Author response to

Comments on Kato and Yamada paper 'Individual Dose Response and Radiation Origin of Childhood and Adolescent Thyroid Cancer in Fukushima, Japan'

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The authors were told from Shigeru Taguchi about the Response Comments from UNSCEAR Secretariat on our paper 'Individual Dose Response and Radiation Origin of Childhood and Adolescent Thyroid Cancer in Fukushima, Japan' [1] This is an author response to the comments written by some UNSCEAR experts (without sign).

Summary of the paper:

In this paper, we presented that "Childhood and adolescent thyroid cancer detected in the Fukushima health management survey (FHMS) was associated with individual external dose estimated in the FHMS basic survey [1]. Increased childhood and adolescent thyroid cancer in Fukushima could most probably be attributed to radiation exposure from the nuclear accident. Individual dose dependence of thyroid cancer incidence was studied by dividing 108,980 examinees into three external dose groups, <1mSv, 1–2mSv, and ≥2mSv from the data of Ohira et al. [2]. We also determined the risk coefficient for thyroid cancer based on the external dose dependence of thyroid cancer incidence of dose groups in the second-round screening. The risk coefficient per millisievert was converted to thyroid doses estimated by UNSCEAR in its 2020/2021 Report, Annex B. This summary accords with the summary by UNSCEAR.

UNSCEAR experts have some substantial comments relevant both to dosimetry and epidemiological parts of the paper under consideration. **We read through the comments very carefully and found no necessity for revision to be made. The conclusion does not change.**

Prerequisite Check

In reading the Comments to our paper 'Individual Dose Response and Radiation Origin of Childhood and Adolescent Thyroid Cancer in Fukushima, Japan', we knew that UNSCEAR experts do not know the situations of researches in Japan on thyroid cancer incidence detected in FHMS.

1. Availability of FHMS data: The data of FHMS belongs to the government of Fukushima prefecture and can only be used within that organization: Radiation Medical Science Center for the Fukushima Health Management Survey, Fukushima Medical University (FMU) is an organization established under contract with the prefectural government to conduct FHMS.
2. Reproducibility of the results: Many Journals encourage authors to provide information that enables other researchers to reproduce their analyses. However, most papers from FMU cannot be reproduced by researchers outside FMU because of the unavailability of the FHMS data. Papers without reproducibility by other researchers cannot be considered as scientific papers in the common sense of Science.

3. Researchers outside FMU cannot access the FHMS data except the published reports from FHMS. Most researches proving positive relation of radiation exposure to thyroid cancer prevalence or incidence were performed by researchers outside FMU, and available data for them are confined. There were so many comments like "The authors did not adjust for age or sex and the failure to take age and sex into account may have produced bias in their results" in the Response Comments by the UNSCEAR experts. These comments mean that the 'United Nations Scientific Committee on the Effects of Atomic Radiation' does not know the situation of research in Japan on the Effects of Atomic Radiation or the Committee wants the research of radiation effects after the Fukushima accident should be confined to FMU.
   If it is considered that the above comments are justified, the UNSCEAR is going to define the effect of atomic radiation only from reports by the organization which owns all the personal data of thyroid screening and which does not provide data open for outside researchers to reproduce their conclusion.

   We sincerely hope the UNSCEAR to take the other way and work for human health by promoting researches in and outside FMU and in a world-wide scientific community.

Requirements on a confounding factor in Epidemiology

We follow the "Properties of a confounding factor" in Epidemiology by Rothman: 1. A confounder must be associated with the disease, 2. A confounder must be associated with the exposure, 3. Causal intermediates are not confounders. [3]

The UNSCEAR 2000 explained that a confounding factor that did not correlate with dose couldn't be a bias in an epidemiological study of the effect of radiation dose on disease [4]. It is necessary to address the potential for confounding, which can lead to bias. A confounding factor is correlated with both the disease under study and the exposure of primary interest. While many factors other than ionizing radiation affect cancer rates, in most epidemiological studies of radiation-exposed groups there is no reason to think such factors will be strongly correlated with radiation dose, although weak associations might arise by chance. For example, in studies of the survivors of the atomic bombings and many medically irradiated groups, it is unlikely that there would be a strong association between, say, levels of smoking and the dose received. This was consistent with "the properties of a confounding factor" by Rothman.

