04-Oct-2017

Dear Dr. Srour

Manuscript ID BMJ.2017.040538 entitled "Consumption of ultra-processed foods and cancer risk: results from the NutriNet-Santé prospective cohort"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Daoxin Yin
dyin@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Julie Morris (stats), Wim Weber, Jose Merino, Georg Roggla, Tiago Villanueva, Daoxin Yin, Rubin Minhas, Sophie Cook

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

Our statistician made the following comments regarding a number of statistical issues that need to be addressed by the authors:

1. The study group is a very select cohort of subjects who are willing, and able, to provide detailed food consumption data every six months. This may introduce bias in various ways (not just to 'weaken' the observed associations, as noted by the researchers), and this should be acknowledged.

2. More information on the definition of ultra-processed food should be provided. For example, a table showing examples of ultra-processed vs non ultra-processed food. The mean % ultra-processed food consumption in this cohort was 18.7% (Table 1). It would be interesting to know what is the estimated average % ultra-processed food in the 'normal' population?

3. The mean number of dietary records per subject over the first two years of follow-up is reported to be 5.4 (Page 9). How does this relate to the fact that three 24-hour dietary records were made every six months? What was the extent of missing dietary information?

4. The statistical methodology used is appropriate, but it is not clear why quartiles of food consumption were selected? Why not quintiles, or the exact % of food consumption?

5. Table 1. The p-value reported for 'ultra-processed' food should be omitted here (differences between quartiles are a consequence of their definition).

6. There are many differences in population characteristics between subjects in the various quartiles of consumption (Table 1). Several adjusting factors were employed in the statistical analysis, however it is very difficult to adjust for all factors related to 'behavioural' aspects. Thus, it would seem more appropriate to give a greater emphasis on the tentative nature of the study findings.

Editors thought the research question is very interesting and the study would have public health implications, and they also made the following comments:

* Please be sure to respond to the comments made by the statistician and reviewers.
* Editors noticed the authors gave a brief description of "ultra-processed food" in "MATERIAL AND METHODS," and they thought the authors could better describe the definition of "ultra-processed food." What is the difference between processed food and ultra-processed food? The paper would benefit from a table listing common ultra-processed foods as examples.
* The gender distribution is very skewed (80% women). In "DISCUSSION," the authors highlighted the limitations of the study, such as "overrepresented women" and some other characteristics higher than the average level of the general French population, please discuss how it would affect the interpretation of the findings.
* Please provide explanation and justification regarding the ascertainment of cancer cases. This concern was shared by some reviewers and editors.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Relevance - Study aims

I was a carer for my husband who died of bowl cancer in less than 2 years of being diagnosed of the disease, and I am also a breast cancer patient on remission for 10 years. We as a family have always believed in eating healthily and taking good care of our body; we never smoke, drink alcohol, nor eating ultra-processed food. However, both my husband and I found ourselves brushed with the dread word of cancer. As a result of our experiences, I have become very interested in how cancer comes about, and how to prevent it to happen.

This study aimed to assessing the prospective association between ultra-processed food and cancer risk, which is important to me as a patient on remission in trying to understand cancer. I also believe this study is important to the general public (carer or non-carer), the health care professionals, and the government who overseeing the health care budget, research and policies for the nation.

Areas that are missing - data collection

Although the participants completed a set of 5 questionnaires related to:

1. socio-demographic and lifestyle characteristics (e.g. date of birth, sex, occupation, educational level, smoking status, number of children),
2. anthropometry 36;37 (e.g. height, weight),
3. dietary intakes(every 6 months),
4. activity (validated 7-day International Physical Activity Questionnaire [IPAQ]) 38,
5. and health status (e.g. personal and family history of diseases, medication use including use of hormonal treatment for menopause, oral contraceptive, and menopausal status),

but emotional well-being has not been included.

Various research suggested stress plays an important part in our health and could lead to disease. A recent TV series broadcasted by the BBC titled 'A doctor in the house', showed how the doctor, a GP, able to help suffering family reverts illness by taking a holistic approach in the care plan; that is, in addition to specialist treatment, he helped the family to understand and change their diet, physical exercises, and relief stress.

Measured outcome

This study concluded that a 10% increase in ultra-processed food consumption leads to 10% increase in cancer risk. This is a very significant finding not only to patients, but to the general public as a whole. It is important that this preliminary study will lead to further investigation.

Conclusion

Due to the significant finding of this study, I strongly believe this paper should be published on the BMJ. So that health care professionals, such as GP's, are aware of the important of this finding and be able to offer a more holistic approach in their patient care.

