Author’s response to reviews

Title: Thyroid cancer risks among medical radiation workers in South Korea, 1996-2015

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Thyroid cancer risks among medical radiation workers in South Korea, 1996-2015

Won Jin Lee; Dale L. Preston; Eun Shil Cha; Seulki Ko; Hyeyeun Lim

Environmental Health

We sincerely appreciate the reviewers’ comments on our manuscript. Based on the reviewers’ suggestions, we have carefully revised the paper and responded to all comments point-by-point. We have included the page and paragraph numbers in parentheses that refer to the revised file with the track changes on.

Reviewer reports:

Reviewer #1: In this prospective cohort study based in Korea, thyroid cancer incidence rates in medical radiation workers were compared to expected rates in the general population, compared according to different job titles and estimated thyroid dose categories, and evaluated in relation to thyroid doses using traditional dose-response models. Important strengths of the study included the estimation of thyroid dose based on objective badge readings obtained from a national dose registry, which also provided information on job title, and assessment of dose-response with thyroid cancer incidence and nearly complete follow-up for cancer incidence.
This study of medical workers, with the largest number of thyroid cancer cases to date, found no evidence of an association between occupational radiation exposure and thyroid cancer risk. More generally, the results provide further confirmation of a lack of association between adulthood exposure to radiation and subsequent thyroid cancer risk.

Overall, the analysis was appropriate, and the manuscript was clear and well-written. I have mostly very minor comments and suggestions.

1. Page 3, lines 3-6: delete the word "there" and combine "over" and "diagnosis"

Response: We have deleted the word “there”, and combined “over” and “diagnosis” in the sentence.

2. Page 6, line 35: Please elaborate on the reasons for considering the probability of apron use and apron attenuation factor in the estimation of thyroid dose. What proportion of workers have an under-apron badge?

Response: We estimated radiation organ doses by considering relevant uncertainty factors such as apron usage, badge location, dominant energy of the diagnostic radiation fields, used in the dose reconstruction for the US radiologic technologists study. Badge dose estimates should be adjusted for use of protective aprons and placement of the badge relative to the apron so that the absorbed doses estimated for the organs of interest properly reflect the shielding afforded by protective aprons when they were worn. A nationwide survey result for Korean radiologic technologists conducted in 2012 provided information on apron use and the placement of the badge. The proportions of “no apron use”, “wearing an apron with a badge outside”, and “wearing an apron with a badge underneath” were 19%, 6%, and 75%, respectively.

To elaborate these, we have revised the text “After reconstructing radiation doses for all diagnostic radiation workers using personal badge doses and survey data [13], we estimated radiation organ doses by considering relevant uncertainty factors such as apron usage, badge location, dominant energy of the diagnostic radiation fields [14], used in the dose reconstruction for the US radiologic technologists study [18,19]. However, unlike the USRT dosimetry, which provides multiple realizations each annual dose, our current dosimetry is a deterministic system that provides only a single estimate for each annual dose.” (page 6, paragraph 3 – page 7) and “To account for the effects of apron usage and badge location, we considered the effect of probability factors of wearing an apron, badge position (i.e., inside or outside the apron), and apron attenuation factors” (page 7).
3. Page 9, line 34-35: This should be changed to "larger elevation for men than women"

Response: Thank you very much for pointing out this error. We have deleted this based on the comment from Reviewer 2.

4. Page 11, line 25: "for thyroid cancer rates" should be "on thyroid cancer risk"

Response: We have corrected the text.

5. Page 12, lines 6-7: Please provide some additional clarification regarding this statement: "Third, radiation effect estimates were based on thyroid organ doses constructed from individual badge dose readings while previous studies used exposure information abstracted from records or badge dosimeter." The U.S. Radiologic Technologists Study used thyroid organ doses constructed from individual badge dose readings, and the Chinese X-ray study used simulated badge readings based on work history characteristics.

