20-Oct-2015

Dear Dr. Oh

Manuscript ID BMJ.2015.028305 entitled "Screening as a cause of the thyroid cancer epidemic in Korea: Evidence from a nationwide study"

Thank you for sending us this paper, which we were pleased to have the chance to consider and enjoyed reading. 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. This is 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 committee meeting, so that we will be in a better position to understand your study and to decide whether The BMJ is the right journal for it.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a decision.

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

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

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are athttp://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option.
If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

3. Open access publication fee: The BMJ is committed to keeping research articles Open Access (with Creative Commons licences and deposit of the full text content in PubMedCentral as well as fully Open Access on bmj.com). To support this we are now asking all authors to pay an Open Access fee of £3000 on acceptance of their paper. If we accept your article we will ask you to pay the Open Access publication fee; we do have a waiver policy for authors who cannot pay. Consideration of your paper is not related to whether you can or cannot pay the fee (the editors will be unaware of this), and you need do nothing now.

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You may also click the below link to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

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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).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Yours sincerely

Kristina Fišter
kfister@bmj.com

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'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

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), Jonathan Deeks (statistician), editors - Wim Weber, Georg Roeggla, Jose Merino, Tiago Villanueva, Rubin Minhas, Kristina Fišter.

Decision: request revisions

Detailed comments from the meeting:

First and foremost, 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:

* The paper is not entirely clear on why this should be considered overdiagnosis, and to what extent. The claims you currently submit can't easily be linked to the data presented in the paper. Please lay out the arguments more clearly, in the point-by-point response to reviewers and editorial comments, as well as in the paper.

* Follow-up seems too short to know conclusively whether these small tumours constitute overdiagnosis. This may be an unavoidable limitation, but worth noting and discussing in the paper.

* Several editors commented that the paper may not be adding enough for a general journal to prioritise. Perhaps you could make the novel points clearer in the text, however we are of course not asking you to go overboard. We considered one of the reviewers' suggestion - to do more on spread to the lymph nodes - a good point on how to improve the paper's value in terms of novelty.

* Once the revised version is in, we may seek further reviewers' opinions, including a statistics report.

IMPORTANT
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.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at
http://resources.bmj.com/bmj/authors/bmj-pico

d. Please include these items in the revised manuscript to comply with BMJ style:

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

Abstract
structured abstract including 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 study registration number and name of register – in the last line of the structured abstract.

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

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
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/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

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)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)
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
Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

Footnotes and statements

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

ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

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transparency statement: a statement that the lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies are disclosed.

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signed patient consent form(s), if the article gives enough personal information about any patient(s): this sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see

http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)

a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
The BMJ has partnered with the Dryad Digital Repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to The BMJ article and back - we encourage authors to use this option
funding statement (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
for studies funded or sponsored by industry (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication
assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
Dr. Park and colleagues have demonstrated that much of the increase in thyroid cancer incidence in Korea is due to screening rather than enhanced clinical detection. This paper is very similar to the studies of Davies and Welch (JAMA 2006;295:2164-7) and others which has shown a global increase in thyroid cancer incidence, with much of it due to use of neck ultrasound and other imaging modalities which pick up incidental nodules. The major advantage of this study is that the authors reviewed the charts of the patients to find out how the thyroid tumors were discovered, which makes their conclusions more solid than prior studies. This is a nicely performed and analyzed study and the conclusions are supported by the data.
I have a few suggestions for the authors to consider:
1. Table I: please provide p-values for differences between groups.
2. Table 1: histologic types--does the decrease in percentage of follicular carcinoma from 1999 (7%) to 2008 (1.8%) represent a true decrease or does it represent more follicular lesions being called Follicular Variant of Papillary Carcinoma? This needs a comment.
3. I think that Supplementary Figure 1 should be included in the text.
4. This study emphasizes the need to try and differentiate between indolent tumors and the more aggressive tumors; otherwise there will be many patients undergoing unnecessary surgeries for tumors that would never have caused problems. One approach is through the use of molecular markers in the FNA specimens, while another is the active surveillance of the small papillary carcinomas as described by Ito and colleagues (Ito Y, et al. Thyroid 2003;13:381-7) as well as others. A brief discussion of this should be added to the Discussion section to allow readers to think about ways to handle the overdiagnosis issue without sending all patients to surgery.
5. Minor corrections
Pg 12, line 14--remove the first "tumor" from the sentence.
Pg 13, line 52--The sentence starts with "Moreover" but there is no rest of the sentence.
Pg 16, last sentence--should connect with prior sentence and connect with a comma.

Additional Questions:
Please enter your name: Glenn D. Braunstein, M.D.

Job Title: Professor of Medicine

Institution: Cedars-Sinai Medical Center

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 (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
Dear Dr. Park and Colleagues,
Hello, and thank you for the opportunity to review your work. This review is for your paper titled 'Screening as a cause of the thyroid cancer epidemic in Korea: evidence from a nationwide study'. Overall, the paper submitted is strong. I think it is important work and hope to see it come to fruition. I hope you find my comments helpful.
Best –
Louise Davies
White River Junction, Vermont, USA

*Originality – does the paper add to literature?
The work adds to the growing body of literature on overdiagnosis. It brings out in more detail the terrible problem of overdiagnosis of thyroid cancer that is occurring in Korea and was first brought to light for people in United States by the New England Journal of Medicine article last year.

The paper focuses quite a bit on the change in the size of detected tumors. This is very similar to the approach that we took the last time we looked at the SEER data when we published our paper (Davies & Welch) in JAMA Otolaryngology in 2014. I think this group is missing a great opportunity by focusing on tumor size

I think that this group has very interesting and unsettling data that they could highlight better in the dramatically increasing incidence of detected regional spread of thyroid cancer to the lymph nodes. Presuming that the regional spread of disease is also a product of overdiagnosis, these results call into question our current thinking about how we might best manage thyroid cancer overdiagnosis. In the thyroid cancer field, the discussions right now are about whether we can monitor cancers of one cm, or 1.5 cm. If it turns out we also need to be thinking about whether people with regional spread should be observed, that is a big shift in thinking. Focusing on the importance of the fact that we are detecting regional spread of disease without a change in mortality would really be a an important new piece of data.

*Importance to this journal's readership – clinicians / patients / policy makers…?
Presuming that the authors agree with my suggestion of how they should refocus this paper to point out the dramatic increase in the detection of regional involvement that still does not increase mortality, I think this paper would be very important. If they feel it is important to maintain a focus on tumor size, it will still out a lot, but it will not be as impactful.

*Scientific reliability – is the question clearly defined / appropriately answered?
The research question is clearly defined. There are some issues with the presentation of results that need to be cleared up

*Overall design – adequate?
The design is adequate.

*Participants – adequately described / conditions defined?
The participants are adequately described
The conditions under study are adequately defined

*Methods – adequately described / consistent with reporting standards?
The methods lacked some key details that would be helpful to most readers.

First, the staging system is the AJCC staging system, not TNM. It should be called the AJCC sixth edition, not the TNM sixth stage.

The use of the SEER summary stage variable requires explanation in the form of a clear definition of local, regional, and distant. Only those of us who work closely with SEER data know what it means, and in fact the definition of local, regional and distant varies by tumor site. Therefore, it is really important to indicate what exactly constitutes 'regional spread' in the seer summary data variable for thyroid cancer. Specifically, I would guess that regional spread means involvement of lymph nodes. If this is the case, there is potentially a problem with table one. Regional lymph node involvement in table 1 does not appear to have change substantially between 1999 and 2008, but the seer summary stage for regional steadily increased from 1999 to 2008. This suggests that either the definition is not what I thought it was for thyroid cancer, or there's an error in the table. The mismatch between the Seer summary stage numbers for table 1 and table 2 also feels unsettling. The numbers are being expressed differently – one is case numbers and the other is age standardized incidence rates, but somehow I feel like they should probably match up better than they do.

