Reviewer’s report

Title: Adherence to the World Cancer Research Fund/ American Institute for Cancer Research cancer prevention recommendations and risk of in situ breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

Version: 0 Date: 10 Aug 2019

Reviewer: Claire Vajdic

Reviewer's report:

The authors have examined the association between a lifestyle score and the incidence of in-situ breast cancer (BCIS) in the EPIC cohort. The EPIC cohort is high-quality and large, the baseline questionnaires were validated, the BCIS diagnoses were histologically confirmed, and sensitivity analyses were performed. The manuscript is well-written. The authors observed no association between the lifestyle score and BCIS risk for the full cohort, and a modest protective association for the sub-cohort recruited mainly via mammographic screening.

However, I think that this is a missed opportunity to comprehensively examine the relationship between established and putative carcinogenic exposures for invasive breast cancer and risk of BCIS in a high-quality cohort. The composite lifestyle score categorises 8 factors (7 in previous studies) into one of three categories (4 categories for consumption of wholegrains, vegetables, fruit and beans), thus ruling out an opportunity to examine plausible exposures to the extent usually performed in large, well-characterised cohorts. Also, for some lifestyle factors the categorisations are potentially misleading. For example, the "be a healthy weight" component gives 1 point to normal weight, half a point to overweight, and no points to those either underweight or obese, thereby misclassifying a likely carcinogenic exposure given the established evidence that body fatness is a risk factor for postmenopausal invasive breast cancer (Lauby-Secretan NEJM 2016). Additionally, given the consistent evidence that 1 glass of alcohol per day increases the risk of postmenopausal invasive breast cancer (and emerging evidence of the same for premenopausal breast cancer), the categorisation of alcohol consumption in terms of BCIS risk is not on strong ground epidemiologically, as 1 point is given to &gt;=10g/d (&gt;=1 glasses per day). Furthermore, the utility of a lifestyle score to strengthen health promotion efforts in cancer control is not justified by the authors.

Other issues
1. I recommend the abstract list the component parts of the WCRF/AICR lifestyle score, especially because it differs from previous studies
2. The abstract conclusion, that lifestyle is associated with BCIS risk among women with regular screening participation appears too strong given the lack of data on screening participation in this cohort, the stated paucity of prior evidence, and the upper bound of the 95% confidence interval
3. Can the authors clarify whether the decision to stratify by recruitment centre type (screening, other) was made a priori?
4. It is now usual practice to perform stratified analyses (by menopausal status) for invasive breast
cancer. Can the authors clarify why that was not the primary analysis in this study, particularly given the justification for the study given in the introductory text?

5. The missing data is a limitation that is not acknowledged in the discussion. From Table 1, the missing data do not appear to be missing at random - they are almost always greater for the women recruited via the non-screening compared to the screening centres. Given this, what is the potential impact of the imputation on the study findings?

6. On what basis were the cut-points for the categories WCRF/AICR lifestyle score chosen?

7. Discussion page 14, line 328. ".. that we observed in the present study is overall consistent with findings from studies on invasive breast cancer risk [18, 24-26], even though for some individual components (e.g. alcohol consumption) associations have been detected [4, 23, 26]." This statement appears to downplay an association that IARC has classified as having sufficient evidence of carcinogenicity (alcohol and invasive breast cancer). I recommend this paragraph be re-written with reference to the many high-quality cohort studies that have examined lifestyle exposures and invasive breast cancer risk, unconfined by the crude categories of a 'lifestyle score'.

8. Discussion page 15, line 349. I don't believe there is sufficient evidence from this study to support the claim "Thus, associations between pre-diagnostic lifestyle and risk of BCIS as well as invasive cancer could suggest that lifestyle acts at a relatively early stage of breast carcinogenesis".

Minor issues
1. As per the STROBE guideline, the numbers of women excluded, and the reasons for exclusion, should be reported
2. A sensitivity analysis using the WCRF/AICR lifestyle score used by previous studies would allow better comparison with those studies
3. All references to associations with invasive breast cancer risk should clarify whether it applied to post-menopausal women, pre-menopausal women, or all women

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?
5. Do you have any other financial competing interests?
6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

**Statement on potential review bias**
Please complete a statement on potential review bias, considering the following questions:

1. Did you co-author any publication with an author of this manuscript in the last 5 years?
2. Are you currently or recently affiliated at the same institution as an author of this manuscript?

If you can answer no to all of the above, write 'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria”. If your reply is yes to any, please give details below.

I co-authored 3 papers with Carlo La Vechia in 2014 - we were members of a consortium and I had no contact or correspondence with him in the course of that study or since.Similarly, I have coauthored 7 papers with Elio Riboli in the last 5 years. All papers are consortium papers and neither of us led the analyses. I have had no contact or correspondence with him in the course of those studies or since.I have no institutional affiliations with any of the authors.
I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.