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Association between the detection rate of thyroid cancer and the external radiation dose-rate after the nuclear power plant accidents in Fukushima, Japan

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Abstract

A thyroid cancer ultrasonography screening for all residents 18 years old or younger living in the Fukushima prefecture started in October 2011 to investigate the possible effect of the radiological contamination after the Fukushima Daiichi Nuclear Power Plant accidents as of March 12 to 15, 2011. Thyroid cancer in 184 cases was reported by February 2017. The question arises to which extent those cancer cases are a biological consequence of the radiation exposure or an artefactual result of the intense screening of a large population.

Experiences with the Chernobyl accident suggest that the external dose may be considered a valid surrogate for the internal dose of the thyroid gland. We, therefore, calculated the average external effective dose-rate (μSv/h) for the 59 municipalities of the Fukushima prefecture based on published data of air and soil radiation. We further determined the municipality-specific absolute numbers of thyroid cancers found by each of the two screening rounds in the corresponding municipality-specific exposed person-time observed. A possible association between the radiation exposure and the thyroid cancer detection rate was analyzed with Poisson regression assuming Poisson distributed thyroid cancer cases in the exposed person-time observed per municipality.

The target populations consisted of 367,674 and 381,286 children and adolescents for the 1st and the 2nd screening rounds, respectively. In the 1st screening, 300,476 persons participated and 270,489 in the 2nd round. From October 2011 to March 2016, a total of 184 cancer cases were found in 1,079,786 person-years counted from the onset of the exposure to the corresponding examination periods in the municipalities. A significant association between the external effective dose-rate and the thyroid cancer detection rate exists: detection rate ratio (DRR) per μSv/h 1.065 (1.013, 1.119). Restricting the analysis to the 53 municipalities that received less than 2 μSv/h, and which represent 176 of the total 184 cancer cases, the association appears to be considerably stronger: DRR per μSv/h 1.555 (1.096, 2.206).

The average radiation dose-rates in the 59 municipalities of the Fukushima prefecture in June 2011 and the corresponding thyroid cancer detection rates in the period October 2011 to March 2016 show statistically significant relationships.

Abbreviations: (.,.) = 95%-confidence interval (95%-CI), μSv/h = Micro-Sieverts per hour, 131-I = Iodine-131, 134-Cs = Cesium-134, 137-Cs = Cesium-137, BMI = body mass index, Bq = Becquerel, df = degrees of freedom, DR = detection rate, cases/person-time or cases per 100,000 person-years, DRR = detection rate ratio, FDNPP = Fukushima Daiichi Nuclear Power Plant, FFSSP = first full-scale screening program, FHMS = Fukushima Health Management Survey, FNAC = fine needle aspiration cytology, FY = Fiscal year in Japan: 1 April to 31 March, kBq/m^2 = Kilo-Becquerel per square meter, MEXT = Ministry of Education, Culture, Sports, Science, and Technology in Japan, mGy = Milli-Gray, mSv/a = Milli-Sieverts/annum or milli-Sieverts/year, OR = odds ratio, PBLSP = preliminary baseline screening program, pBq = Peta-Becquerel, 10^{15} Bq, PTO = person-time observed, PY = person-years, RR = rate ratio, SAS = statistical analysis system, software produced by SAS Institute Inc., TC = thyroid cancer (ICD-10: C73-C75), TEPCO = Tokyo Electric Power Company, TUE = Thyroid Ultrasound Examination in the Fukushima prefecture, UNSCAER = United Nations Scientific Committee on the Effects of Atomic Radiation, WHO = World Health Organization.

Keywords: children and adolescents, ecological study, exposed person-time, ionizing radiation, radiation induced health effects

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The employed data has exclusively been published previously and/or it is contained in the Tables and in the Figures included in this paper.

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1. Introduction

A large amount of radioactive material was released after the Fukushima Daiichi Nuclear Power Plant accidents. The activity emitted is estimated to be 900 pBq (131-I: 500 pBq, 137-Cs: 10 pBq). Compared to the Chernobyl accident, the discharged quantities of 131-I and 137-Cs are 10% and 30%, respectively.[1]

The sensitivity of the thyroid to radiation was already known since the atmospheric nuclear weapons tests, for example by studies in the Marshall islanders affected by the fallout from the atomic bombing of the Bikini Atoll,[2] or after low-dose X-ray exposure in children treated for tinea capitis with about 90mSv thyroid dose.[3–6] The association between the radiation exposure after the Chernobyl nuclear power plant accident and the prevalence or incidence of thyroid cancer has been investigated by many ecological, cohort, and case control studies. Numerous investigations show the existence of distinct positive dose-response relationships between the radiation exposure and the presence or the occurrence of thyroid cancer.[7–24] Nagataki and Yamashita describe the historical evolution of the thinking about thyroid cancer and the causal role of radiation, from the initial conviction that there can be no (statistically detectable) radiation-induced Chernobyl health effects, to the currently recognized causal link between Chernobyl fallout and thyroid cancer.[25] Consequently, thyroid cancer was expected to increase after the nuclear power plant accidents in Fukushima.

1.1. The Fukushima Health Management Survey (FHMS)

A thyroid sonography screening for children and adolescents living in Fukushima Prefecture at the time of the accident began in October 2011. For a detailed description of the FHMS see Akiba.[26] The FHMS is organized in 4 rounds. The data of the 1st and the 2nd round will be scrutinized and analyzed in the present investigation. The third and the fourth rounds of examinations are in progress, but because these are not yet finished, and since less spatially differentiated protocols compared to the previous screenings are being employed, they will be excluded from our investigation.[27,28]

1.2. Epidemiological assessments of the FHMS

In the interim summary of the Prefectural People's Health Council in March 2016, the observed thyroid cancer prevalence in the Fukushima prefecture was roughly quantified as to be "*an order several tens of times as high as the prevalence estimated from thyroid cancer prevalence statistics*".[29] However, in the same summary, regarding the relationship between radiation exposure and thyroid cancer, it is claimed that "*because the radiation dose is considered to be less than that of Chernobyl at that time, it cannot be made a decision on the relationship between radiation exposure and thyroid cancer. And there is the opinion that the excess of thyroid cancer would be due to over-diagnosis*".[29] We emphasize that the presumption of possible 'over-diagnosis' in this summary report has not been substantiated with data or references.

Several studies evaluated the thyroid cancer data of the FHMS. Tsuda et al analyzed the 1st and the 2nd round by internal and external comparisons;[30] they observed a 50-fold increase of the thyroid cancer incidence in several contaminated areas compared to the national annual incidence and a difference in the prevalence by area in the Fukushima prefecture. Therefore, Tsuda et al provided evidence for a causal relation between increased thyroid cancer incidence and the nuclear catastrophes. For the debate following the publication by Tsuda et al see[31–40] as well as the rejoinder by Tsuda et al.[41]

Suzuki et al[42,43] questioned the association between the increased incidence of thyroid cancer and the nuclear accidents on the basis of a presumed 'screening effect'. Ahn et al provide an interesting example of a strong screening effect.[44] Katanoda et al[45] questioned the correlation between cancer and radioactivity on the account of 'over-diagnosis'. Suzuki, Katanoda, and colleagues claim no relation between the prevalence of thyroid cancer and the external exposure assessed by a self-reported questionnaire in the FHMS. However, these reports do not exhaust the available information sufficiently. In particular, the observed spatially and temporally structured person-time (from the onset of the exposure to the municipality-specific examination periods) as an appropriate reference parameter for the observed cancer cases in the municipalities was not determined and accounted for.

1.3. The objective of the present investigation

As a refinement of previously published analyses, the aim of our study is to estimate the detection rate of thyroid cancer in the screenings after the Fukushima nuclear power plant accidents for each municipality using the screened cancer cases in the municipalities as Poisson distributed events and the corresponding observed approximate municipality-specific exposed person-time as the reference quantity to examine a possible association between the thyroid cancer detection rate and the effective dose-rate. The null hypothesis is 'no association between the external effective dose-rate and the thyroid cancer detection rate'. If the null hypothesis can be rejected, this can be interpreted as evidence of a causal effect of radiation exposure.