We consider that there is no need to consider gender, age, etc. that do not correlate with external exposure doses as confounding factors for exposure dose groups. Confidence intervals of odds ratio and relative risk in Table 1 and Figure 1A were calculated using the formula of Rothman.

1. Dosimetry

Comment 1. The UNSCEAR comments that the relationship between the doses presented in the UNSCEAR 2020/2021 Report and those shown in Figure 1B of the paper is not clear and needs to be clarified and justified.

However, the UNSCEAR experts seem not to understand the meaning of Table A18.5 (Attachment A-18) of estimated absorbed doses to the thyroid of 10-year-old children. Figure 1B is a plot by municipality, not by evacuation scenario. The municipalities with thyroid doses exceeding 10 mGy are 4 municipalities in the evacuation area (Futaba, Katsurao, Namie, and Iitate), and Minamisoma (>20 mGy), and 2 in the non-evacuation area (Fukushima City and Koori Town; 7 municipalities in total; 11 mGy of Date City should be revised to 9.3 mGy for 10-year-old children). The highest value was used if multiple doses were given for a municipality in evacuation area, and the average value was used in the non-evacuation municipalities (Table A-14.2 UNSCEAR2020/2021 Attachment A14).
The thyroid doses from UNSCEAR 2020/2021 were used as they were, with the utmost respect. The external exposure doses for each municipality [5] were correlated with the UNSCEAR 2020/2021 thyroid doses. The UNSCEAR experts should know the exact correspondence between the scenarios and the name of the municipality to understand that Figure 1B is correct. Please read the UNSCEAR2020/2021 report and our paper carefully.

It is unbelievable and inexcusable that we must explain the most important part of thyroid dose estimation Table A-18.5 in UNSCEAR 2020/2021 Attachment A-18, to experts of epidemiology of UNSCEAR. This is the main part of the revised estimates of thyroid dose in UNSCARE 2020/2021 and is the reason for its conclusion that "future radiation-associated health effects are unlikely to be discernible".

C2. The experts comment that the findings of Kato et al seem to be compromised by four factors. C21 comes from their misunderstanding of UNSCEAR report as pointed out in C1.

In C22 the UNSCEAR confesses the large uncertainty of thyroid dose estimation in saying that "there are large uncertainties associated with thyroid dose estimation, in particular at lower doses where according to UNSCEAR the largest contribution is from ingestion and the assumption is that the whole of Fukushima Prefecture received the same dose. Not clear if the uncertainties in dose have been taken account of in confidence limits of risk estimates". However, this is not a shortcoming of this paper, but rather a statement that the UNSCEAR 2020/2021 estimates are uncertain. UNSCEAR 2020/2021 estimated the supposedly region-dependent ingestion dose as a constant and reduced the ingestion dose for 1-year-old infants to be 1/30 of UNSCEAR 2013 without evidence.
UNSCEAR 2020/2021 can never conclude that, on the basis of unreliable thyroid dose estimates, 'significant excess of thyroid cancers, as seen in the FHMS screening program, would not be expected at the thyroid absorbed doses estimated by this committee' (UNSCEAR 2020/2021 226(a)).
Similarly, the belief of UNSCEAR2020/2021 that the high incidence of thyroid cancer detected among exposed children is not the result of radiation exposure derived on the basis of thyroid dose estimates with large uncertainty should be retracted (UNSCEAR2020/2021, 268 (q)).

C23 will be discussed in Epidemiology, and C24 is related to the unavailability of FHMS data from outside FMU, and also to requirements on a confounding factor in Epidemiology because age is not related to exposure dose from nuclear accident.

2. Epidemiology

Radiation origin of thyroid cancer in Fukushima
We found in this paper that the incidence proportions of dose groups in the 2nd round showed a linear response to mean individual external dose in the 0.5~2.5 mSv range, and concluded that the increased childhood and adolescent

thyroid cancer in FHMS could most probably be attributed to radiation exposure from the nuclear accident.

