Peer Review File

Article Information: http://dx.doi.org/10.21037/gs-20-346.

Reply to reviewer A:

Comment 1:

This is a retrospective cohort study, comparing 3 time-periods: 1 without iodine, 1 with a lot of iodine, and 1 with moderate iodine. They assume causality in their conclusion, between increases in TC/ PTC and iodine. This is hard to justify with such a retrospective study, as no multivariate analysis has been performed, nor have confounders and biases been adjusted for. Variables, such as sex, age, radiation history, family history need to be adjusted for, as they all influence prevalence. As well as the diagnostic methods.

These diagnostic methods have changed over this 33-year included time-period, which makes it hard to not think there is a big confounder there.

Thank you for your careful reading and valuable feedback. We have found it very helpful to perfect the article.

In the **conclusion** section, we demonstrated a certain degree of relationship by using the word "link", which is ambiguous and can lead to different intrepretations. Thus, we have modified the sentence as shown in **333**.

Admittedly, the study covers a 33-year span and it has become a major challenge to trace the information as detailed as radiation history and family history of patients. What's more, the collection of information over a long time could be mistakable and could lead to further biases.

Nonetheless, we tried a propensity score matching (PSM) method to adjust for **age** and **sex** and filtered out the unmatched cases. To compare the difference between during and after USI, we performed PSM and 6397 paired cases of **thyroidectomy** were eligible for the study:

subtype	During USI (n=6397)	After USI (n=6397)	P Value
PTC	29.09%	72.76%	<0.001
FTC	0.52%	0.36%	0.23
MTC	0.55%	0.31%	0.06

To compared the difference between before USI and during USI with PSM:

subtype	Before USI (n=1086)	After USI (n=1086)	P Value
PTC	5.62%	26.6%	<0.001
FTC	0.28%	0.64%	0.34
MTC	0.64%	1.10%	0.37

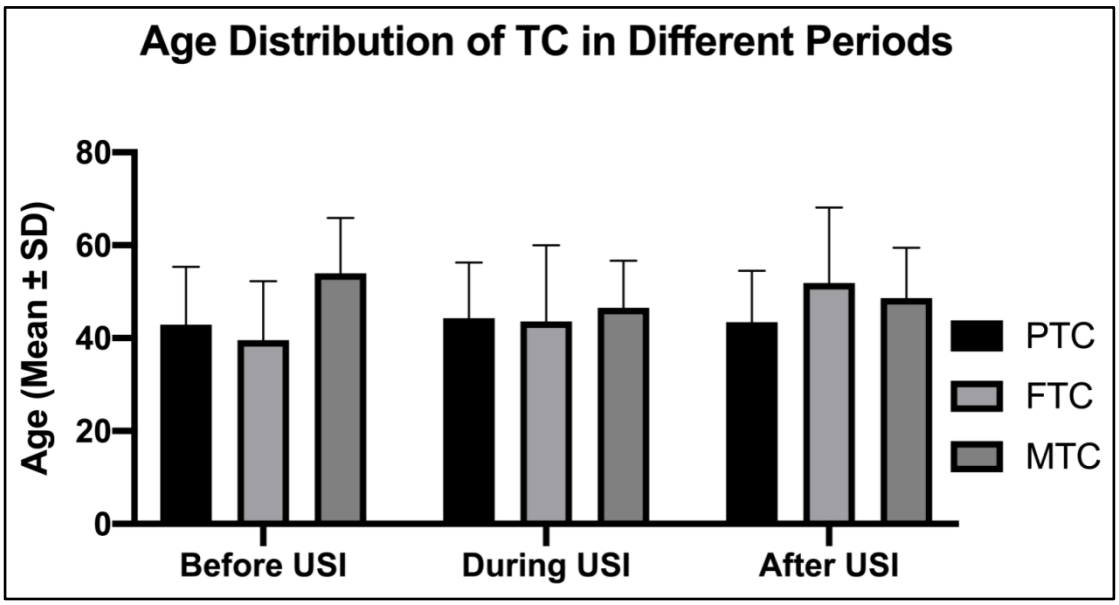
Below is the table in the original manuscript (note that "75.05%" has been corrected, as indicated in reply 4)

Table 1. Time Trend of the Detection Rate of PTC, FTC and MTC in All Thyroidectomy