2. Methods

2.1. Study population and medical examination

The health effect information used in the present investigation is exclusively confined to data published by the Fukushima Health Management Survey.[28,46,47,48] The first round of the thyroid cancer screening was titled 'Preliminary Baseline Survey' and was conducted from October 2011 to March 2014 targeting at all 367,674 Fukushima residents born from April 2, 1992 to April 1, 2011. There were 300,476 (81.7%) participants in the first round. The first round began in the most contaminated area closest to the nuclear power plant at October 9, 2011 in the FY 2011, see dark area in Figure 1. In the FY 2012, the screening was performed mainly in the central Fukushima prefecture, see medium gray level area in Figure 1; and in the FY 2013, the inland municipalities relatively far from the nuclear power plant have been covered, see light area in Figure 1.

The second round, which was reported by Fukushima Prefecture as a 'First Full-Scale Screening Program', began in April 2014. This round of examinations comprised in principle all residents/participants from the first round and added children born April 2, 2011 to April 1, 2012. It was labeled 'Full-Scale Survey'. The second round was aimed at 381,286 residents and was carried out from May 2014 to March 2016. There were 270,489 (70.9%) participants in the second round.[49,50] The first screening of the second round was conducted in the two areas of the first round 'FY 2011 area' and 'FY 2012 area' combined and carried out in the FY 2014. Similarly, the first round 'FY 2013 area' was covered as the 'FY 2015 area' in the second round. The first screening of this area was scheduled from May 2015 to June 2016.[47]

The diagnostic procedure was performed in 2 steps: a 'Primary Examination' was followed by a 'Confirmatory Examination'. Participants with abnormalities such as a nodule with a diameter of 5.1 mm or more and cysts with a diameter of 20.1 mm or more at the 'Primary Examination' were sent to the 'Confirmatory Examination' where they were subjected to a precise echography, and if judged necessary, to a fine needle aspiration cytology (FNAC), see Figure 2.[28] The most suspicious or malignant cases as a result of the FNAC underwent surgery. Of those who underwent surgery, 1 person was excluded from the analysis since her tumor was benign, although the initial needle biopsy was positive. Nevertheless, all patients with suspicious or malignant status who did not undergo surgery were counted as cancer. Eventually, as reported at the 26th survey meeting on February 20, 2017, 184 cancer cases were detected, 115 in the 1st round and 69 in the 2nd round. Ethics approval and consent to participate are not required, since only publicly available data and previously published information is being used.

2.2. Induction and latent period, point prevalence, incidence proportion and incidence rate, and detection rate

Induction period means the time from causal action to disease occurrence and latent period is the time from disease occurrence to detection.[51] In children and especially in newborns, minimum induction and latent periods for cancer can be rather short or may approach even zero. Certain types of cancers (lymphoproliferative and hematopoietic) can be present at birth or may occur shortly after birth.[52] Beach and Dolphin[53,54] and Schmitz-Feuerhake et al[55] provide data and evidence that the combined minimum induction and latent periods for thyroid cancer in children are in the order of magnitude of 1 year. In principle, the development of uncontrolled cell proliferation may start immediately after mutagenic or carcinogenic exposure (causal action). De Groot et al state "*The data suggest that the abnormality induced by radiation occurs at or close to the time of original irradiation, and that carcinoma is detected earlier than benign lesions*".[56] More recently, John Howard compiled findings on 'Minimum Latency & Types or Categories of Cancer'.[57] For thyroid cancers in children and adults he reports (average) minimum latency periods of 1.0 and 2.5 years, respectively.

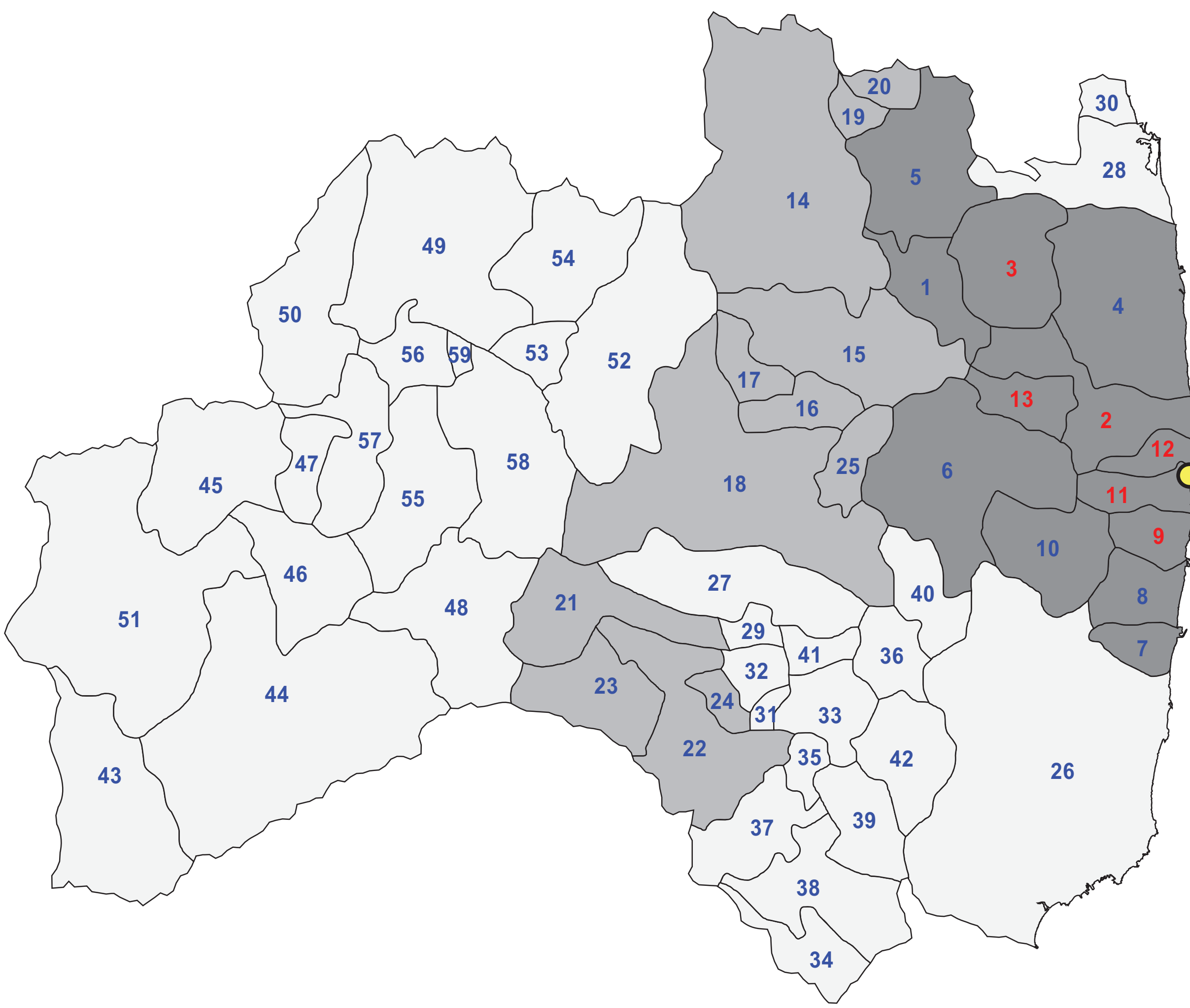

Figure 1. Target municipalities (n=59) of the 1st round of the Fukushima Health Management Survey partitioned into 3 organizational strata; dark: FY 2011 area, No. 1–13; medium: FY 2012 area, No. 14–25; light: FY 2013 area, No. 26–59; the red indexed municipalities are subject to an average dose-rate greater than 2.0 μSv/h; see Table 1 for a list of the municipalities by consecutive number; http://fmu-global.jp/?wpdmdl=1563.