ERR/Gy: Excess relative risk per unit dose Gy (Gray)

C23 UNSCEAR experts commented that there is an arbitrary assumption that "The mean doses of the first two groups (<1 mSv and 1-2 mSv) were assumed to be 0.5 mSv and 1.5 mSv (a) " without any justification of those numbers.

Because we cannot access the individual data of FHMS, we analyzed individual dose response for two other set of assumed mean dose. The results were ERR/Gy =170 (95%CI=159, 182; p=0.003) for mean doses of the first two groups 0.4 mSv and 1.4 mSv (b), and 142 (95%CI=109, 174; p=0.01) for mean dose of dose groups 0.3 and 1.3 mSv (c). The ERR/Gy became smaller, but still was found to be high if the mean dose value of dose groups shifted to low dose side. The high-quality studies that UNSCEAR cited and the results of our paper are summarized in Table 1.

Table 1. Comparison among epidemiological studies of thyroid cancer in Ukraine, Belarus, Fukushima and of thyroid cancer exposed to external radiation dose at thyroid under 100 mGy.

	[Author, Pub. year]	ERR/Gy, EOR/Gy (95%CI; Thyroid cancers /Total cases)	ERR/Gy (normalized to1)
Belarus & Russia 1991-1995	[Jacob et al.1999]	23 (8.6, 82)	1 (95% CI=0.37, 3.6)
Ukraine 1998-2000	[Tronko, 2006]	5.25 (1.70, 27.5; n= 45 /13,127)	1 (95%CI= 0.32, 5.2)
Belarus 1996-2001	[Zablotska, 2011]	2.15 (0.81, 5.47, n= 85 /11,611)	1 (95% CI= 0.38, 2.5)
Ukraine 2001-2007	[Brenner, 2011]	1.91 (0.43, 6.43, n=65 /12,514)	1 (95% CI= 0.23, 3.4)
External exposure <100mGy	[Lubin, 2017]	9.6 (3.7, 17.0) for < 0.1 Gy	1 (95%CI=0.39, 1.77)
Fukushima 2011-2015	Kato & Yamada 2022(a)	213 (129, 297; n=36 /108,980)	1 (95% CI=0.61, 1.39)
	Kato & Yamada 2022(b)	170 (159, 182; n=36 /108,980)	1 (95% CI=0.93, 1.07)

C3. The UNSCEAR criticized that a rough estimate of excess relative risk per Gray, ERR/Gy= 213 (95% CI 129, 297) based on only 36 thyroid cancer cases is unbelievable.

Thyroid cancer cases of n=45 and 84 after the Chernobyl accident were comparable with 36 cases in FHMS.
A point estimate (central estimate?) of ERR/Gy = 213 in Fukushima was about 10-100 times of ERR/Gy values reported after the Chernobyl accident in the 1.91~23 range [6-10]. It has been observed in Chernobyl that ERR/Gy tends to be smaller as time passes since the accident (Table 1). There may be an effect of higher natural incidence as the age of the population increases. We have not seen the analysis of the relationship between ERR/Gy and years

elapsed since the Chernobyl accident.

Although the age of the examinees is younger than that in the studies after Chernobyl, the age difference between Chernobyl and Fukushima subjects cannot explain the much higher ERR/Gy in Fukushima than that in Chernobyl **The 10-40 times higher ERR/Gy value observed in Fukushima than those after the Chernobyl accident (excluding the Belarusian and Ukrainian data 10-21 years after the accident) might come from either an underestimation of thyroid dose in UNSCEAR2020/2021 or that the radioactive iodine caused more thyroid cancers per Gy in Fukushima than in Chernobyl. In the former case, 10–40 times or more thyroid dose than the dose in UNSCEAR2020/2021 was consistent with the ERR/Gy observed after Chernobyl.**

For example, in UNSCEAR 2020/2021, estimation of thyroid dose from ingestion was reduced by 1/30 from 33 mGy in the UNSCEAR 2013 to 1.1 mGy. If thyroid dose were of the level of the UNSCEAR 2013 and area dependent, the ERR/Gy would decrease by a factor of 30, ERR/Gy ≈ 7. This value would be in the same range as the ERR/Gy from Chernobyl studies and from external dose.

