Reviewer's report

Title: Coffee consumption and risk of cancers: a meta-analysis of cohort studies

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Reviewer: Francesca Bravi

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- MAJOR COMPULSORY REVISIONS

1) RESULTS, first paragraph: the authors state that they “identified 59 publications, 40 prospective cohort studies”. I do not understand from the text nor from the flow diagram what causes the difference between 59 and 40. It does not seem the case-control design (153 papers have already been excluded for this reason) nor the multiple publishing of the same study (8 studies have already been excluded for this reason). The authors should clarify this point.

2) RESULTS AND TABLE 2: for ease of reading, RRs stratified by cancer type and geographical area should be reported in the Results section and in Table 2 following the same order (in the text it seems alphabetical order, while in table it is not clear). Moreover consistent wordings should be adopted throughout manuscript and table, whereas the same neoplasm is often reported with different nouns/adjectives (see for example, hepatocellular vs liver, stomach vs gastric, kidney vs renal, endometrial vs endometrium, and so on…).

3) RESULTS and DISCUSSION: as a general rule, estimates of summary RRs and corresponding CIs should be given in the Results section and should not be repeated in the Discussion. They authors should modify the Discussion providing comments on their findings and avoiding the repetition of results already shown in the Results section.

4) DISCUSSION: some sentences are not clear since the authors cite previous publications without specifying what neoplasm or population they refer to. Specifying this information would add clarity to the discussion. In particular:

- Discussion, 9th paragraph: “The inverse relation between coffee drinking and endometrial cancer risk was consistently observed in a population that was characterized by different endometrial cancer incidences[80]”. The authors refers to Global cancer statistics, 2002. Thus it is impossible to argue which is the population characterized by different incidences. Please, modify.

- Discussion, 11th paragraph: “A meta-analysis, including 6 case-control studies from southern Europe and Japan (1,551 cases) and 4 cohort studies from Japan (709 cases) reported a statistically significant 41% reduction in the risk among coffee drinkers compared with never drinkers…” The authors should specify which cancer the meta-analysis investigated.

- Discussion, 11th paragraph: “A population-based study in the United States
showed that higher intake of coffee”; is it a population-based case-control study? Please, specify the study design.

- MINOR ESSENTIAL REVISIONS

1) ABSTRACT: as concerns the studies included in the meta-analysis, the authors should specify that they included only prospective cohort studies and all types of cancer.

2) METHODS: the authors should specify in the Statistical Analysis paragraph if they established a minimum number of studies per stratum needed to perform stratified analysis.

3) DISCUSSION, 5th paragraph: the authors state that “A possible link between insulin sensitivity and renal cell cancer risk is suggested by the strong positive association between obesity and renal cell cancer risk.” Providing a reference for this point would be advisable.

4) DISCUSSION, 14th paragraph: I agree with the authors when they say that cohort studies are less susceptible to recall bias as compared to case-control ones. However, prospective studies may have another limitations, since subjects may have modified their coffee intake during the follow-up period, after the baseline assessment. The authors should discuss this point in the Discussion and in the Background. Moreover, it would be also advisable to add a comment on this issue in the Background, where the authors declare that the meta-analysis was conducted on prospective cohort studies only.

5) DISCUSSION, 14th paragraph: the authors state “Third, we extracted the risk estimates that reflected the greatest degree of the control potential confounders, because it was hard to obtain raw data from each study for conducting standardized adjustments.” The authors should modify this sentence in a clearer way. It is not clear to me why the authors refer to the difficulties in obtaining raw data and conducting a standardized adjustment. This would be the case of a pooled analysis, whereas the present is a meta-analysis. Meta-analysis are always based on published estimated risks (and not raw data), and thus it is obvious that the estimates from the studies are adjusted for different confounding variables.

6) A thorough reading of the entire manuscript and a revision by a native English speaker would be useful, given the presence of several typos and grammatical errors, including the following:

- Background, 1st paragraph: please, rephrase the following sentence which is not clear: “Polyphenols is an important ingredient in coffee, such as lignan phytoestrogens and flavonoids and polyphenols are found to exhibit anticarcinogenic properties in several studies”.

- Background, 1st paragraph: please, change “Polyphenols is an important ingredient” into “Polyphenols are an important ingredient”.

- Background, 1st paragraph: “Caffeic acid has the ability to inhibit DNA
methylation in cultured human cancer cells and associates with inactivation of various pathways...” please replace “associates” with “is associated”.

- Methods, Statistical analysis, 1st paragraph: “The measures of interest were the RR and the corresponding 95% CIs for included cohort studies.” Replace with “for the included cohort studies”.

- Methods, Statistical analysis, 1st paragraph: “If coffee consumption was indicated by milliliter”, please substitute with “was indicated in milliliters”.

- Methods, Statistical analysis, 3rd paragraph: “in which 1 study at a time was removed and the rest analyzed to estimate”. Please replace “the rest” with “the others”.

- Discussion, 1st paragraph: “So, the evidence presented above suggests that coffee intake might reduce cancer occurrence in human.” Please change “human” in “humans”.

- Discussion, 3rd paragraph: “a meta-analysis on 25 case-control studies giving a summary effect estimate of 1.04 (95% CI, 1.0-1.07)”; please, correct the lower limit of the confidence interval.

- Discussion, 3rd paragraph: “a summary RR of 1.00 (0.94-1.07) per 1 cup/day for 10 cohort studies.5 Since the WCRF report...”; 5 is a reference? Please, modify.

- Discussion, 7th paragraph: “A meta-analysis of 9 cohort and 9 case-control studies found a borderline significant influence of highest coffee consumption (RR 0.95; 95% CI, 0.90-1.00) and an increment of 2 cups/day of coffee consumption (RR 0.98; 95% CI, 0.96-1.00) on the risk of breast cancer.” Please modify “and an increment” in “and of an increment”.

- Discussion, 7th and 8th paragraphs: please replace “mete-analysis” with “meta-analysis”.

- Discussion, 9th paragraph: “In 2009, A meta-analysis conducted by Bravi et al” please modify “A” into “a”.

- Discussion, 12th paragraph: “A recent review without meta-analysis presented the specifics from 4 cohorts and 17 case control studies”. Please, replace “specifics” with “characteristics” and “case control” with “case-control”.

- Discussion, 13th paragraph: “An example is from the Lutheran Brotherhood Cohort study of 17,633 White males age 35 and older followed for 20 years that identified 149 fatal prostate cancer cases, which found coffee consumption unrelated to risk.” Please, replace “age 35” with “aged 35”; moreover, the sentence should be rephrased since it is quite tortuous.

- Table 1: please, replace “pancrease” with “pancreas” throughout the table.

- DISCRETIONARY REVISIONS

1) As suggested in a previous comment, I recognize that case-control studies are more prone to bias than cohort ones. However, also the latter are observational studies, and they may be affected by biases too. Thus I believe that the inclusion of both study types in the meta-analysis would provide a more complete
representation of the association between coffee consumption and cancer, and would add and a considerable value to the manuscript. Indeed, many of the meta-analyses cited by the authors included both study design. However, I recognize that this revision would imply a substantial additional work, thus I do not consider it mandatory.

2) In 1991 a Monograph on coffee consumption was published by IARC. The authors may cite this publication in the Background and/or Discussion.

Moreover, other meta-analyses have been recently published on the association between coffee consumption and various cancer types. These include:


The authors may improve the Discussion including comments on these publications.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests