW and HOP studies is very different from the distribution of alcohol intake of the other included studies. Moreover, the two forest plots of Figure 1 seem to show some heterogeneity. Nevertheless, similar parameter estimates for both the fixed and random effects based models could be indeed obtained considering the large sample size of this investigation. … I wonder whether authors were aware of this technical aspect, and if they planned during the analysis the possibility of fitting to the data random-effects models, and why they decided to analyze data with fixed-effects modeling. Were results of the models similar?

Response: Methodological issues related to combining data across studies in the Ovarian Cancer Association Consortium (OCAC) have been an active topic of discussion at annual OCAC meetings. Our statistician colleagues, including the senior author of this report, showed that a two-staged approach that first derives study-specific ORs and 95% CIs and then combines the individual study estimates using fixed-effects meta-analytic techniques produces essentially the same estimates as does what we performed here, a model that includes interaction terms between the study site and all model variables except the exposure of interest (e.g., a pooled analysis). Our analysis does not use meta-analysis data synthesis per se, yet still derives exposure estimates that take into account study-specific covariate adjustments and between-study heterogeneity. It appears that our use of the $I^2$ statistic, which is associated with meta-analytic data synthesis procedures, was confusing. Within the context of our pooled analysis, we used the $I^2$ statistic as a descriptive measure following our formal evaluation of statistical heterogeneity using the likelihood ratio test. We have now clarified this on pages 7-8.

Additionally, our analysis fairly clearly shows a lack of increased risk with moderate alcohol consumption, and even with the large number of subjects included, does not provide strong evidence for a decreased risk with consumption. Had we included a heterogeneity variance component (as used in random-effects meta-analysis according to the methods described by DerSimonian and Laird), the confidence limits of our adjusted pooled estimate would have been slightly wider, showing even less support for an association, in either direction.

Although the distributions of alcohol among HAW (which has a diverse ethnic make-up) and HOP look different according to the descriptive nature of Supplemental Table 1, the associations with ovarian carcinoma following multivariable adjustment (including age and ethnicity) are not statistically different, as shown in the Figure and in the $I^2$ statistic (=0) stated on page 12 for North American studies.

2. The authors “re-assigned EOC histology type according to the expected distributions of histology combined with grade observed from large population-based series” (page 8). The application of this pathology-based algorithm was seen by the authors as strength of the investigation (page 14). However, this algorithm could also introduce a bias. Thus, this could also be a limitation. I wonder whether authors evaluate the association between total alcohol and wine intake and histological types of EOC (Table 3) on the original data, i.e. without the application of the pathology-based algorithm. Are there differences in the magnitude of the association between
total alcohol and wine intake and histological types of EOC without the application of the pathology-based algorithm? This point could be better described within the discussion.

Response: Application of the algorithm tended to shift estimates and confidence intervals a little farther from the null, although there was no appreciable difference in statistical significance of estimates when the pathology-based algorithm was not implemented. This is now stated under “Alcohol and ovarian tumor histologic types”, discussed briefly on page 15 and the results added as Supplementary Table 3. It should be noted that the pathology-based algorithm was carried out blind to case exposure status and thus, on average, such reclassification would not introduce any biases in the histology-specific exposure-risk associations.

3. I would recommend the authors to use the term “epithelial ovarian carcinoma” or its abbreviation (EOC) when appropriate.

Response: Carcinomas, by definition, are epithelial.

4. Please define the abbreviation OCAC (“Ovarian Cancer Association Consortium”) within the text (page 5 row 12).

Response: We added the abbreviation as requested (page 5).

5. Page 5. Reference number 43 is not informative. In fact, Table 1 of this manuscript is essentially the same as Table 1 of the referred article. So, there is no need to include this citation.

Response: The reference has been deleted from this sentence.

6. Page 5. In the Study Subjects section (page 5), I wonder whether it is possible to add a reference to each included case-control study after the study abbreviation. This consideration also applies to Table 1. Is it possible to add a reference after the study abbreviation in Table 1?

Response: We have now added additional references for each study on page 5 and in Table 1.

