**Subject:** BMJ - Decision on Manuscript ID BMJ.2015.028305.R2

**Body:** 26-Jun-2016

Dear Dr. Oh:

Manuscript ID BMJ.2015.028305.R2 entitled "Screening as a cause of the thyroid cancer epidemic in Korea: Evidence from a nationwide study" which you submitted to BMJ,

Thank you for sending us your revised paper. We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it in line with the additional comments from the reviewers. The report is available below.
We are provisionally offering acceptance but will make the final decision when we see the revised version.

We are looking forward to reading the revised manuscript and, we hope, making a final acceptance decision.

Please note that the BMJ might choose to shorten content or replace or re-size images for the print issue.

https://mc.manuscriptcentral.com/bmj?URL_MASK=14df33548da14d1997b616ea673c4db7

Yours sincerely

Kristina Fišter
kfister@bmj.com,

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 the external peer reviewers**

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
Dear Drs Oh, Park and Colleagues –
Thank you for the opportunity to serve as a reviewer of your manuscript, titled "Screening as a cause of the thyroid cancer epidemic in Korea: evidence from a nationwide study". Overall I think this is a carefully constructed paper that will be a useful addition to the literature – I think some will continue to be concerned that the epidemic is real – but it is still very useful and I think quite powerful.

I think the problem detractors will point out is that rates of small clinically detected tumors also went up (which you rightly point out could be either misclassification or inaccurate insurance claims). I think an additional effective argument here might be to add that 8-9mm tumors are just too small for any patient to notice or physician to find at such high rates. To be palpable or cause symptoms at such a size they would have to all be located at the isthmus (easier to feel) or external surface of the thyroid (also easier to feel), or be invading/pressing on the trachea or recurrent nerve or esophagus (not likely for every single one of these tumors). It falls into the category of what Gil Welch has taught me to label as - 'possible, but not particularly plausible'. The clinically detected rates going up as they did is likely reflective of more complex changes in medical practice than can be seen in higher level data reviews, and also the problems you point out of misclassification and insurance claim issues.

The remainder of my comments are directed at readability and making sure your discussion section is complete.

1. Methods section is very well written. I feel like I clearly understand what you did.

2. I like the supplemental tables 3 and 4 (incorrectly labeled in the discussion text as supplemental tables 2 and 3). They help the reader feel confident in your sampling methods. Waiting until the discussion seems late to bring them up. Consider mentioning them in the methods or results.

3. There are just so many results, it was a really a struggle for me to cognitively shift gears every time

I was looking at a new way to organize the counts, rates, and changes. Are we really helping the reader learn something by showing the data so many different ways? This is an editorial and authorial decision, of course, but I have a few thoughts.

Would it help if it was explained in the text what the value is of seeing an absolute number instead of a proportion, etc.? Or, another idea - maybe the tables and figures could be notarized in the 'white space' to help the reader see why each way of looking at the data adds something unique to the paper? This may not be fixable (in some ways, it is the curse of epidemiology that I always struggle with as an author, myself), but worth thinking about. Also, I know it may not be something the editors want in their journal, but if it spurs discussion, about how best to present the results, then I will have helped.

4. In the discussion, reporting relative survival rates of >100% may not be easily understandable to readers not closely familiar with the various kinds of survival calculations. You may want to take a minute to explain it, such as by saying 'rates are >100% because the life tables used to make the calculation are not exactly representative of those undergoing the screening - those undergoing screening are healthier than the general population'. Alternatively, you could truncate the rates at 100%.

5. Page 16 line 21: 'the truth seems to be the opposite" is not followed immediately by a strong argument of why the truth is opposite. Consider rephrasing to strengthen /clarify the argument or altering the flow of the discussion.

6. Page 16 line 25 : typo - "and the most" was probably meant to be "and most"

7. Page 17 line 24: 'one of the first to show a direct association' of routes of detection, or is this actually better stated to be 'the first'? I don't know of another study that is quite like this one, but have not done an in depth literature search. There are others that were similar, and it would be polite to reference them – for example a 2014 study authored by Udelsman in the journal Thyroid that correlated the density of surgeons, endocrinologists and insurance claims for ultrasound with rates of thyroid cancer in the U.S. might be a good one.

8. Page 18, lines 24-29: "Although many experts suggested that the increase in the incidence of thyroid cancer was mainly due to the increasing utilization of imaging tools for thyroid cancer screening…", this is an oversimplification of what we now recognize about how thyroid cancers are detected (and of what Dr. Welch and I said in the discussion section of the paper referenced for this statement). The problem starts at the macro level, with how health care is paid for at the system level, and extends all the way down to the microscopic level, with how pathology specimens are processed these days compared to how they were examined 30 years ago. You will help readers understand the complexity of the problem by indicating this more fully. I was the head of a task force that looked at this and published a review paper in 2015 in the journal Endocrine Practice outlining the known contributors (and non contributors) to the increasing incidence of thyroid cancer, and there was also another similar paper written in 2013 in the Journal of Cancer Epidemiology with the first author Pellegriti. Both have good reference lists to show the other work that has been done to illuminate the various ways thyroid cancers can be detected.

9. Page 20 line 22: typo - "provides an evidence" should be revised to "provides evidence that'.
10. Page 20 line 33: typo – "conserted" is spelled 'concerted'.

Best –
Louise Davies

Additional Questions:
Please enter your name: Louise Davies

Job Title: Associate Professor of Surgery

Institution: Dartmouth College, Hanover, NH

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

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 (please see BMJ policy) please declare them here: I have been an invited speaker on thyroid cancer epidemiology at academic conferences. I have received funding for research on thyroid cancer epidemiology and also on the patient experience of thyroid cancer. The National Cancer Institute contracts with my employer (The Federal Government, Department of Veterans Affairs) to pay for time that I work with them on cancer epidemiology research - although this is for work related to other head and neck cancers and not thyroid cancer, per se.

**Information for submitting a revision**

Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

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a. Title: this should include the study design eg "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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**Date Sent:** 26-Jun-2016