Additional Questions:
Please enter your name: Kin Cheung

Job Title: patient reviewer

Institution: bmj

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
I have reviewed with great interest the manuscript; is a document mostly well written.
The article is interesting and relevance to the field of this journal and is importance to general medical readers, and scientific reliability.
However, the authors might consider some minor recommendations:
INTRODUCTION
line 27-29, these sentences need correction and Language editing is required.
Matherial and Methods
Data collection
1. line 7, since dietary supplements effect on overall daily nutrient intake, how did you assess use of multivitamin and selected individual dietary supplements?
Did you consider it in analyzes?
2. line 12, place space between "periodfor" and correct it to "period for"
Case ascertainment
The participants are adequately described, on the whole.
1. However, it was unclear how this physician diagnose case event?
2. No information is available on how participants were followed for example if subjects change their address?
Statistical analysis
line 25, Given reference (35) is not about IPAQ, please correct this reference to (38).
Results
line 5, participants among the highest quartile of ultra-processed food intake tended to be younger,...
Which group was reference?
Discussion
1. line 14, about reference 50: is it online vebsite or article? reference should be corrected.
2. line 28-32 need references. please provide correct references. as well as, line 32-34, experimental studies require references.
3. line 43, provide references.
Reference
1. reference 24: provide correct reference of website.
2. reference 46 is not correct according to journals format.
3. about reference 50: is it online website or article? Reference should be corrected
Recommendation: This manuscript is rigorous and provides a useful contribution to its area of research and should be published.

Additional Questions:
Please enter your name: mahdieh

Job Title: Ph.D candidate of nutrition

Institution: Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Reviewer: 3

Recommendation:

Comments:
Dr Andrea Darling
Thank you for inviting me to review this interesting and well written manuscript. There is little existing
data in this area so the results of this paper are original and will have an impact of public health
messages in terms of diet for cancer avoidance.
I think the main limitation of the study is how the cases were ascertained. This was done through
self-report measures. Although validated by a physician and patient medical records there may be bias
in that some people with cancer may not report this to the study investigators. Therefore some of the
controls may actually have cancer. Although classification is never perfect in any study with medical data
linkage this would be less of a problem as the quality of an individual's linked data (accuracy, coverage)
is not likely to be linked to characteristics of the participant, unlike self-report. I think the authors need
to add a sentence to the discussion regarding the limitations of their method of ascertaining cases.
However, otherwise the study design and methodology appears strong, the paper comprehensively
covers all the methods used and presents the results well. Details of the participants are
comprehensively given. It has a clear research question, which was appropriately answered. The results
and conclusions are credible, clear and well presented. Most importantly it highlights an important
message about the consumption of ultra processed food and cancer risk. This will be important to public
health providers and policy makers, but is not as relevant for clinicians.
I am an epidemiologist (not a food scientist) so I can't comment on the science/methods surrounding
analysing ultra-processed foods content of diets.
Very minor comments
P6 L5 Can you clarify here whether the higher lipidaemia is prevalence or incidence (also for obesity and
hypertension).
P8 L40 You say that 'for physical activity a missing class was included in the analysis'. Can you just
clarify why this was included, especially why it was included for physical activity but not the other
confounding variables.
P8 L56 What do you mean by 'censored'? Do you mean excluded?
Table1 There is a typo for premenopausal status. 728% should be 72.8%?

Additional Questions:
Please enter your name: Andrea Darling

Job Title: Postdoctoral Researcher

Institution: University of Surrey

Reviewer: 4

Recommendation:

Comments:
The manuscript is well-written and presented quite interesting results. The association between
ultra-processed food and cancer incidence were significant and remain there in the sensitivity analysis by
removing cases that occur within the first years of follow up. The authors have described clearly the
limitation and strength of the manuscript. However, there are some improvement should be made to
improve the quality of the manuscript.

Page 7: the author stated that "Usual dietary intakes were assessed every 6-months through a series …
… … considered as baseline usual dietary intakes in this prospective analysis." It means that in a perfect
assumption that there will have 12 days 24h-dietary records. However, in the results, the mean number
of dietary records per subject over their first two years of follow-up was 5.4 (SD=2.9). It seems that
more than half of the participants did not accomplished the half of the 12-days surveys, isn't it? There
lacks of sufficient information about the of 24h-dietary records in the four times surveys during the two
years. If most of individuals answered the questions only in the first half of the years or in second half of
the years, the dietary information collected might may lacks of sufficient accuracy.

Page 8: The author said "Participants self-declared health events through the yearly health status
questionnaire" . So, it means that the outcome was self-reported. The participants in the cohort was
invited to send their medical records the study physicians contacted the participants' treating physician
or the medical structures in any necessary time. Certainly, medical records might provide a good
approach to ascertain the outcome. However, how about with those who did not report the medical
records but in fact had the interested outcomes, such as cancer in this study. If there is a higher
proportion about this, the credibility of the results might be discounted largely. In addition, what's
proportion of the cases who provided the medical records? Did all participants finish the yearly health
status questionnaire?