7. Page 6. Authors state that ”Daily alcohol intake for all studies was calculated by summing the product of the frequency of consumption...using national estimates of alcohol content for that country”. However, considering that the ethanol content of a specific alcohol beverage could be very different across countries, I wonder whether it is possible to add a sentence describing briefly the range of ethanol content across countries for beer, wine and liquor (for example, beer from 4% in Europe to 6% in USA, or somewhat similar).

Response: We did not ask individual study sites for % alcohol content by volume. The data that were provided to us, in units of grams of ethanol consumed daily as described above, had already taken into account the % alcohol content by volume as separately evaluated by each study.

8. Page 7. Please add “consumed daily” at the sentence “Alcohol intake categories were derived in increments of one standard drink consumed daily”.

Response: We have added the qualifying phrase (page 7).
9. Page 7. The authors state that “The trend in risk were evaluated treating the category values of alcohol intake as continuous variables in the regression models.” Please specify if the mean or median value of each category was used.

**Response:** We modeled the ordinal variable representing the category values of alcohol intake as continuous, now stated on page 7. In the absence of observing a dose-response relation (stated within the section “Alcohol consumption and risk of ovarian carcinoma”), our approach is unlikely to violate major assumptions.

10. Page 7. I would remove the paragraph “In addition, among a subset of studies, primary analyses were also adjusted for total energy intake,…..again in increments of alcohol grams of one standard drink per day”. In fact, as stated by the authors within the Results section, “Further adjustment for total energy intake had little effect (data not shown)”. So, considering that data adjusted for energy intake was not shown, I think that there is no need to describe so extensively the adjustment for total energy intake within the Statistical analysis section.

**Response:** We have re-written this section more concisely (page 8).

11. Please add within the Statistical analysis section a paragraph describing methods related to the forest plots of Figure 1, i.e. DerSimonian and Laird paper (Control Clin Trials 1986;7(3):177-88). Did the authors use random effects modeling for pooling estimates across studies?

**Response:** The funnel plots represent the estimates from the study-specific and pooled (combined data) analysis from logistic regression models and are not estimates derived from any meta-analytic data synthesis, although they are equivalent to fixed-effects meta-analysis results as described in our response to comment #1. We now clarify this on pages 8 and 9.

12. Page 11 row 10. I think that the P of heterogeneity was computed on 4 df (number of categories -1), and not 5. Is it true?

**Response:** The P heterogeneity was calculated using 5 df as stated in the manuscript. It was derived from the type 3 analysis of effects in the polytomous regression model that simultaneously models each of the 5 histologic types to the control group using an exposure variable coded at two levels (no vs high alcohol intake). The dfs for the test are (6 – 1) x (2 – 1) = 5 df. This is now described under “Statistical analysis” on page 8.

13. Page 12. Within the second paragraph of the discussion, the authors state that “alcohol has been equivocal for ovarian cancer [17, 26-33, 36, 38]”. However, the recent meta-analysis (reference 38) provided no evidence of an association between alcohol and epithelial ovarian cancer. So, the findings of this manuscript are consistent with the results of the recent meta-analysis. The use of the term equivocal for reference [38] is not correct.

**Response:** References 36 (Genkinger et al) and 38 (Rota et al), as reviews, have been removed from the listing of primary studies.

14. A general issue in case-control studies is the possible presence of recall and selection bias. I
think that this should be listed within the discussion as a limitation of pooling case-control studies.

Response: We now mention these biases on page 15 as a potential limitation of all primary case-control studies.

15. Table 1. The last column of Table 1 is not informative. In fact, authors clearly state within the Study subjects section (page 5) that all the studies used population-based ascertainment methods. Is it possible to substitute this column with a new one including the period of enrolment of each case-control study? Furthermore, could authors add a column in Table 1 with the (main) matching factors of each case-control study, along with a brief description in page 6?

Response: Table 1 has been amended as requested with reference made to the matching factors on page 5.

16. Table 2 and Table 3 (and also supplementary table 3). Please define the abbreviation DK (don’t know?), please specify in the table notes “1 drink (10 g of alcohol)...”.

Response: “DK” has been replaced with “unknown” in all instances. The footnote to the tables has been modified to state that “1 drink” represents 10 grams of ethanol since that is how we modeled “drinks”. The actual amount of ethanol per type of drink varied according to the alcoholic beverage type (as defined in the manuscript under “Statistical analysis”).

17. Figure 1A and 1B. Please add the I² heterogeneity statistics and the P-value for heterogeneity within the two forest plots.

Response: We derived the P value for statistical heterogeneity from the interaction term of alcohol and study as described under “Statistical analysis”; we now add the P values to the legend of the figures. The I² was not calculated across all studies.

Reviewer 2.

1. In your tables, it appears that you include a missing indicator variable for covariates included in the model. However, in the supplementary table, it appears that some of those variables have a higher percentage of missing data (e.g., family history, ethnicity). With a higher percentage of missing data, it may introduce bias into your analysis. Have you considered or examined other models taking into account missing values? If so, were the results similar?

Response: Only two variables, family history and education, had a higher percentage of missing observations and likely represents the difficulty obtaining accurate information on these two variables from participants. Missing responses for the remaining variables mostly comprised <1% of the data and occasionally 4% of the data. We respectfully disagree with the reviewer and believe the proportion of missing responses for the remaining variables was reasonable given the size of the harmonization project and our efforts to clean the data and follow up discrepancies with each study site (as stated on page 7). We also did not observe any overall statistically significant interactions between any of the covariates and alcohol or wine intake, as stated under
“Potential sources of effect modification” on page 13, and the proportion of missing responses was similar (nondifferential) between cases and controls. Thus, no other approaches were considered.

2. The categories for some of the analyses include a small number of cases (>3 drinks/day), particularly when examining by histology. I believe it would be worthwhile to collapse the top categories for these analyses. Or where the results similar to what was presented when collapsed?

Response: We had initially considered a smaller range of intakes as raised by the reviewer but felt we had an opportunity to assess a wider range with our large sample size. We now include as separate rows in Table 3 and Supplementary Table 3 (the histology analyses) risk estimates that are associated with collapsing the two higher categories of intake, along with the associated P trend value, and state the results under “Alcohol and ovarian tumor histologic types”.

3. A clarification – the analysis conducted within the Pooling Project for mucinous ovarian cancer was based on continuous models of alcohol intake and not comparing >30g/day compared to 0g/day.

Response: We thank the Reviewer for the clarification since that was not clear from the primary report. We have rephrased the sentence on page 4.

4. Although you discuss heterogeneity of your results when you examine the different histological types, did you observe statistically significant heterogeneity of your risk estimates across studies for the analyses of total ovarian cancer?

Response: Yes, this was described under “Potential sources of effect modification” and is now also captured in the Figure legend in response to comment #17 from Reviewer 1.

5. You stated that you reclassified the outcomes of select types of ovarian cancer as the classifications may not accurately represent the type of ovarian cancer. Please include the N(%) of those that were changed. Did you examine the associations without the change and were the results similar?

Response: Please see our response to comment #2 from Reviewer 1. The number of cases by histologic type in the original data (new Supplementary Table 3) and following re-assignment of histology (Table 3) is now included in both tables.

6. The discussion should also include statements on recall and selection bias as potential concerns with this data.

Response: This was added in response to comment #14 from Reviewer 1.

7. Under the statistical analysis, I believe it would be helpful for the reader to state that you combine the data from each of the studies into a single dataset to examine these associations instead of doing analyses within each study and then pooling the estimates across the studies.

Response: We now add this clarification under “Statistical analysis”.
8. Do you have the ability to examine long term drinking patterns, “binge drinking” or even conduct analyses on former drinkers? If so, this would greatly add to the literature to date on this topic.

Response: Information on long-term drinking patterns was not available for most studies and, when asked, was asked in varying ways (e.g., age-category intake of any alcohol [yes/no]; age-category intake of drinks of alcohol; year-period intakes of drinks of alcohol), all of which precluded harmonizing such aspects of the data confidently. At the time that we conceptualized the analysis for this manuscript, it was decided that we would not evaluate associations with former drinkers, as they include the extremes of health-conscious women and also alcoholics who stop drinking.