Response: We have clarified the sentence by revising the text to “Third, radiation effect estimates were based on thyroid doses constructed from individual badge dose readings while previous studies used exposure information abstracted from a combination of data from occupational records and badge dosimeters or simulated badge readings based on work history characteristics." (page 14, paragraph 2).

6. Page 12, line 13: "overall figure" should perhaps be "more complete picture"

Response: We have deleted the sentence based on the comment from Reviewer 2.

7. Table 2: None of the SIRs or RRs may be negative. Please correct.

Response: We thank the reviewer for pointing this out and we have corrected the expression in Table 2.

8. Table 4: "No lagged" should be changed to "No lag" or "Not lagged"

Response: We have corrected all instances of this wording in the text and titles of Tables.
9. All tables: some of the estimates are given with three figures beyond the decimal point, which gives the impression of much more precision than the authors are likely to have had in this study. I suggest using no more than two figures beyond the decimal point (e.g., 1.35 instead of 1.357).

Response: As the reviewer suggested, we have revised the estimates with two decimal points at all tables except for very small estimates and trend p values.

10. Please explain how badge readings were considered when they were below the lower level of detection. Are a high proportion of undetectable levels likely to have biased the findings toward the null? I imagine that this is a particular problem if a large proportion of workers used a below-apron badge (see comment #2 above).

Response: The lowest detectable quarterly level in our national dosimetry registry is 0.01 mSv. The proportion of dose per quarter less than 0.01 mSv varied over time ranging from 19.9% in 1996 to 60.2% in 2011 (average, 46.0% from 1996–2011). To minimize the over- and under-estimation of cumulative doses, we assigned 0.005 mSv, the midpoint between 0.01 mSv and zero, for cases with doses below the lowest detectable level. We examined how relevant this value (0.005 mSv) was by fitting a Tobit regression model and the fitted expected dose below 0.01 mSv was 0.00465 mSv – which was nearly identical to our assumed value of 0.005 mSv. This process was described in our previous paper cited as number 14 (Choi et al., Estimation of organ doses among diagnostic medical radiation workers in South Korea. Radiat Prot Dosimetry. 2018;179(2):142–50). Although we agree that the treating detection limit value is a challenging issue in the field of exposure assessment, we believe that our approach for undetectable levels would not significantly bias the findings. We have added a sentence to explain this in the Methods: “The lowest detectable quarterly level of the national dosimetry registry, 0.01 mSv, were taken as 0.005 mSv to minimize bias in the estimated doses” (page 7).

Reviewer #2: General comments

The paper reports an analysis of thyroid cancer in a cohort of Korean radiation technologists. The findings are largely null, as one would expect given the fact that exposure is in adulthood and the doses are low. The authors make too much at various points (e.g. beginning of the Discussion) of the elevation in SIR, which given the possibility of ascertainment (screening) bias is probably meaningless.

The analysis has been generally well done (but note the additional censoring specified below). However, the presentation of results and the writing are in need of polish. The paper could usefully give more details on the dosimetry. The dosimetry appears to parallel what was done in
the USRT cohort (Simon et al 2006 ref 17), but I suspect that the parallel is not exact, and in any case readers should not have to go to another paper to work out details. The language is occasionally opaque, and would benefit from the services of a native English speaker (which I note that the paper has on its authorship).

Response: Thank you for the comments. We note that our cohort included all diagnostic medical radiation workers and was not limited to radiation technologists as the reviewer pointed. Please find below our responses to each of the comments. We have substantially revised the text for dosimetry part and endeavored to improve the English as the reviewer suggested.

Specific comments (page/line)

p.4 1.55-57 Does this exclusion of previous cancers include non-melanoma skin cancers (NMSC)? If so, I think there is no good reason to exclude these individuals. Also, is follow-up censored at cancer occurrence after baseline (as it should be, again for all cancers apart from NMSC)?