Table 1

Target population, participants, and the numbers of thyroid cancer cases for the 1st and the 2nd rounds of the TC screening in the 59 municipalities of the Fukushima prefecture, October 2011 to December 2016.

Location No.	Location, municipality	Target population 1st round	Target population 2nd round	Participants 1st round	Participants 2nd round	Thyroid cancers screened 1st round	Thyroid cancers screened 2nd round	Total thyroid cancers screened
1	Kawamata Machi	2,396	2,460	2,221	1,763	2	0	2
2	Namie Machi	3,643	3,772	3,249	2,510	2	2	4
3	Iitate Mura	1,084	1,123	943	765	0	0	0
4	Minamisoma Shi	12,526	12,982	10,789	8,908	2	4	6
5	Date Shi	11,400	11,742	10,605	9,111	2	7	9
6	Tamura Shi	7,069	7,323	6,325	5,006	3	2	5
7	Hirono Machi	1,077	1,108	838	680	0	0	0
8	Naraha Machi	1,432	1,490	1,153	1,001	0	0	0
9	Tomioka Machi	2,962	3,101	2,302	2,002	1	0	1
10	Kawauchi Mura	357	360	280	213	1	0	1
11	Okuma Machi	2,385	2,499	1,973	1,758	1	2	3
12	Futaba Machi	1,207	1,258	949	685	0	0	0
13	Katsurao Mura	234	241	184	150	0	0	0
14	Fukushima Shi	53,552	55,737	47,307	42,700	12	10	22
15	Nihonmatsu Shi	10,255	10,596	8,856	7,885	5	1	6
16	Motomiya Shi	6,112	6,345	5,234	4,809	3	3	6
17	Otama Mura	1,617	1,684	1,373	1,264	2	0	2
18	Koriyama Shi	64,378	66,762	54,063	48,042	25	18	43
19	Koori Machi	2,065	2,137	1,874	1,635	0	1	1
20	Kunimi Machi	1,594	1,624	1,437	1,240	0	0	0
21	Ten-ei Mura	1,061	1,101	879	793	0	0	0
22	Shirakawa Shi	12,160	12,742	10,811	9,667	6	1	7
23	Nishigo Mura	3,976	4,173	3,618	3,178	1	1	2
24	Izumizaki Mura	1,289	1,337	1,157	997	1	0	1
25	Miharu Machi	3,067	3,183	2,730	2,386	1	0	1
26	Iwaki Shi	62,293	64,308	49,429	45,260	24	7	31
27	Sukagawa Shi	15,308	15,879	12,081	11,449	4	1	5
28	Soma Shi	6,812	7,087	5,209	4,749	0	1	1
29	Kagamiishi Machi	2,597	2,705	2,030	1,979	0	1	1
30	Shinchi Machi	1,434	1,476	1,150	1,038	0	0	0
31	Nakajima Mura	1,079	1,115	832	754	0	1	1
32	Yabuki Machi	3,273	3,422	2,567	2,412	1	0	1
33	Ishikawa Machi	2,847	2,956	2,163	2,028	1	0	1
34	Yamatsuri Machi	1,010	1,056	794	740	0	0	0
35	Asakawa Machi	1,337	1,389	1,093	1,030	0	0	0
36	Hirata Mura	1,209	1,272	873	855	1	0	1
37	Tanagura Machi	2,987	3,089	2,321	2,160	1	1	2
38	Hanawa Machi	1,661	1,715	1,255	1,166	1	0	1
39	Samegawa Mura	694	723	522	495	0	0	0
40	Ono Machi	1,936	1,990	1,450	1,262	0	0	0
41	Tamakawa Mura	1,332	1,372	1,015	964	0	0	0
42	Furudono Machi	1,040	1,084	822	794	0	0	0
43	Hinoemata Mura	107	110	62	66	0	0	0
44	Minamiaizu Machi	2,823	2,913	1,869	1,762	0	0	0
45	Kaneyama Machi	203	203	144	121	0	0	0
46	Showa Mura	128	134	102	93	0	0	0
47	Mishima Machi	192	197	130	121	0	0	0
48	Shimogo Machi	1,007	1,011	710	614	1	0	1
49	Kitakata Shi	8,910	9,237	5,897	5,727	0	3	3
50	Nishiaizu Machi	1,019	1,055	646	654	0	0	0
51	Tadami Machi	710	735	510	458	0	1	1
52	Inawashiro Machi	2,662	2,757	1,945	1,730	1	0	1
53	Bandai Machi	617	628	428	401	0	0	0
54	Kitashiobara Mura	557	581	392	377	0	0	0
55	Aizumisato Machi	3,658	3,790	2,609	2,538	1	0	1
56	Aizubange Machi	3,081	3,183	2,139	2,063	1	0	1
57	Yanaizu Machi	590	612	387	386	0	0	0
58	Aizuwakamatsu Shi	22,987	23,926	15,235	14,579	7	1	8
59	Yugawa Mura	676	696	515	516	1	0	1
Total		**367,674**	**381,286**	**300,476**	**270,489**	**115**	**69**	**184**

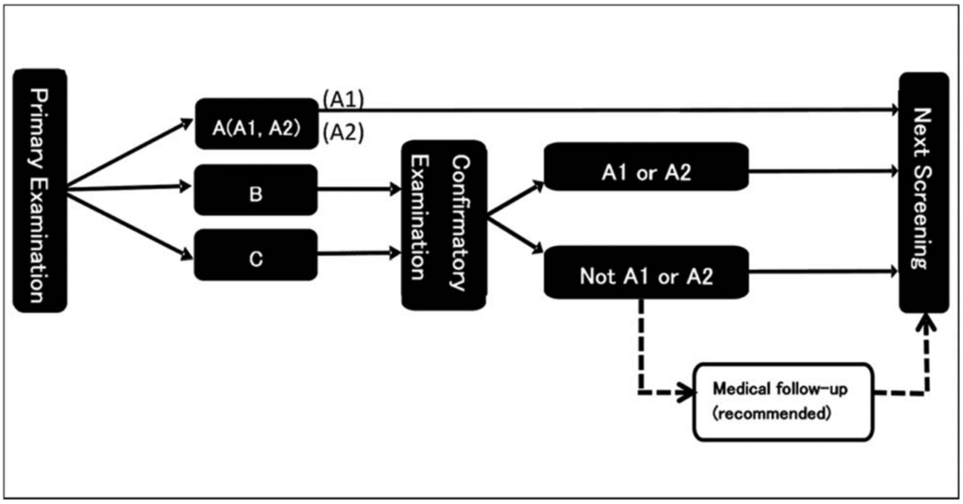

Figure 2. Flow chart of the thyroid cancer examination in the FHMS.[28] Decision criteria: A1: no nodules or cysts; A2: nodules ≤ 5.0 mm or cysts ≤ 20.0 mm; B: nodules ≥ 5.1 mm or cysts ≥ 20.1 mm; C: need for immediate confirmed examination.

Point prevalence is the proportion of a population with a disease at a specified time and incidence proportion is defined as the proportion of a closed population at risk that becomes diseased within a specified period of time.[51] Proper estimation of point prevalence means exclusion of newly diseased (i.e., incident) cases during the study period and accurate estimation of incidence proportion means exclusion of the cases already diseased (i.e. prevalent cases) at the onset of the study. In a strict sense, therefore, the FHMS is not suited for estimating the point prevalence or the incidence proportion[58] since there is no means of separating prevalent and incident cases based on one single medical examination per participant and screening round.

The problem of not being able to accurately distinguish between prevalent and incident cancer cases is frequently encountered in cancer screenings. In the literature on repeated screenings often 'prevalence' is used for the first screening round and 'incidence' is employed to the subsequent screenings.[59–61] As an alternative, and as prevalence and incidence cases cannot be separated, several authors consistently use the term 'detection rate' for both the first and subsequent screenings.[62–65] For the FHMS, it suggests itself to consider the detection rate of thyroid cancer using the screened cancer cases in each municipality as Poisson distributed events. The natural logarithm of the municipality-specific average person-time since the exposure (March 11, 2011) to the date of the medical examination defines the reference parameter (offset). Therefore, the detection rate (DR) quantifies the thyroid cancers detected in the corresponding exposed person-time observed. A possible relationship between the rate of detection of thyroid cancer and the effective dose rate can then be analyzed using Poisson regression and this relationship is expressed and estimated by the corresponding detection rate ratio (DRR) per μSv/h.

Evidence for the assumption of very rare thyroid cancers in unexposed children is provided by several authors.[20,30,66,67] If it is true that only few thyroid cancer cases would have occurred in Fukushima without the nuclear accidents, then our detection rate would be conceptually identical to the incidence rate. We, however, prefer the term 'detection rate' over 'incidence rate' to indicate that the accurate point prevalence of thyroid cancer in Fukushima prior to the nuclear accidents is not known.

2.3. Person-time observed

The base population (among those aged 0–18 years) for the determination of the thyroid cancer detection rate is the cumulative group of the individual subjects by municipality who had undergone thyroid ultrasonography reported at the 26th survey meeting on February 20, 2017. For each of the 59 municipalities in the Fukushima prefecture, the person-time observed (PTO) was calculated as follows: We set the basic initial observation time from March 11, 2011 (T_0), when the nuclear accidents were triggered, until the begin of the period when the thyroid ultrasonography in each municipality and screening round (r) was started ($S_{i,r}$ i = 1 to 59, r = 1 or r = 2, see Fig. 3). This basic period is extended by one quarter of the length of the interval between the start date $S_{i,r}$ and the first round-specific summary date $t_{1,r}$ in round r = 1 and in round r = 2. Similarly, the collective average observation time for any municipality (m_i, i = 1 to 59) is incremented step by step by one quarter of the respective length of the consecutive summary date intervals of the FHMS. These incremental time periods are multiplied by the corresponding incremental number of cumulative participants reported in the respective FHMS meetings. Finally, these quantities are totaled to obtain the observed approximate municipality-specific and round-specific exposed person-time in years ($PTO_{i,r}$). The detection rate is computed by dividing the screened or observed thyroid cancer cases by the person-years for all municipalities and for the 2 rounds. The combined person-years of the both rounds together result from incrementing the person-years in round 2 by the (small) fraction of the person-years in round 1 corresponding to participants in round 1, who did not participate in round 2. The combined person-years total is 1.045 times the person-years total in round 2. See Tables 1 and 2 for a list of the resulting cumulative participants, the exposed person-years observed, and the detection rates per 100,000 for the 2 screening rounds and the screening rounds combined. Note that the number of the incremental cumulative participants is zero while the summary date is not beyond the starting date in any municipality. The rationale behind this approach is the following: whereas we do not know the precise examination date of the individual participants in the FHMS, we, nevertheless, know this date up to an accuracy of approximately 90 days, since the medium

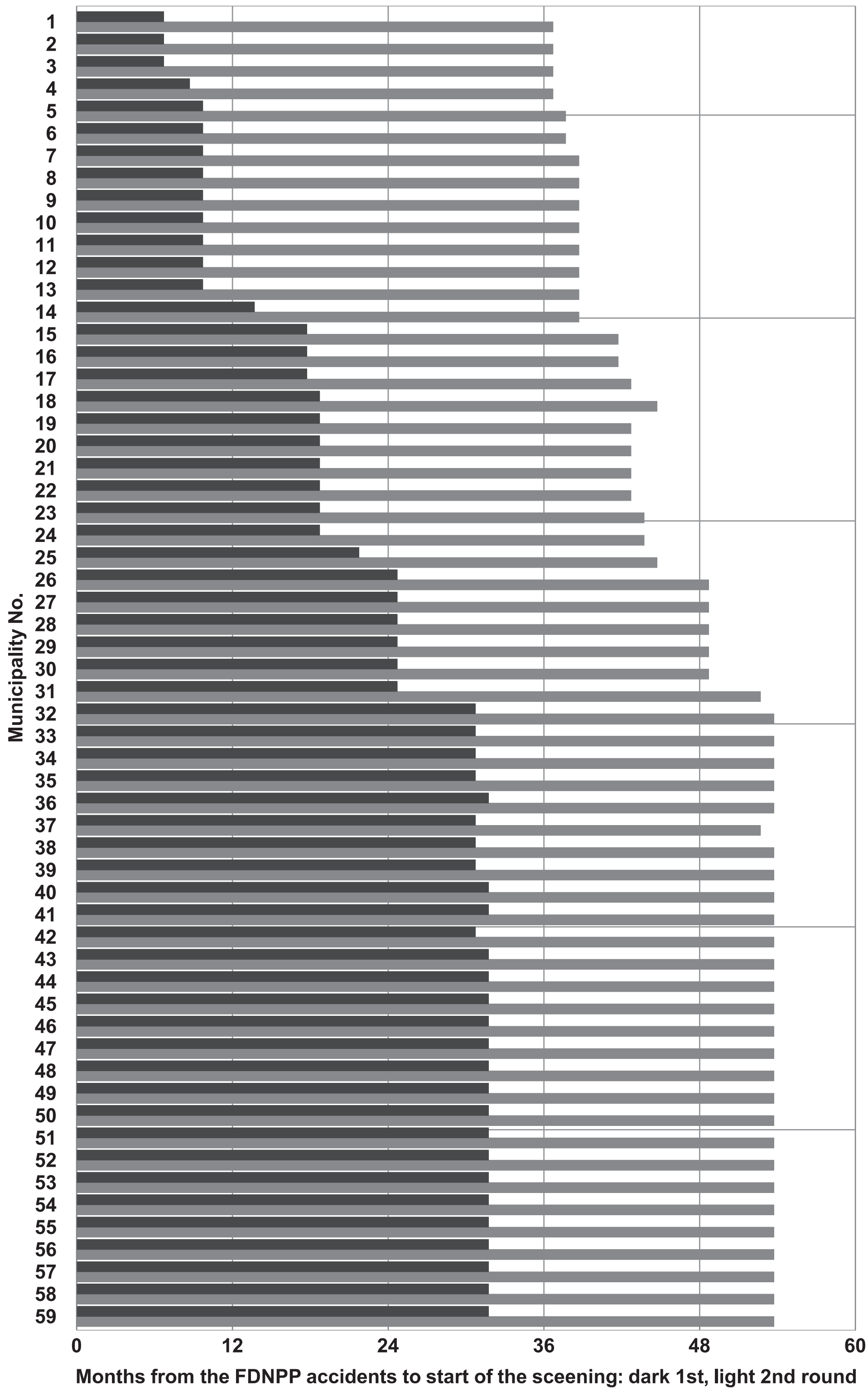

Figure 3. Time schedule of the 1st and the 2nd thyroid cancer screenings in units of 1 month relative to the date of the beginning of the nuclear accidents in the FDNPP in March 11, 2011; dark: 1st screening round, light: 2nd screening round; see Table 1 for the municipalities by index number.

interval length between the reported summary dates in round 1 and round 2 combined is precisely 91 days. Assuming an approximate natural exponential probability density of the participants' time-to-examination within 2 successive summary dates, which density approaches zero at the end of the observed period of ca. 90 days, implies that the mean of this incremental observation time is assumed at 90/4 = 22.5 days, which is one quarter of the observed period of 90 days. In short, the average incremental person time in the period between two reporting dates (in any municipality) is approximately 1 quarter of that period-length. Note that this approach is rather robust, in as much as realistic alternative assumptions about the location of the mean examination date between two consecutive summary dates do not change our findings in principal. Altogether, our municipality-specific and round-specific framework and the formula for the determination of the exposed person-time observed ($PTO_{i,r}$) are summarized in the following box:

- T_0 March 11, 2011, when the nuclear accidents were triggered
- $S_{i,r}$ start of the FHMS in municipality m_i $i=1$ to 59 of round $r=1$ or $r=2$, see Figure 3
- $t_{j,r}$ $j=1$ to k_r dates of the FHMS report summaries $r=1$ or 2 and $k_1=16$ and $k_2=11$
- $n_{i,j,r}$ cumulative number of participants for m_i, at summary date $t_{j,r}$ $j=1$ to k_r of round $r=1$ or $r=2$
- $PTO_{i,r} = \left(\left(S_{i,r} - T_0\right) + \frac{t_{1,r}-S_{i,r}}{4}\right) \times n_{i,1,r} + \sum_{j=2}^{k_r} \left(\frac{t_{j,r}-t_{j-1,r}}{4}\right) \times \left(n_{i,j,r} - n_{i,j-1,r}\right)$

2.4. Radiation dose assessment

Figure 4 shows the locations and a contour plot of 1710 positive dose-rate measurements published by the Ministry of Education, Culture, Sports, Science, and Technology in Japan (MEXT) in the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2013 report.[68] These data were provided by the Government of Japan as described in the report titled 'Summarized version of the results of the research on distribution of radioactive substances discharged by the accident at TEPCO's Fukushima Daiichi NPP'. The Japan Atomic Energy Authority (JAEA) conducted the survey with cooperation of universities and research institutes. MEXT was responsible for the measurements and their validity. UNSCEAR reviewed, verified, and published the dataset submitted: www.unscear.org/docs/publications/2013/UNSCEAR_2013_Annex-A_Attach_C-7.xls. The single dose measurements range from 0.05 μSv/h to 50.00 μSv/h, with mean 1.47 μSv/h and median 0.51 μSv/h. The municipality-specific average dose-rates range from the practically normal minimum level of 0.08 μSv/h to a more than 200 fold elevated maximum level of 17.68 μSv/h, with the overall mean 1.60 μSv/h and the median 0.34 μSv/h. Gavrilin et al reconstructed the thyroid dose for the inhabitants of the Republic of Belarus after the Chernobyl accident based on the

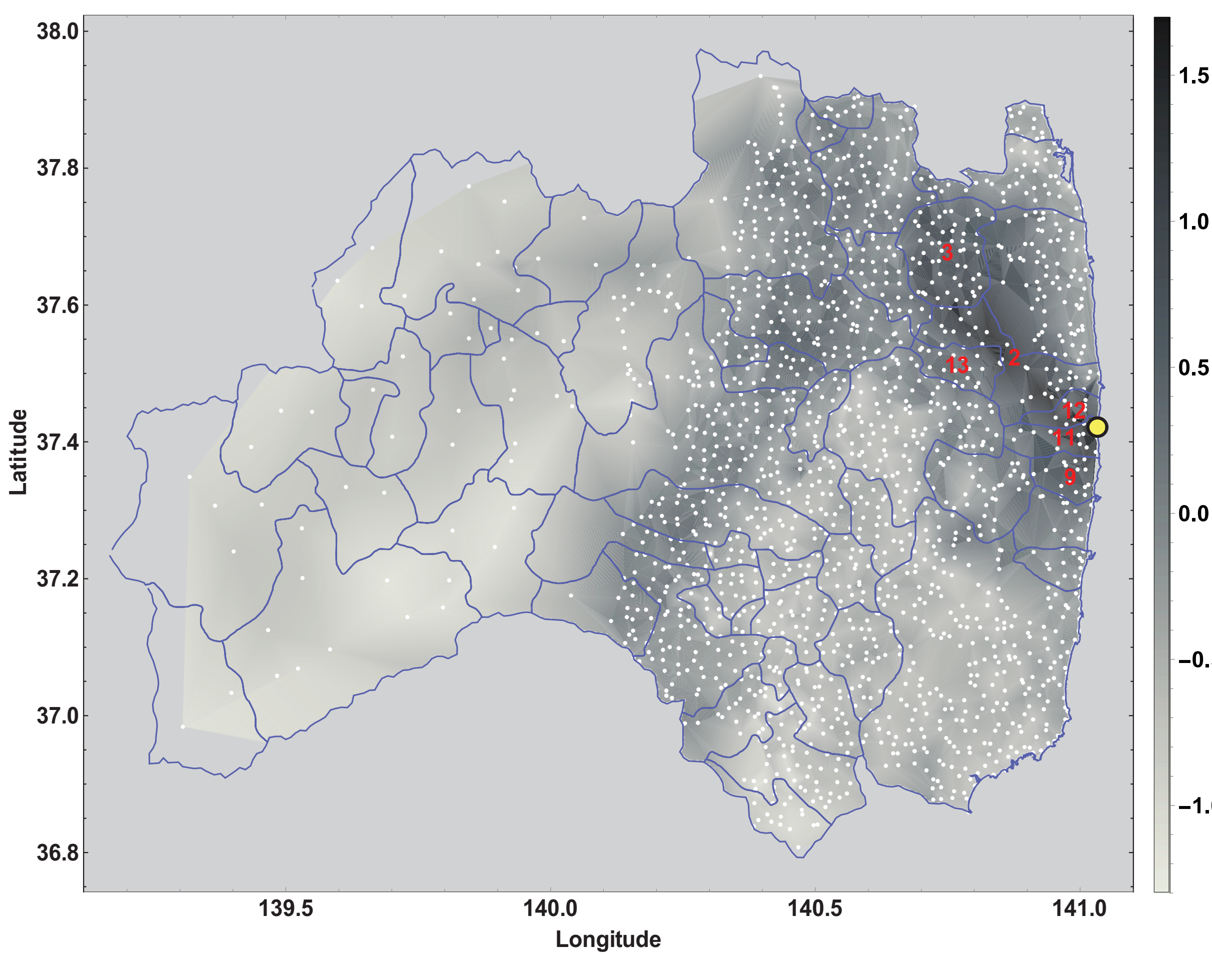

Figure 4. Contour plot of the dose-rate [μSv/h] on a log_{10} gray level scale for 1710 dose-rate measurements taken at locations (white dots) in the Fukushima prefecture in June 2011; the red indexed municipalities are subject to an average dose-rate of greater than 2.0 μSv/h, see the UNSCEAR 2013 report.[68]

available area-wide fallout measurements.[69] With their equation (8), they provide a monotone relationship for estimating the thyroid dose based on ground deposition densities of iodine (I-131) and cesium (Cs-137). As the Cs-137 deposition as well as the I-131 deposition in Fukushima are linearly related to the external effective dose-rate, see Figure 5 A and B, we consider the average external effective dose-rate (μSv/h) per municipality of the Fukushima prefecture as an appropriate (proportional) surrogate exposure measure for the internal dose of the thyroid gland. In the UNSCEAR 2013 report in attachment C-9,[68] the 'calculated Thyroid equivalent dose (mSv)' is linearly related to the cesium fallout.

2.5. Municipalities' distances from the FDNPP and the dose rate

The distances of the municipalities from the power plant range from 3.4 km to 155.7 km with median and mean of 65.4 km and 69.0 km, respectively. As a proxy for the geographical location of a municipality we used the center of its area-polygon, see Figure 1. The 3 most contaminated prefectures (> 10 μSv/h) are within 15 km from the FDNPP. The 48 municipalities with distances over 40 km have mean dose rates below 1.5 μSv/h. There is a distinct negative association of the mean dose rate with distance (x), which can be described with a power function: $dose(x) = 143.6 * x^{-1.397}$; $R^2 = 0.72$, see Figure 5C. Note that this is an interesting empirical confirmation of the theoretical distance law for the activity concentration $C_a(x) \sim x^{-1.42}$ proposed by UNSCEAR in 2017.[70,71]

2.6. Statistical analysis

The detected cancer cases in the 2 screening rounds separated and combined are assumed to be Poisson distributed in the municipalities within the respective exposed person-time observed. The detection rate (DR) is defined as the ratio of the cancer cases divided by the corresponding person-time. Therefore, a natural and straightforward approach is Poisson regression with the number of the observed cancer cases as the dependent variable and the average dose-rate of the municipality

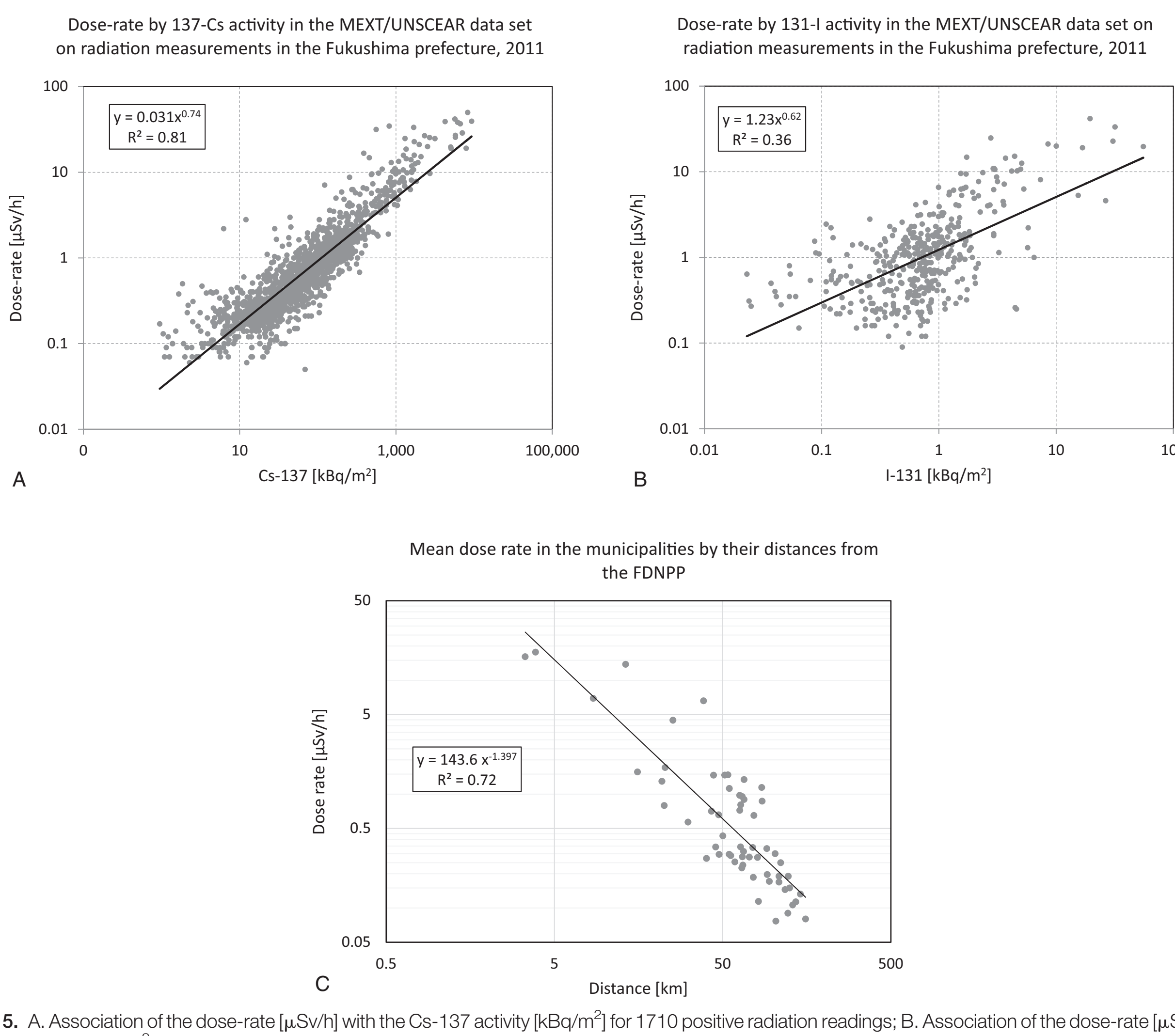

Figure 5. A. Association of the dose-rate [μSv/h] with the Cs-137 activity [kBq/m^2] for 1710 positive radiation readings; B. Association of the dose-rate [μSv/h] with the I-131 activity [kBq/m^2] for 418 positive radiation readings; C. Mean dose rate in the municipalities by their distances from the FDNPP; see the UNSCEAR 2013 report.[68]

as the independent variable.[51] The natural logarithm of the person-years per municipality serves as the corresponding auxiliary offset variable in the Poisson regression (see the SAS 9.4 documentation of procedure GENMOD).

Note that the assumption of a Poisson distribution implies that the variances of the random deviations are determined by the Poisson parameter. In practice, the empirical variances are always smaller or larger than theory predicts, for mere randomness or for diverse unknown reasons, for example, unspecified or unknown co-variables. Therefore, the models can be generalized by introducing a heterogeneity parameter, and, to be conservative, we allow for this extension in case of overdispersion (extra-Poisson variation[51]) but not in case of underdispersion. In all Poisson regression models presented in this paper there was always minor underdispersion with the deviance/df in the range of 0.7 to 1.0. Consequently, there was no need for any heterogeneity correction. In other words, the analyzed Fukushima thyroid cancer data comply very well with the Poisson assumption. The parameter of main interest in the present context is the detection rate ratio (DRR) per unit dose-rate (1 μSv/h). For data processing, statistical analyses, and results display, we used Microsoft Excel 2016 (Office 365), R 3.5.1 (Version 2017-10-04), Wolfram MATHEMATICA 11.3, and mostly SAS/STAT software 9.4 (SAS Institute Inc: SAS/STAT User's Guide, Version 9.4, Cary NC: SAS Institute Inc, © 2002–2012).

3. Results

Table 1 shows the target population, the participants, and the detected thyroid cancers by municipality and examination round (PBLSP and FFSSP). Likewise, Table 2 lists the cumulative person-years from exposure to medical examination, the detection rate per 100,000 person-years and the dose-rate in μSv/h. As the exposure quantification and the exposure distribution may influence epidemiological findings,[51] we took a closer look at the distribution of the dose-rates in Table 2, with emphasis on possible outliers: the mean of the doses below 2 μSv/h is 0.54 (0.41, 0.67) whereas the remaining 6 doses above 2 μSv/h have a mean of 10.94 (5.05, 16.82), which is a highly significant contrast of more than one order of magnitude between those mean values. The doses in the 6 most extreme municipalities are single as well as collective outliers in the dose distribution over the 59 municipalities. Therefore, we considered it instructive to exclude those outliers by way of trial from the analyses. This led to the discovery that the dose specific effects (DRR per μSv/h) are consistently pronounced below 2 μSv/h compared to the overall analyses. Somewhat different population-protective mechanisms such as the evacuations and/or different biological or carcinogenic processes may be relevant in the dose ranges below and above 2 μSv/h in Fukushima. The following paragraphs detail the determination of the DRR per μSv/h using Poisson regression for the 1st, the 2nd, and the combined examination rounds. All analyses are characterized by the criterion 'all data vs below 2 μSv/h'.

Figure 6 shows the thyroid cancer detection rate per 100,000 exposed person-years by dose-rate in the Preliminary Baseline Screening Program as well as the results of the Poisson regression analysis. Figure 6A displays the data and the regression line for all 59 municipalities with 115 cancer cases and 527,734 person-years. The detection rate ratio per μSv/h is 1.086 (1.012, 1.165). In Figure 6B, the analysis is restricted to the 53 municipalities with dose-rate < 2 μSv/h, see Figure 1. For the reduced data set, the detection rate ratio per μSv/h is 1.672 (1.062, 2.631) based on 111 cancer cases in 520,383 person-years.

