

Point-by-Point Responses to Editors' Comments  
Response to the Comments from Editorial board.

Regarding the comments on the way of interpreting the result;

1. The language used is still overly strong in places (for example, direct means "causal" and we are unconvinced that this is 100% shown in the data).

Response: As recommended we deleted or changed strong languages, such as "cause" and "direct" from title and manuscript as possible, and corrected some sentences as follows:

(Title)

Screening as a cause major contributor of the thyroid cancer epidemic in Korea: Evidence from a nationwide study

(What this study adds on)

- This is the nationwide study utilizing medical record review demonstrated that correlates the increase in thyroid cancer incidence with the routes of tumour detection, directly extracted by a review of medical records. The great majority of increased thyroid cancer cases was attributed due to the increase in the incidence of small-sized tumours, detected mainly by screening.
- Thyroid cancer screening can detect notably small-sized tumours, but also clinically indolent asymptomatic tumours with local extension and lymph node involvement.
- Our study provides clear evidence that the increase in the incidence of thyroid cancer in Korea was mainly due to over-detection.

(Abstract, Page 5 Line 4-6) Introduction

Concerted efforts are needed at local and global levels to discourage reduce unnecessary thyroid ultrasound examination in asymptomatic general population.

(Page 7. Line 13-16) Introduction

To better elucidate the cause of reason for the steep increase in the incidence of thyroid cancer in Korea and other countries, we need more sophisticated epidemiologic studies it would be helpful to know the underlying mechanism of recent increase in thyroid cancer according to the routes of tumour detection.

(Page 8. Line 2- 3) Methods

To investigate the cause of reason for the rapidly rising incidence of thyroid cancer in Korea, in 2010 the Korea Central Cancer Registry (KCCR) conducted the National Epidemiologic Survey of Thyroid cancer (NEST), which was designed to collect a nationally representative sample of thyroid cancer patients diagnosed in the years 1999, 2005, and 2008.

(Page 17. Line 2-4) Discussion

Obviously, a large portion of This increase was attributed to is most likely to be associated with the widespread practice of thyroid cancer screening with ultrasonography, which started around the turn of the century in Korea.

(Page 17. Line 15-17) Discussion

Although some might argue that this finding is inconsistent with the idea of over-detection as a cause of major contributor to recent thyroid epidemic, the truth seems to be the opposite.

(Page 18. Line 15-17) Discussion

our findings provide further supporting evidence for the over-detection as a cause of major contributor to the current thyroid cancer epidemic in Korea.

(Page 18. Line 20-Page 19. Line 11) Discussion

Our study is meaningful as a nationwide survey study that demonstrated the change in the incidence rates over time using a representative random sample of thyroid cancer patients from cancer registry data. In addition, it helped better understand the underlying mechanism of recent increase in thyroid cancer incidences by analyzing the data according to the routes of tumour detection and detailed pathologic findings, including the size of tumour and the nodal status. shows a direct association at the individual level between the routes of thyroid cancer detection and an increase in thyroid cancer rates through the medical record review. On the other hand, previous studies showed only indirect and ecological association between ultrasonography uses and the incidence of thyroid cancer.[8, 27] Our study is meaningful as a nationwide examination of the association between increased thyroid cancer incidence and thyroid cancer screening using a representative random sample of thyroid cancer patients from cancer registry data. In addition, our study also showed that the increase in thyroid cancer incidence was associated with increase in screen-detected tumour, directly extracted by a review of medical records.

(Page 20. Line 3-6) Discussion

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,8 9 11 26 30 [8-10, 26, 31] others remained sceptical and called upon more epidemiologic studies searching for yet unidentified causal factors

(Page 21. Line 1-2) Discussion

Even if there were some increase in thyroid cancer incidence by all those environmental causes factors, their contributions

seems to be very small.

(Page 22. Line 18-19) Discussion – this sentence was deleted  
But, it alone doesn't seem to explain the magnitude of thyroid cancer epidemic in Korea.

(Page 22. Line 10-12) Discussion  
Our study provides evidence shows that the increase in the incidence of thyroid cancer in Korea was mainly due to overdiagnosis, most likely to be that resulted from widespread utilization of sensitive imaging tools such as ultrasound (e.g. ultrasound examination).

(Page 22. Line 17-20) Discussion  
Concerted efforts are needed at local and global levels to discourage reduce the unnecessary routine thyroid ultrasound examination in asymptomatic general population unless clinically indicated.

Regarding the comments on the way of presenting the numbers in the result and discussion;  
2. We would strongly suggest to cut down showing this many numbers in the text of the results section, in particular when the numbers are shown in Tables.

Response: As recommended we deleted many numbers through the results and discussion. Now, the numbers were kept to a minimum level in the results and discussion.

Regarding the conclusion;  
3. You say that the issues raised in the paper are not limited to Korea, but you do not show data to support this statement. Please stay within limits of what the data show.

Response: A recent study of International Agency for Research on Cancer (IARC) published in the New England Journal of Medicine and it showed that the growing epidemic of thyroid cancer in recent decades in several high-income countries is largely affected by overdiagnosis.  
(Reference: Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L (2016). Worldwide thyroid cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med. Available from: <http://dx.doi.org/10.1056/NEJMp1604412>.)

However, we agreed with editor's view and comment that we should make the conclusion within the limits of our findings. We also agreed that our case (Overdiagnosis of thyroid cancer in Korea) is not always adapted to cases of other countries (e.g. thyroid cancer epidemic among young people in Fukushima in Japan, following the release of radionuclides). Therefore, as recommended, we revised the discussion as follows:

(Page 22. Line 15-18)  
"These problems are not limited to Korea. Concerted efforts are needed at local and global national levels to discourage reduce the routine unnecessary thyroid ultrasound examination in asymptomatic general population unless clinically indicated."

Regarding the way of presenting figures;  
4. We are unconvinced that all the figures are needed in the manuscript.

Response: We fully agree that there are so many results. Maybe, concerted efforts of authors and editors are needed to reduce redundant results. To reduce redundant figures, we changed figure 2 to supplementary figure 1. Because figure number was changed, subcategories of result section were re-arranged according to the revised figure number.

5. Please make sure the manuscript follows the BMJ manuscript guidelines in data presentation.  
Response: We revised the manuscript by following the BMJ manuscript guidelines in data presentation.