Response: Cancer registries worldwide often do not include data on non-melanoma skin cancers (NMSC) because the data regarding these cancers are frequently incomplete and their clinical significance is considerably lower than for other cancers. Therefore, NMSC may be not an acceptable exclusion criterion for prevalent cancer cases as the reviewer pointed out. However, the Korea Central Cancer Registry (KCCR), which covers the entire Korean population, has provided reliable nationwide incidence data of histologically confirmed NMSC including squamous cell carcinoma and basal cell carcinoma as well as cutaneous melanoma since the year 1999 (Oh CM et al., Nationwide Trends in the Incidence of Melanoma and Non-melanoma Skin Cancers from 1999 to 2014 in South Korea. Cancer Res Treat. 2018;50(3):729–37), and NMSC have been reported as a potential risk factor for other cancer sites. Therefore, we prefer to exclude NMSC cases prior to enrollment. In addition, there were only 6 cases of NMSC among the total of 462 excluded prevalent cancer cases (please see the table below; the incidence of NMSC in Korea is much lower than those of Western countries); therefore, including or excluding NMSC cases would have a negligible effect on our findings.

The distribution of 462 excluded prevalent cancer cases by organ site

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip, oral cavity and pharynx (C00-C14)</td>
<td>12</td>
<td>2.6</td>
</tr>
<tr>
<td>Digestive organs (C15-C26)</td>
<td>152</td>
<td>32.9</td>
</tr>
<tr>
<td>Respiratory (C30-C39)</td>
<td>12</td>
<td>2.6</td>
</tr>
<tr>
<td>Disease Category</td>
<td>Count</td>
<td>Percentage</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Bone (C40-C41)</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Melanoma (C43)</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Non-melanoma (C44)</td>
<td>6</td>
<td>1.3</td>
</tr>
<tr>
<td>Mesothelial and soft tissue (C45-C49)</td>
<td>5</td>
<td>1.1</td>
</tr>
<tr>
<td>Breast (C50)</td>
<td>26</td>
<td>5.6</td>
</tr>
<tr>
<td>Female genital organs (C51-C58)</td>
<td>33</td>
<td>7.1</td>
</tr>
<tr>
<td>Male genital organs (C60-C63)</td>
<td>16</td>
<td>3.5</td>
</tr>
<tr>
<td>Urinary tract (C64-C68)</td>
<td>21</td>
<td>4.5</td>
</tr>
<tr>
<td>Eye, brain and CNS (C69-C72)</td>
<td>6</td>
<td>1.3</td>
</tr>
<tr>
<td>Thyroid (C73)</td>
<td>127</td>
<td>27.5</td>
</tr>
<tr>
<td>Adrenal gland (C74)</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Unspecified (C76-C80)</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Lymphoid, hematopoietic (C81-C96)</td>
<td>33</td>
<td>7.1</td>
</tr>
<tr>
<td>Myelodysplastic syndromes (D46)</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>Unknown behavior of lymphoid, hematopoietic and related tissue (D47)</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>462</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Regarding the follow-up, we censored follow-up at any cancer occurrence after baseline as the reviewer pointed out. For clarification, we have revised the text to: “The end of follow-up was taken as the earliest of the following: the date of thyroid or other cancer diagnosis, the date of death, or December 31, 2015.” in the Statistical analysis section (page 8, paragraph 2).

p.5 l.49-56 This sentence ("Thyroid organ dose … study methods [17].") is incomprehensible, and should be re-written. Also, why is the 2006 report of Simon et al (ref. 17) referred to here? Is there some reason why this outdated methodology, rather than that of the currently used USRT dosimetry report (Simon et al Radiat Res 2014 182 507-28) be referenced?

Response: After reconstructing radiation doses for all diagnostic radiation workers using personal badge doses and survey data, we estimated radiation organ doses by considering...
relevant uncertainty factors such as apron usage, badge location, dominant energy of the diagnostic radiation fields, used in the dose reconstruction for the US radiologic technologists study. However, unlike the USRT dosimetry, which provides multiple realizations each annual dose, our current dosimetry is a deterministic system that provides only a single estimate for each annual dose.