Figure 7 displays the thyroid cancer detection rate per 100,000 exposed person-years by dose-rate in the First Full-Scale Screening Program, as well as the Poisson regression results. Figure 7A shows the data and the regression line for all 59 municipalities with 69 cancer cases and 1,032,817 person-years. The detection rate ratio per μSv/h is 1.101 (1.031, 1.176). In Figure 7B, the analysis is again restricted to the 53 municipalities with dose-rate < 2 μSv/h. For the reduced data set representing 65 cancer cases and 1,007,554 person-years, the detection rate ratio per μSv/h is 2.498 (1.446, 4.315).

Tables 1 and 2 contain the thyroid cancer data and the exposed person-years for the combined 1st and 2nd screening rounds. Figure 8 shows the thyroid cancer detection rate per 100,000 person-years by dose-rate in the combined data set as well as the parameters of the Poisson regression analyses. Figure 8A displays the data and the regression line for all 59 municipalities with 184 cancer cases and 1,079,786 person-years. The detection rate ratio per μSv/h is 1.065 (1.013, 1.119). In Figure 8B, the analysis is once more restricted to the 53 municipalities with dose-rate < 2 μSv/h. With the reduced data set, the detection rate ratio per μSv/h is 1.555 (1.096, 2.206) based on 176 cancer cases in 1,053,236 person-years.

4. Discussion

In brief, the detection rate of thyroid cancer in the FHMS was determined using the screened cancer cases and the approximate person-years between exposure onset and the medical examination periods in the municipalities. From the MEXT dataset,[68] we calculated the average radiation dose-rates for all 59 municipalities of the Fukushima prefecture after the nuclear accidents. In both the first and second rounds of investigation and in both cycles combined, we found clear positive and significant dose-response relationships between the thyroid cancer detection rate and the external effective dose-rate.

4.1. Necessity of the person-year method

The thyroid ultrasonography screening in the first round of examinations in Fukushima started 7 months after the accidents in some areas, but in other areas it started more than two years later, see Figure 3. Therefore, the period lengths between the accident and the timing of the screenings vary 3 to 4-fold depending on the municipality. Moreover, in areas with a higher contamination level the screening began earlier and the time between the accident and the screening was shorter, see Figure 1, Figs. 3 and 4. In such cases, since a person once screened is not monitored any longer in the FHMS, it is appropriate to use the effective exposed person-time observed to determine the municipality-specific detection rate. For the first time, we investigated the relationship between the detection rate of thyroid cancer and the average radiation dose-rate at the municipality level in the Fukushima prefecture.

4.2. In context with Chernobyl research

In the aftermath of Chernobyl, ecological spatiotemporal correlation studies,[7,11,12,23] case control studies,[13–15] and cohort studies[16–18] were carried out. These studies have demonstrated that radiation exposure of the thyroid gland and the thyroid cancer incidence rate are associated significantly. In the UNSCEAR 2008 report accounting for more than 1800

Table 2

Person-time observed and thyroid cancer detection rate (100,000) for the 1st and the 2nd rounds of the TC screening and for both rounds combined in the 59 municipalities of the Fukushima prefecture, October 2011 to December 2016; average dose-rates [μSv/h] in the municipalities based on overall 1710 positive measurements in the Fukushima prefecture in June 2011[68].

Location No.	Person years 1st round	Person years 2nd round	Person years	Detection rate 1st round	Detection rate 2nd round	Detection rate 1st+2nd rounds combined	Dose-rate [μSv/h]
1	1,365	5,509	5,790	146.520	0.000	34.542	1.467
2	2,011	7,846	8,304	99.453	25.491	48.170	13.820
3	575	2,393	2,502	0.000	0.000	0.000	6.606
4	8,474	27,855	29,333	23.602	14.360	20.455	1.714
5	9,275	29,105	30,411	21.563	24.051	29.595	1.219
6	5,531	15,979	17,133	54.240	12.516	29.183	0.568
7	734	2,221	2,359	0.000	0.000	0.000	0.794
8	1,011	3,268	3,401	0.000	0.000	0.000	1.566
9	2,030	6,547	6,812	49.261	0.000	14.680	6.947
10	246	696	755	406.504	0.000	132.450	1.298
11	1,739	5,744	5,933	57.504	34.819	50.565	16.119
12	836	2,243	2,475	0.000	0.000	0.000	17.681
13	163	491	521	0.000	0.000	0.000	4.463
14	56,706	140,691	146,213	21.162	7.108	15.047	0.953
15	14,354	28,049	29,623	34.833	3.565	20.255	1.469
16	8,486	17,099	17,788	35.352	17.545	33.731	1.477
17	2,227	4,600	4,777	89.807	0.000	41.867	0.978
18	91,892	181,784	192,018	27.206	9.902	22.394	0.721
19	3,189	5,891	6,298	0.000	16.975	15.878	1.343
20	2,444	4,473	4,808	0.000	0.000	0.000	0.899
21	1,497	2,863	3,009	0.000	0.000	0.000	1.145
22	18,439	34,895	36,846	32.540	2.866	18.998	0.650
23	6,166	11,749	12,499	16.218	8.511	16.001	0.868
24	1,972	3,681	3,954	50.710	0.000	25.291	0.280
25	5,320	9,025	9,695	18.797	0.000	10.315	0.659
26	105,178	186,481	195,353	22.818	3.754	15.869	0.343
27	25,685	47,170	48,513	15.573	2.120	10.307	0.806
28	11,103	19,566	20,546	0.000	5.111	4.867	0.708
29	4,316	8,153	8,262	0.000	12.265	12.104	0.344
30	2,445	4,276	4,515	0.000	0.000	0.000	0.431
31	1,765	3,358	3,524	0.000	29.780	28.377	0.282
32	6,731	10,947	11,354	14.857	0.000	8.807	0.313
33	5,672	9,205	9,559	17.630	0.000	10.461	0.254
34	2,082	3,359	3,500	0.000	0.000	0.000	0.114
35	2,866	4,675	4,840	0.000	0.000	0.000	0.238
36	2,363	3,881	3,929	42.319	0.000	25.452	0.296
37	6,086	9,620	10,042	16.431	10.395	19.916	0.340
38	3,291	5,292	5,526	30.386	0.000	18.096	0.186
39	1,369	2,247	2,317	0.000	0.000	0.000	0.224
40	3,924	5,728	6,237	0.000	0.000	0.000	0.272
41	2,748	4,375	4,513	0.000	0.000	0.000	0.288
42	2,155	3,604	3,677	0.000	0.000	0.000	0.296
43	168	300	300	0.000	0.000	0.000	0.080
44	5,060	7,998	8,288	0.000	0.000	0.000	0.106
45	390	549	612	0.000	0.000	0.000	0.113
46	276	422	447	0.000	0.000	0.000	0.150
47	352	549	574	0.000	0.000	0.000	0.190
48	1,922	2,787	3,047	52.029	0.000	32.819	0.077
49	15,965	25,995	26,455	0.000	11.541	11.340	0.169
50	1,749	2,968	2,968	0.000	0.000	0.000	0.090
51	1,381	2,079	2,220	0.000	48.100	45.045	0.133
52	5,266	7,852	8,435	18.990	0.000	11.855	0.278
53	1,159	1,820	1,893	0.000	0.000	0.000	0.197
54	1,061	1,711	1,752	0.000	0.000	0.000	0.333
55	7,061	11,520	11,713	14.162	0.000	8.538	0.190
56	5,789	9,364	9,570	17.274	0.000	10.449	0.250
57	1,047	1,752	1,755	0.000	0.000	0.000	0.145
58	41,233	66,175	67,951	16.977	1.511	11.773	0.171
59	1,394	2,342	2,342	72	0.000	42.699	0.300
Total or mean	**527,734**	**1,032,817**	**1,079,786**	**21.791**	**6.681**	**17.040**	**1.600**