Page 9: The author established four different model to estimate the effect of ultra-processed food on the
cancer incidence. The author adjusted for western dietary pattern in model 3 and model 4. Because the
western pattern is a new generated variable, some more detail description is needed. Previous study
also reported the fresh food and nutrients might contributed to the cancer incidence. Thought the author

in this study considered the confounding effect from lipid intake, sodium intake, carbohydrate intake and western dietary pattern, the dietary effects from less ultra-processed food can not be balanced.

Page 10 Ultra-processed food is the major exposure in this study, the author provided the information of the Relative contribution of each food group to ultra-processed consumption in the diet. However, more information about the distribution among the participants are needed.

Page 10: Participants among the highest quartile of ultra-processed food intake tended to be younger. What's the age range of participants in this study? Age is a major confounder. A stratified analysis by age may be necessary. This study overrepresented women, hence, a stratified analysis by sex may be also necessary.

Additional Questions:
Please enter your name: LIU, XUDONG

Job Title: Research Associate

Institution: JC School of Public Health and Primary Care, Chinese University of Hong Kong

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way
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HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: none

Reviewer: 5

Recommendation:

Comments:
Reviewer: Martin Lajous

In this paper the authors evaluate the relation between ultra-processed foods and total and site-specific cancer incidence. This is a timely topic that is complex that requires thoughtful evaluation of the challenges faced by epidemiologic studies in evaluating the health impact of food processing. Unfortunately, excitement for the paper is dampened by lack of detail on the description of the design and methods for data collection, limited information on the validity of exposure and outcome assessment, and a restrained discussion on the limitations of the study. Confounding is perhaps the biggest limitation of this study. Consumption of ultra-processed foods is related to behavioral risk factors

for several cancers. Nevertheless, the authors should be commended for a creative study design that undercuts the limitations of new epidemiological studies on diet and health.

Major comments

1. Validity of the dietary assessment. Usual dietary intake was assessed using computer-based 24-hr records. Investigators report that that participants were asked to record daily dietary intake for 3 days on a 2 week period every 6 months. More information on the validity of the assessment would reassure the reader. Was seasonality taken into account? Some participants appear to have less than 3 records. Is having one record every 6 months on three occasions equal to having 3 records on the same 2 week period? Also, did the timing of dietary assessment ever coincide with that of self-reported cancer? Were the assessments averaged? Individuals with 1 assessment were excluded suggest considering sensitivity analyses to determine the impact of individuals with fewer records.

2. Definition of the exposure. The exposure is the proportion of ultra-processed foods in the diet (processed foods in weight/total food intake in weight) including beverages and solid foods. More detail should be provided on what were the main food components of this composite measure. More detail should be given to the reader of what this composite exposure means. In terms of public health advice, individuals would want to know which foods to avoid. Also, I suggest evaluating the main contributors to the exposure independently to assess the presence of a food item that could be exerting a particularly important impact on cancer risk.

3. Outcome assessment. Participants self-reported cancer cases that were then validated via record review. Were all cancer cases validated? What happened to cases that were not validated? Is the cancer incidence in this cohort what would be expected for the age distribution? No detail is provided on morality follow-up. How was this performed? Were there any cases identified in mortality follow-up? What was the follow-up rate? Acknowledging that some cases may have been missed and pointing out how this may affect the interpretation of results would be useful to the reader.

4. Confounding. Perhaps the most important challenge for this analysis is the possibility of residual confounding. Several strong risk factors for cancer (i.e. smoking, physical inactivity) appear to be associated to consumption of ultra-processed foods. I would suggest aiming at lowering as much as possible the risk for residual confounding (e.g. estimating cigarette years and/or conducting analyses among non-smokers only). In addition to conducting analyses, the authors should discuss at length the possibility of missmeasured confounders in the discussion section. Do the authors believe that the dietary assessment allows for a good estimation of sodium intake? Please provide details to support this.

5. Various issues. Please provide more detail regarding the mediation. These analyses are complex and require several sometimes untenable assumptions. The reader is left wondering if the assertions made by the investigators regarding mediation are warranted. I would suggest separating fat into different types of fat. As the authors are aware the relation of fatty acids with different health outcomes including cancer appears to differ by type. Adjusting for Western dietary pattern seems odd in that the correlation between the exposure and this cofounder that is derived from the exposure may be strong and the resulting estimate difficult to interpret. Why were quartiles chosen? Using quintiles may have provided more insight on the nature of the relation. Please comment on the average follow-up time and how this affects the interpretation of results.

Minor points

1. Abstract. Please consider the use terms that may not be understandable to a general reader (ie. food contact materials). Include the median age of the population and specify that models were adjusted for risk factors.

2. Page 6 line 29 delete the s in "details".

3. Page 7 line16 check "periodfor"

Additional Questions:
Please enter your name: Martin Lajous

Job Title: Faculty-Researcher

Institution: National Institue of Public Health

Reimbursement for attending a symposium?: No

Information for submitting a revision