To enhance clarity, we have revised the sentence “Thyroid organ dose was previously estimated for all diagnostic radiation workers after the badge doses were calculated for workers exposed before 1996 [13], by adapting the US radiologic technologists study methods [17]” to “After reconstructing radiation doses for all diagnostic radiation workers using personal badge doses and survey data [13], we estimated radiation organ doses by considering relevant uncertainty factors such as apron usage, badge location, dominant energy of the diagnostic radiation fields [14], used in the dose reconstruction for the US radiologic technologists study [18,19]. However, unlike the US radiologic technologists dosimetry, which provides multiple realizations each annual dose, our current dosimetry is a deterministic system that provides only a single estimate for each annual dose.” (page 6, paragraph 3 – page 7)

p.6 l.6-9 What is the meaning of this phrase "which were determined as the log-linear function of time and age"? As it stands, this barely standard English (e.g. "the" should surely be "a").

Response: We developed a dose reconstruction model as a function of time and modified the model by adding age at the year of exposure as an additional predictor variable: log\(\hat{(\text{Annual dose})}\) = \(\beta_0 + \beta_1 (\text{year}-1970) + \beta_2 \text{(age)}\) (Choi et al., Reconstruction of Radiation Dose Received by Diagnostic Radiologic Technologists in Korea. J Prev Med Public Health. 2016;49(5):288-300). The model features a log-linear function to account for the log-normal distribution of individual annual badge doses.

To clarify this, we have revised the sentence as “Historical badge doses were reconstructed for workers who began working with radiation before 1996 (n = 13,144; 14.0% of the total enrollees in the NDR), using an annual dose model that describes doses as a log-linear function of calendar year and age at the year of exposure [13]” (page 7).

p.6 l.9-13 This ("Organ-specific doses were estimated … [19].") is a carelessly written sentence. As it stands it implies organ doses were estimated by multiplying measured and reconstructed badge doses and some conversion coefficients i.e. [measured dose] x [reconstructed dose] x [conversion coefficient]. What is presumably meant is that measured doses were multiplied by
one coefficient, reconstructed doses by another coefficient; as below why this should be should be made clear.

Response: We apologize for the misunderstanding. The measured doses and reconstructed doses were not treated separately. Both were combined as individual cumulative doses for each worker and we multiplied each individual cumulative dose with two ICRP coefficients for estimating organ doses. The equation was $D_T = H_p(d) \left( \frac{D_T/K_a}{(H_p(d)/K_a)} \right)$ where $D_T$ is the organ dose; $H_p(d)$ is the equivalent dose; $D_T/K_a$ is the air kerma-to-organ dose conversion coefficient; and $(H_p(d))/K_a$ is the air kerma-to-personal dose equivalent conversion coefficient.

To clarify this, we have revised the text as follows: “Organ-specific doses were estimated as the product of the individual cumulative badge doses and two conversion coefficients provided by the International Commission on Radiological Protection (ICRP): the organ-absorbed dose per unit of air kerma free-in-air [18] and the personal dose equivalent per unit of air kerma free-in-air [19]. The equation was $H_p(d) \left( \frac{D_T/K_a}{(H_p(d)/K_a)} \right)$, where $H_p(d)$ is the equivalent dose; $D_T/K_a$ is the air kerma-to-organ dose conversion coefficient; and $(H_p(d))/K_a$ is the air kerma-to-personal dose equivalent conversion coefficient” (page 7).

p.6 1.11-13 What are the values of these ICRP-provided conversion coefficients? The values should be given here. Also, why are the measured and reconstructed components of dose treated differently?