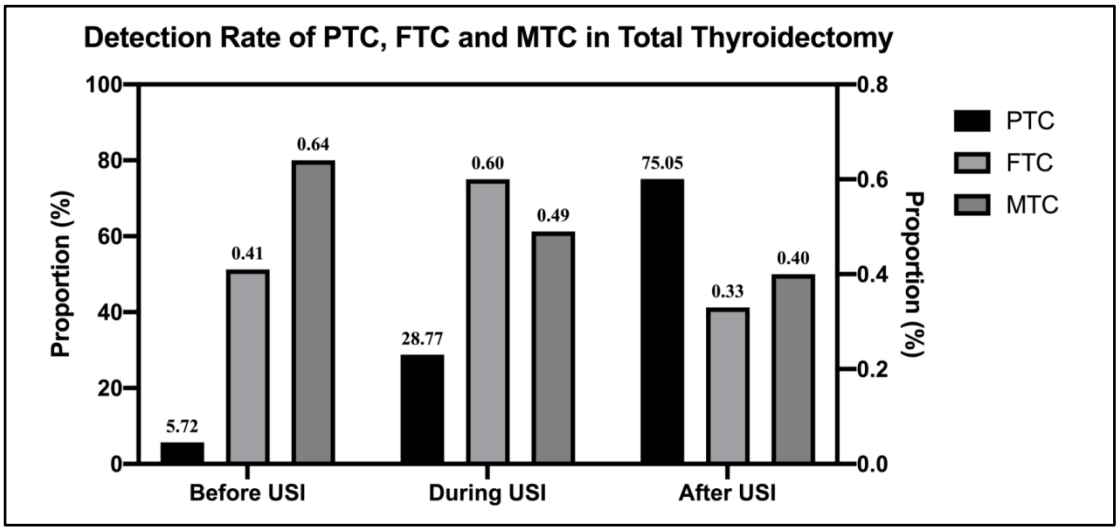
Histological type	Before USI	During USI	After USI	*P*
PTC	5.72%	28.77%	75.05%	<0.001
FTC	0.41%	0.60%	0.33%	<0.01
MTC	0.64%	0.49%	0.40%	NS

PTC: papillary thyroid cancer; FTC: follicular thyroid cancer; MTC: medullary thyroid cancer; USI: universal salt iodization

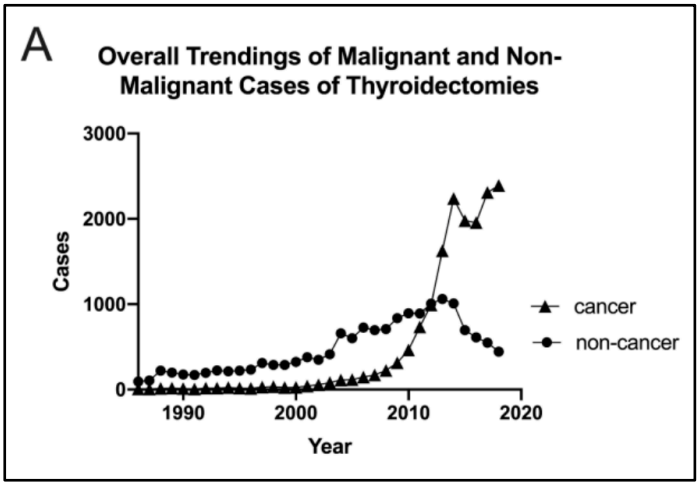
After adjusting for age and sex, there are no major alterations in the results. This is especially true for papillary thyroid cancer, as we think the greater changing trend of this subtype can overcome the many potential confounders.



We plotted a new figure 3 (see above). The figure illustrates that age in PTC are quite evenly distributed, compared with other types (see the dark column in figure 3). Beside, the sex ratio lies within the usual range of 3:1, so the influence should be minor, if it had any. Still, the change in sex ratio could be the consequence of universal salt iodization, which makes it lesser a confounder.



Other confounders, such as diagnostic techniques, exist throughout the periods. However, in a new figure 2 (see above), we can see that FTC, a counterpart of PTC among differentiated TC, remained very stable. The changing rate of FTC and MTC between the three periods never go beyond 50%, while changes of PTC could go up to several hundred per cent. By illustrating this (**259**), we can partly say that diagnostic techniques may be a confounder, but may not be so influential as it seems, as the FTC should have increased if there had been a big confounder there in diagnostics. Besides, being a major hospital located at the very center of the capital city Beijing, it also has the advantage of reducing biases like inconsistency in patient managements, and constant changing in medical instruments.