Although region-dependent thyroid dose from ingestion was not evaluated at all, inhalation plus external thyroid dose was evaluated and improved from UNSCEAR2013. **A clear linear relationship was found between the "inhalation plus external" dose and thyroid cancer incidence of areas [11]. The increased childhood and adolescent thyroid cancer in Fukushima could most probably be attributed to radiation exposure from the nuclear accident.** The size of 108,980 subjects were almost the same as that in the epidemiological study of Atomic-bomb survivors. It seems to be the UNSCEAR's responsibility to protect people's health by fully analyzing the observed data and obtaining more information.

C4. The UNSCEAR questions about using “linear regression” analysis, and claims that the results are questionable.

Since thyroid cancer incidence detected in FHMS increased almost proportionally to individual external dose, and external dose increased proportionally to thyroid dose estimated in UNSCEAR 2020/2021, there was no advantage of using other models. The epidemiological significance of the linear regression analysis between thyroid cancer and thyroid dose is clear. The dose-response of the incidence proportion and relative risk of dose groups were analyzed by the linear regression analysis of Microsoft Excel 2019 MSO (2112).

C5. The UNSCEAR comments that inaccuracies may be especially pronounced because the analysis was based on only a small number of thyroid cancers as in our case.

Although the confidence interval of ERR/Gy seemed to be wide because of the highest ERR/Gy value in Fukushima, 95%CI normalized to ERR/Gy =1 was the sharpest than those of epidemiological studies after the Chernobyl accident as the UNSCEAR experts pointed out. The reason for the difference in confidence intervals of ERR/Gy, is presumably the software or definition of 95%CI used in each paper. We could reproduce the EOR/Gy by Zablotska et al. but 95%CI was a little sharper in the regression analysis by Microsoft Excel: EOR/Gy =2.21(1.9, 4.2) compared to their EOR/Gy=2.15 (0.81, 5.17) [9].

C6. The UNSCEAR claims that the dose estimations are uncertain in individuals’ behaviors that were modeled in estimating thyroid doses. UNSCEAR seems to consider that the health effect due to radiation exposure is likely to be discernible from sound analyses based on uncertain thyroid dose estimates by UNSCEAR 2020/2021.

We regret very much that UNSCEAR dismisses the radiation associated thyroid cancer in Fukushima by the word 'not discernible'. The phrase was not used in UNSCEAR 2008 report for the Chernobyl accident.

C7. Incorrect comment by UNSCEAR: "Of importance, the author's estimates were based on only 36 of the ~~150~~ **(71 cancer cases)** thyroid cancer cases they mention in the second screening. There was clearly a substantial potential for bias when ~~only 24%~~ **(47%)** of the cases were included, and when the reasons for the availability of dose information or lack of it for given individuals (which was apparently the criterion for inclusion of individuals) were unknown."
(Number of cancer cases should be corrected from 151 to 71, and English is difficult to understand.)

C8. The UNSCEAR commented individual dose-participation biases in constructed dose groups inflated the estimated risks much higher than those of other major studies in Chernobyl.

We just used the data from the paper of FHMS group,[2] and we (outside FMU) are unavailable to access the original individual dose data. The FHMS estimated external doses of Fukushima residents based on self-reported whereabouts. [5] Those who responded to the questionnaire of external exposure dose were 1.5 times more likely to have thyroid cancer than those who did not respond, RR=1.52 (95%CI=0.96, 2.62). There may be some selection bias in dose groups because response rate in high dose evacuation Soso and Kenpoku areas were 46.1% and 30.2%, respectively, while response rate of the lowest dose area Aizu was about 21%. Radiation dose of those who responded the dose questionnaire is expected to be higher than those who did not respond.

This might have made ERR/Gy slightly higher, but not inflated the estimated risks much higher than those of other major studies in Chernobyl. Selection bias of dose group shows that the effect of radiation exposure increased thyroid cancer incidence in the second round.

Part II is a warning about the possibility of a high incidence of thyroid cancer already occurring outside Fukushima Prefecture. For part III, we only ask the UNSCEAR experts to read our paper more carefully.

After careful reading of the comments by UNSCEAR experts, we found no necessity for revision to be made. The results of the data analysis and conclusions do not change.

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