Response: The International Commission on Radiological Protection (ICRP) provided the organ absorbed dose per unit of air kerma free-in-air (Gy per Gy) (ICRP publication 116, 2010) and the personal dose equivalent per unit of air kerma free-in-air (Sv per Gy) (ICRP publication 74, 1996). We assumed an antero-posterior irradiation geometry, which is the most common in occupational exposure scenarios among medical workers. The dominant energy of the diagnostic radiation fields in South Korea was assumed to be between 30 keV and 40 keV. Therefore, we used the average of 30 keV and 40 keV values. All values are listed below and we added the values in the text as the reviewer suggested “(i.e., the conversion coefficients were 0.88 for males and 0.95 for females)” (page 7).
<table>
<thead>
<tr>
<th>Organ or Tissue</th>
<th>30 keV</th>
<th>40 keV</th>
<th>35 keV</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT/Ka Hp(d)/Ka</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DT/Ka)/[Hp(d)/Ka]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.88</td>
<td>0.94</td>
<td>1.11</td>
</tr>
<tr>
<td>Female</td>
<td>0.79</td>
<td>0.85</td>
<td>1.45</td>
</tr>
<tr>
<td>Male</td>
<td>1.45</td>
<td>1.56</td>
<td>1.49</td>
</tr>
<tr>
<td>Female</td>
<td>0.97</td>
<td>1.05</td>
<td>0.88</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is not quite clear what is going on here. I assume that the thyroid will generally be above the apron, but that the badge will sometimes be under the apron, sometimes above, which is why one has to adjust for the probability of wearing the badge in these two locations. Perhaps the introductory sentence ("We also considered …") could be expanded to make this clear.

Response: As the reviewer assumed, the thyroid was outside the apron without shield. Because there was no direct dose measurement on thyroid, we need to adjust the badge reading to account for badges worn below or above the apron for computing an appropriate thyroid dose. A nationwide survey result for Korean radiation technologists conducted in 2012 provided information on apron use and the placement of the badge. The proportions of “no apron use”, “wearing an apron with a badge outside”, and “wearing an apron with a badge underneath” were 19%, 6%, and 75%, respectively.

To elaborate this, we have revised the text “To account for the effects of apron usage and badge location, we considered the effect of probability factors of wearing an apron, badge position (i.e., inside or outside the apron), and apron attenuation factors” (page 7).

As above, follow-up should also be censored at cancer occurrence after baseline (for all cancers apart from NMSC).

Response: We censored follow-up at any cancer occurrence after baseline as the reviewer pointed. For clarification, we have the text as follows “The end of follow-up was taken as the earliest of the following: the date of thyroid or other cancer diagnosis, the date of death, or December 31, 2015.” in the Statistical analysis section (page 8, paragraph 2). For NMSC cases, please refer to our previous response above.
What is the default lag period if sensitivity analyses used unlagged and 5-year lagged dose? Table 4 indicates that in fact both lag periods were used. However, unlagged analyses make no sense; the dose five or so years before the point at risk is essentially irrelevant. There is evidence from Chernobyl-exposed populations (e.g., Kazakov et al Nature 1992 359 21-2) that at much higher doses that thyroid cancer has a lag period of no more than five years (and probably not much less). So in Table 4 and elsewhere I recommend reporting only 5-year lagged results and confine unlagged and (perhaps) 10-year lagged results to an Appendix.

Response: We thank the reviewer for pointing this out. According to the reviewer’s comment, we set the 5-year lagged results as the default findings, and we have revised Table 3 by including the 5-year lagged results both for all workers and workers employed for at least one year. The unlagged findings have been moved to Supplementary Table 2. We have also added the 10-year lagged results in Supplementary Table 3.

SIR for an endpoint like thyroid cancer are almost meaningless, as screening effects could easily account for variations by factors of 2, which encompass the range of SIRs shown in Tables 2-3. It is probably better to report an overall SIR, and otherwise give relative risk (RR) e.g. in relation to some low dose group (Table 3) or occupational group (Table 2). A Figure showing the variation of RR with dose would be useful.