9. You state in the discussion that “alcohol, in general, has been reported to reduce cellular proliferation by influencing the insulin-insulin-like growth factor (IGF) pathways [68,69], which have been implicated in early development and prognosis of these carcinoma types[70,73].” Did you also see if the association held, if you adjusted for diabetes? Or stratified on whether an individual had been diagnosed with diabetes or not? This would similarly hold for stratifying on obesity? In addition, there is an extra “insulin” in “insulin-insulin-like growth factor”.

Response: We did not request information on diabetes status from the study sites. Estimates that stratified the total alcohol-ovarian carcinoma association by BMI were not statistically significant across strata. However, we re-evaluated the estimates stratified by BMI among alcohol and wine intake with the histologic types. Although inconclusive, some suggestive associations were observed at lower BMI. We now include this in the Results on pages 12-13.

We have re-written the sentence as “insulin and insulin-like growth factor (IGF) pathways…” on page 12.

Reviewer 3.

1. Essentially the analysis is null, which is what the authors conclude. That said, this study essentially only considers alcohol intake relatively shortly before diagnosis (1-5 years depending on study). Given that ovarian cancer has a long latency period, it is possible that alcohol intake at other points in the life cycle may influence risk, even if intake near diagnosis does not influence risk. Perhaps some studies in this paper have information about alcohol intake at other times in life, which could be examined. Also, it would be nice to see if there is heterogeneity by studies that evaluate alcohol at different times before diagnosis. At a minimum, this should be mentioned in the discussion as a possibility.

Response: Please see our response regarding life-time drinking patterns to comment #8 from Reviewer 2. There was no statistical heterogeneity (P=0.61) between studies that captured alcohol intake (none vs any) in the 4-5 years prior to diagnosis (CON, DOV, GER, NCO, POL: OR=0.91, 95% CI=0.79-1.05) compared to the remaining studies that captured intake in the 1 year prior to diagnosis (OR=0.96; 95% CI=0.85-1.08). This is not too surprising because, unlike prospective studies, the actual recall of alcohol intake in the 5 years prior to diagnosis still occurred at the time of diagnosis and is subject to the same recall bias. Findings from the California Teachers Study also support that recent alcohol intake patterns likely bias long-term
recollection of intake patterns. We now add to the Discussion on page 15 the possibility of alcohol effects during different lifetime exposures and qualify our investigation as evaluating “recent” moderate intake throughout the text including the title.

2. It is possible that inverse associations observed in this study, could be due to changes in alcohol intake among cases before diagnosis, as we know that many women with ovarian cancer feel unwell for some time before diagnosis. It would be nice to see if the inverse associations for endometrioid and clear cell tumors remain when restricting to studies that asked about intake 5 years before diagnosis.

Response: We agree that this would be a useful analysis in a prospective study design, which is the context we believe the Reviewer might be interpreting the exposure periods. Nevertheless, we derived the following estimates by modeling endometrioid and clear cell histologies independently in (binary) logistic regression models among studies that captured alcohol intake in the 4-5 years prior to diagnosis (CON, DOV, GER, NCO, POL):

Total alcohol (any vs none):
Endometrioid: 1.04 (0.74-1.48), n=183 cases consuming any alcohol
Clear cell: 0.77 (0.53-1.11), n=161 cases consuming any alcohol

Wine (any vs none):
Endometrioid: 0.99 (0.71-1.39), n=183 cases consuming any alcohol
Clear cell: 0.74 (0.51-1.06), n=161 cases consuming any alcohol

3. For the statistical analysis looking at the heterogeneity by tumor type, it would make sense to look at the heterogeneity of the trend variable to reduce df.

Response: Thank you for this suggestion. We have made this change to Tables 3 and 4 and Supplementary Table 3. Because of the way df are calculated in polytomous regression (see our response to comment #12 from Reviewer 1), we still have 4 or 5 df when the trend variable is used. We have deleted the sentences describing models comparing only the highest and lowest intake categories (previously under “Alcohol and ovarian tumor histologic types”).

4. One minor point is that it would be nice to include the main total alcohol OR and CIs in the results text.

Response: We have now added the estimates under “Alcohol consumption and risk of ovarian carcinoma” on page 10 and have added this to the Abstract.