*Results – answer question / are credible / are well presented?
The results are somewhat confusing in places because the data that are presented visually do not always match data that are reported in the results text. For example, the authors refer on page 11 to a supplementary table 2. This is said to be data on regional lymph node involvement over time by tumor size. There is no such table in the data set, and even looking to see if something was mislabeled, I could not find any display of these data. This is too bad, because I'm very interested in seeing these data.

Table 1 is clear and useful. Table 2 also provides useful data. Figure 1 is helpful, but might benefit from a clear divider to separate the screen detected plots from the clinical detected and total. I personally find figures 2A and 2B to be very hard to interpret. It needs a label on the Y axis, but also I'm not sure what I'm supposed to get from this figure. It may need a different method of illustration. Supplementary figure 1 should be part of the primary data in my opinion. Even though it is a familiar figure to many, it is still very striking and helps to place the problem of overdiagnosis in perspective.

*Interpretation and Conclusions – warranted by / sufficiently focused on the data?
The interpretation is warranted by and sufficiently derived from/focused on the data. The message is clear.

*References – up to date / relevant
References are up to date
References are relevant

*Abstract/summary/key messages – all consistent / accurately reflect the paper?
The abstract, conclusions, key messages all accurately reflect what the paper says.

*Grammar and language – acceptable?
There are some grammar and English language issues to address, they are minor.

Additional Questions:
Please enter your name: Louise Davies

Job Title: Associate Professor of Surgery - Otolaryngology

Institution: - VA Outcomes Group, White River Junction VA and Dartmouth College

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 received honoraria for giving grand rounds and invited talks about thyroid cancer and over diagnosis. I also have a grant to research the impact of over diagnosis on patients.

Reviewer: 3

Recommendation:

Comments:
In this submission entitled "Screening as a cause of the thyroid cancer epidemic in Korea: Evidence from a nationwide study" the authors present the results of a detailed epidemiologic study to support the conclusion from recent publications suggesting that the epidemic of thyroid cancer observed in South Korea are a result of overdiagnosis stemming from the adoption of nationwide screening in 1999. The manuscript is well written. I have only the minor comments below.

- Further clarification for what constitutes "screen-detected" versus "clinically detected" cases would be helpful. For the former, the assumption is that these are cases discovered by screening ultrasound, and not other forms of screening such as physical exam or radiologic studies done for other reasons (incidental findings)? For the latter, more details regarding what tumor-related symptoms led to clinical detection would be informative (pain?, detection of a painless lump?, etc…).

- I certainly agree with the author's central premise that increased screening is primarily responsible for the overdiagnosis of clinically insignificant thyroid cancers, and this is the predominant cause for the rise of thyroid cancer incidence in South Korea. The three publications highlighted by the authors (refs 11-13) as challenges to this premise, however, were not analyses performed in the Korean population and did not completely discount the primary contribution of overdiagnosis, but suggested that other factors may be minor contributors given the observation of small increases in more advanced disease. The authors do also make note of minor increases in larger thyroid cancers, extrathyroidal invasion, and to a lesser extent distant metastases (in the screening group of Table 2) in their own data set. Is it possible that in addition to overdiagnosis there is also a small, minor increase in more advanced disease as well that may speak to other contributors?

- The results regarding regional lymph node involvement needs greater clarification. The text refers to a Supplementary Table 2, but none was included in the manuscript that I reviewed. Criteria for what constitutes lymph node involvement would need to be included. While there is an increase in nodal involvement noted over time, I suspect this is related to greater detection of small regional nodes that were of marginal clinical significance?

- Would it be possible to break down the regional stage tumor category (according to the SEER criteria) to disease that qualified because of lymph node involvement only versus those that did because of direct extension? Likely, the increase in regional stage over time is the result of clinically insignificant nodal involvement, but clearly delineating this and establishing that an increase in extensive, invasive primaries did not contribute would be important to support the central premise of the paper.

Additional Questions:
Please enter your name: Alan Ho

Job Title: Assistant Member

Institution: Memorial Sloan Kettering Cancer Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

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 received research funding and fees for consulting regarding investigations of experimental drugs for thyroid cancer, projects which do not directly conflict/compete with this submitted manuscript.

END

Date Sent: 20-Oct-2015