Response: We agree that the SIR of thyroid cancer was mainly affected by the likelihood of health care access and has limited meaning for explaining the relationship with occupational factors. However, we also believe that the SIR findings for different demographic and occupational characteristics would be informative in figuring out overall thyroid cancer risks among medical radiation workers. Although one of our purposes was to examine the overall thyroid cancer risk, we did not adequately address this in the Abstract. Therefore, we have revised the text in the Background section as follows: “This study examined radiation effects on thyroid cancer rates as well as an overall evaluation of thyroid cancer risk among medical radiation workers” (page 2, paragraph 1).

We have deleted the sentence in the Results to minimize the explanation of SIR findings (page 10, paragraph 2). We have also deleted the SIR results in Table 3 and the trends of RR have been replaced in Figure 1 as the reviewer suggested.

As above, SIR for an endpoint like thyroid cancer are almost meaningless. The elevation of SIR is made too much of in this para given this. The authors later rightly qualify this
finding, but it is not necessary to raise this straw man at all. Therefore, I would not recommend beginning the Discussion with treatment of this finding.

Response: As noted above, we would like to present the overall thyroid cancer risk among medical radiation workers and we believe that the SIR findings are helpful in assessing the nature of thyroid cancer risks among medical radiation workers (e.g., whether the risk is from occupational factors or screening, and how much screening effect might be differed by demographic or occupational characteristics).

We have revised the beginning of the Discussion considering the reviewer’s point. “Although thyroid cancer incidence rates were significantly greater than expected based on population rates among South Korean medical radiation workers, the RRs with the association of occupational factors and the ERR with cumulative radiation doses after adjusting for age, sex, and calendar year did not provide any evidence of a statistically significant effect on thyroid cancer risk. Findings were similar for the analysis limited to workers who were employed for at least one year or using unlagged or 10-year lagged cumulative doses. Our findings suggest that the higher SIRs observed in medical radiation workers may be a consequence of non-occupational factors although this should be reconsidered using longer follow-up and more detailed information on lifestyle and environmental exposures, especially during childhood.” (pages 11, paragraph 2).

p.911 l.29-56 Somewhere in this para the authors should point out another weakness of the cohort, namely that exposures are entirely in adulthood. As there are remarkably few cohorts, even at much higher levels of dose, that exhibit risk after adult exposure (Mabuchi et al Radiat Res 2013 179 254-6), excess thyroid cancer risk would scarcely be expected in this low-dose adult-exposed cohort.

Response: We have added the weakness of the cohort to the text: “It could be difficult to find an association between radiation exposure and thyroid cancer in this low-dose adult-exposed cohort; therefore, medical and environmental radiation exposure among children or adolescents should receive special attention because of the marked and persistent radiation effects of such exposures on thyroid cancer rates [39].” (page 13, paragraph 1).

p.911 l.53-56 The authors should perhaps specify what these other risk factors may be, and give references in support. Apart from ionizing radiation exposure in childhood and female sex I would judge that there are remarkably few such, in particular, familial risk, and possibly obesity and cigarette smoking. All of these are unlikely to confound the thyroid cancer radiation dose response in this cohort, and perhaps this should be stated here.
Response: We have added a few other specific risk factors in the text “Therefore, more research is needed to identify potential thyroid cancer incidence risk factors, including: lifestyle factors such as obesity, smoking, and diet; predisposing medical conditions; reproductive and hormonal factors; and environmental factors [38]” (page 13, paragraph 1). We have also updated the contents of cited reference.

We have also added a sentence to explain their possible effect on thyroid cancer risk: “…however, these were unlikely to confound the thyroid cancer risk from radiation exposure in this cohort” (page 14, paragraph 1).

p.12 l.11-16 It is reasonably common to report SIR, RR and ERR so the reported findings are not peculiar to this cohort. I would therefore remove this sentence ("Fourth, the comprehensive …workers.").

Response: We have deleted this sentence from the text.

We hope that we have satisfactorily addressed the comments from the reviewers.