This study reflects the changing pattern of thyroid cancer imposed by a couple of important factors in this historical period: mandatory implementation of iodized salt, rapidly growing industrial life, improving medical techonology, population aging and so on; and more factors are yet to be discovered. However, by confining the research in this specific period, we have the chance to observe how an artificial mode of diet may affect the prevalence of a disease. Based on the conception that confounders inevitably exist, we can avoid interpreting the result without giving consideration to other confounders, so as to draw the conclusion more scientifically.

Changes in the text: We have modified the text as advised in **333/page 18,** and added some sentences in **259/page 14.**

Comment 2:

Add a limitation section to the manuscript.

A limitation section has been added at the end of the discussion.

Changes in the text: We have added a limitation section in **311/page 16.**

Comment 3:

For the subsection on microPTC (mPTC), their detection rate is from 2009 onwards, which makes this a shorter USI period for the during, andmost importantly, is not compared to without iodine. Please document, as there is comparison only between 2 time-periods.

Also, the mPTC data in PTC is not mentioned in the result section, as is in abstract and table. And again, diagnostics for mPTC play a huge role, as do changes in management (more conservative), which might limit the numbers of here included mPTC, as selection is based on thyroidectomies.

Could you solve this by adjusting everything by size?

For the subsection of mPTC, an auxillary instruction has been added in **178** to fully ducument the subdivided period.

The detailed mPTC data were supplemented in **180** as is in abstract and table. As for the bias in diagnostics and management, we discussed the possibility that the conservative management outweighed advances in diagnostic techonology in **275**. As mPTC is a special subtype closely relating to diagnostic and treatment preferences, and more importantly, data before USI are not available for further study, we tried not to give out definite conclusions in the context but tried to present valuable data.

Changes in the text: We have added some sentences in **178, 180 (page 9),** and added some information in **275/ page15.**

Comment 4:

Unclear what exactly the constituent ratio represents, what is the denominator? All thyroidectomies?

"Constituent ratio" has been changed into a corrected one (detection rate) in the first paragraph of **result section (133, 136)**. Denominator is exactly all thyroidectomies. Furthermore, we corrected some careless mistakes which should have been avoided:

① **143** "TC" should be "all thyroidectomies"

② **Table 1** "TC" should be "Thyroidectomies"

③ **Table 1** "95.05%" should be "75.05%"

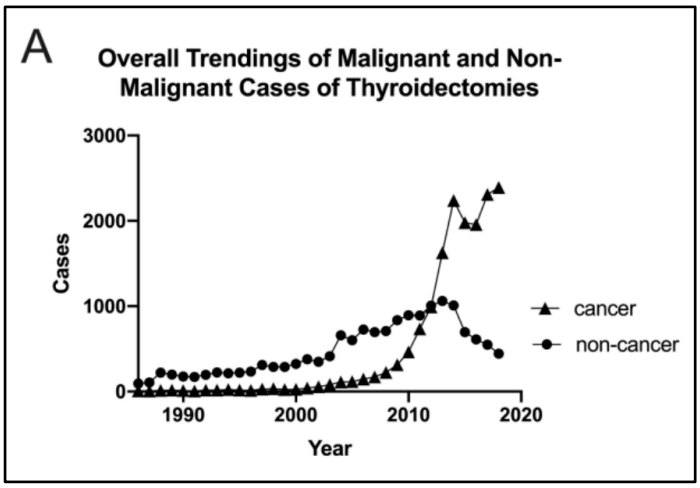
Changes in the text: We have modified some words in **133, 136 (page 7), 143 (page8).** A number and some words were modified in **Table1.**

Comment 5:

In Figure 1, total I assume is always thyroidectomy cases? How do you explain your very impressive reduction in benign cases?

In figure 1, the total is exactly the total thyroidectomy cases. Many factors contributed to the impressive reduction in benign cases. The growing proportion of thyroid cancer, the reduction

of benign cases due to prophylactic effects of USI are two important contributors.



To better illustrate this, a new figure is displayed in **figure 1A (above)**. Both the benign cases and the malignant cases increased year by year, but while the benign remained relatively stable, the malignant arised drastically from 2005 (fluctuations did took place because of tightening indication for thyroid surgeries, but if we look at the overall tendency). This makes us believe that some factor did occur that caused the ultimate steep change in thyroid cancer, while USI could probably be an important contributor.

Comment 6:
Minor:
26 iodine, not inodine
86 put in abbreviation PUMCH
108 histological
133 before USI versus during USI
273 Geneva, Switzerland
In the tables, the p values are confusing, what is listed in tables, and what is listed below with the *, or **
They have been corrected at the corresponding place.
Changes in the text: 26, 86, 109, 135, 298

Reply to reviewer B:
Comment 1:
why is there a significant difference in sex during 3 historical periods?
Reply 1:
Thank you very much for your valuable and useful feedback.
The sex ratio of TC was observed to drop from 3.7 to 2.8 for PTC. The mechanism of the higher prevalence in female remains inconclusive, but studies have pointed out that estrogen may play a role in the molecular pathway of tumorigenesis. One study found iodine stimulated the transcriptional activity of estrogen receptor and increased the expression of several ER regulated genes in breast cancer cells. It is thus tempting to argue that iodine may

also stimulate ER-related pathways in thyroid cancer to result in the changing sex ratio. However, there's currently no straightforward evidence to support this thesis. Also, we discussed the situation in other countries, where the F/M ratio dropped **(298)**, but was not clearly related to iodine intake. In another study in Shenyang, China, the F/M ratio of PTC actually elevated with the increase of iodine **(306).** From our perspective, the cause for the changing sex ratio can be multifactorial and needs to be further studied.

Changes in text: We have added some sentences in **291,306 in page15.**

Comment 2:

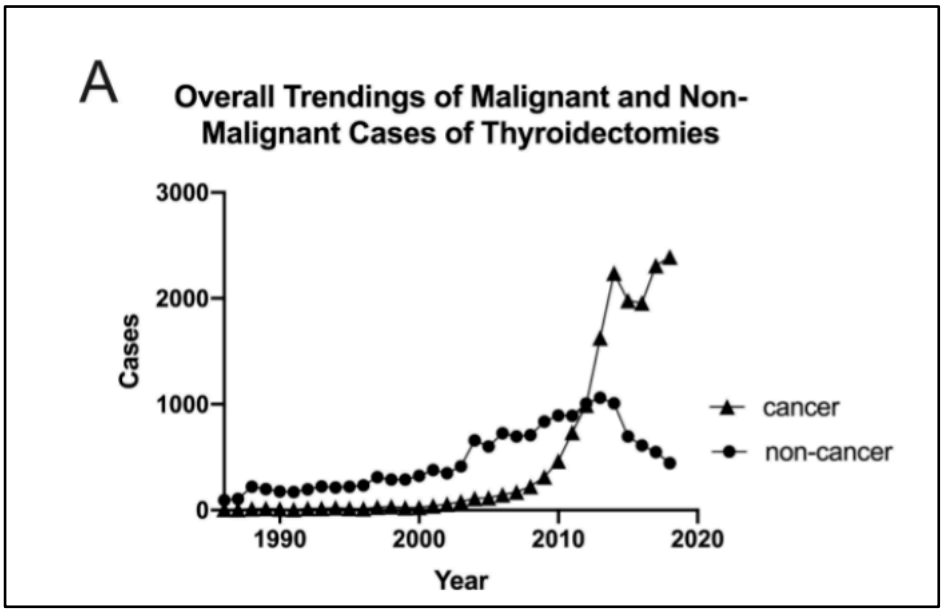
why is there a significant difference in age during 3 historical periods?

Both PTC and FTC were observed to have significant difference in age (After USI versus During USI). For PTC, as the change of age is actually small (around 1 year of age), we assume the change of age is only significant statistically, but not clinically significant. As for FTC, the mean age increased by 8 years of age. Some studies **(214)** have already found that introduction of iodine could decrease the incidence of FTC, while PTC increased. The increased diagnostic age of FTC in our study is consistent with these findings, suggesting iodine is a protective factor for FTC.

Change in text: We have added some sentences in **214/page 11.**

Comment 3:

In fig.1, the trend of increasing proportion of PTC is very similar to the pattern of PTC conducted the epidemiological study in the USA and other countries without universal salt iodization. Please explain if there are any other contributing factors to this phenomenon.



The result can be explained partly by the reduced proportion of benign cases due to the prophylactic effects of USI; other contributing factors include improving diagnostics, population aging and health awareness. This study reflects the changing pattern of thyroid cancer imposed by a couple of important factors in this historical period: mandatory implementation of iodized salt, rapidly growing industrial life, improving medical

techonology, population aging and so on. And the the result shall not be interpreted without giving consideration to other confounders. To better illustrate this question, we plotted a new figure 1A. While the benign cases remained relatively stable over the period, the malignant (which is mainly PTC) arised drastically aound 2005, a decade after the initiation of USI, leading us to believe that iodine intake might be one of the important contributing factor to this trend. We also agree that the limitation of this study should be fully documented, so a limitation section has been added at the end of **discussion (311).**

Changes in text: We have added a limitation section in **311/page 16.**