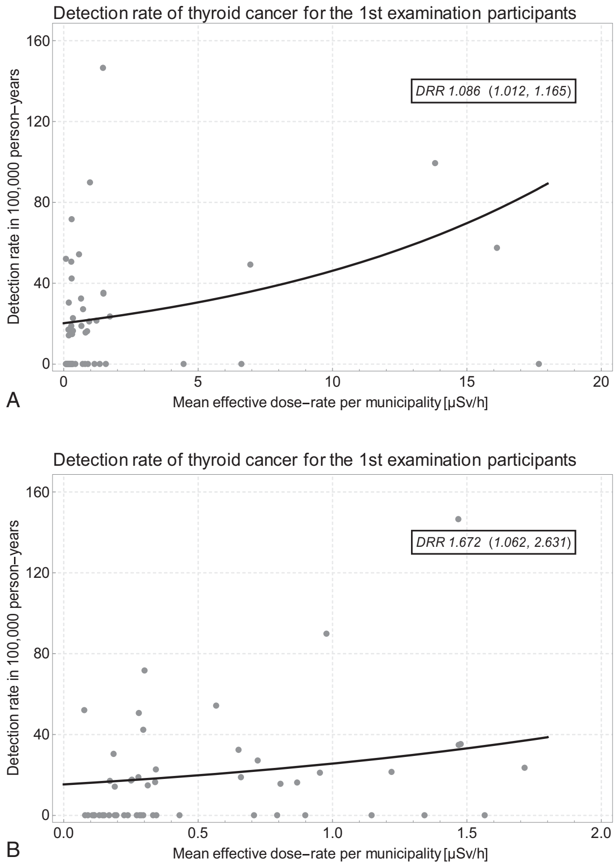

Figure 6. A. Thyroid cancer detection rate by dose-rate and Poisson regression line in the Preliminary Baseline Screening Program in all 59 municipalities; B. data restricted to 53 municipalities with dose-rate < 2.0 μSv/h; one outlying data point not shown for prefecture No. 10 Kawauchi Mura with 1 TC in 280 1st round participants.

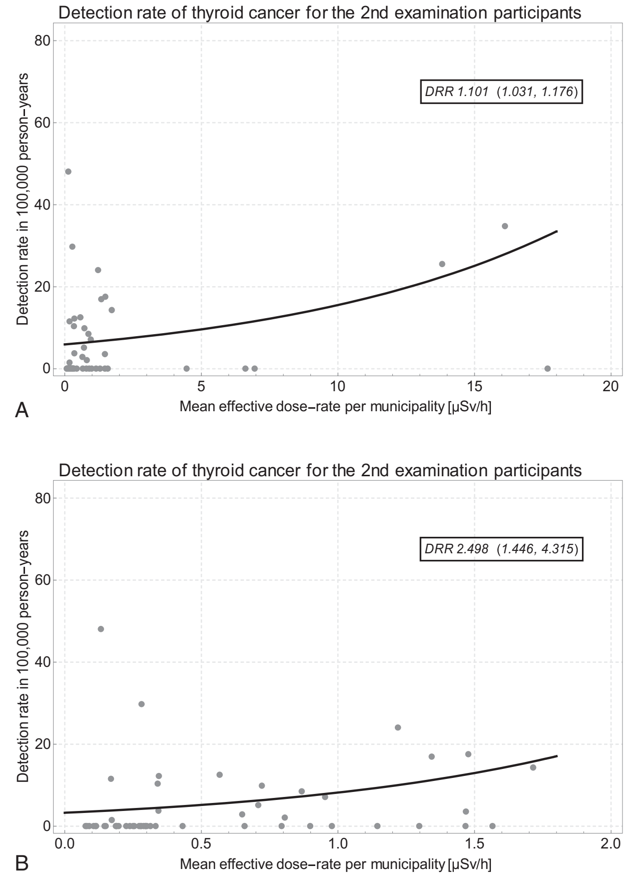

Figure 7. A. Thyroid cancer detection rate by dose-rate and Poisson regression line in the First Full-Scale Screening Program in all 59 municipalities; B. data restricted to 53 municipalities with dose-rate < 2.0 μSv/h.

children with thyroid cancer, the statistical relationship between radiation and thyroid cancer after Chernobyl was confirmed. However, the causal association of ionizing radiation with the induction of thyroid cancers was still considered uncertain, and the increased thyroid cancer rates were attributed to the mass screening: “*The estimates of radiation risk from these studies remain somewhat uncertain, however, and may have been influenced by variations in the use of ultrasonography and mass screening after the accident*”.[72] In principle, it is possible that screening may detect thyroid cancers which progress slowly, and which would never have become clinically manifest.

Zablotska and colleagues repeated the thyroid screening examinations in Belarus with ultrasonography on a cohort whose exposure dose was known. The initial screening was called pre-screening, and it was distinguished from the regular second-time screening. As a result of both the pre-screening and the combined screenings, a dose-response relationship between thyroid cancer and radiation dose was established.[19] This is consistent with our result, indicating that the influence of radiation is stronger than a possible ‘screening effect’.

In several investigations after Chernobyl, the thyroid dose was estimated by personal interviews, radio-ecological models assessing the spatiotemporal variation of 131-I, as well as direct thyroid dose measurements. For Fukushima, there is the possibility that the true exposure was larger than the exposure estimated using the MEXT dataset.[73] Looking at the degree of soil pollution by 137-Cs in the Fukushima prefecture, 137,084 people lived in an area with a contamination level above 185kBq/m^2. On the other hand, in the oblast Gomel in Belarus 218,303 people lived in an area with over 185kBq/m^2 137-Cs, and 118,795 people lived in an area with over 185kBq/m^2 137-Cs in the remainder of Belarus.[74] Regions where 137-Cs concentration exceeded 185kBq/m^2 were designated as the ‘Zone of obligatory re-settlement’, in Belarus after Chernobyl.[75] Therefore, as concerns the 137-Cs soil contamination, highly populated areas in Fukushima are comparable with large areas in Belarus.

4.3. In context with Fukushima research

From the data provided by the ‘System for Prediction of Environmental Emergency Dose Information (SPEEDI)’, the accumulated thyroid equivalent dose in the evacuation area of Fukushima from March 12 to April 24 has exceeded approximately 100mSv: “*Children in Iitate-mura and Iwaki Prefecture have been hypothesized to have thyroid radiation exposure possibly reaching 100mSv by SPEEDI, although they were residing outside the 20 km range*”.[76] The UNSCEAR 2013 report estimates that the absorbed thyroid dose was 47–83mGy, and might have been as high as 36 to 795mGy in case inhabitants would not be or have not been evacuated.[68] In 2012, the WHO reports an estimate of 100 to 200mSv.[77] Therefore, the thyroid equivalent dose in Fukushima was considerably increased.

Most of the papers cited above dealing with thyroid cancers in Fukushima claim that the height of the radiation dose to the residents was extremely low, thus additional thyroid cancers could not have been induced. However, since the detection rate of thyroid cancers is abnormally high and cannot be ignored or discarded, there are the following two arguments to explain that nevertheless the (true) incidence rate of thyroid cancer has not changed. A typical claim is the 'screening effect theory' according to which thyroid cancers are found before any symptoms emerge simply since they are sought by applying an ultrasonic examination screening to a large population.[34,43] Since this point cannot explain the fact that many persons have already undergone surgery on semi-international standards, there are also publications maintaining that many of the cancers detected and operated were due to 'over-diagnosis'.[45] Both lines of reasoning are extensively employed in the scientific literature to deny any possible causal relationship between the observed and widely accepted excesses of thyroid cancers after nuclear accidents and radiation exposure.[58] Moreover, before Fukushima, thyroid cancers have not been found in excess by ultrasonic screening in generations that were not exposed to radioactive iodine, or were exposed to only low doses after Chernobyl.[20] If there were really no biological effects from the elevated ionizing radiation, only few, if any, thyroid cancers should have been detected after the nuclear accidents in the Fukushima prefecture. Further evidence of possible radiation induced detrimental health effects arises from exposure-dependent increases in perinatal mortality and increased congenital malformations in Japan from 2012 onward.[78–81]

Hayashida and colleagues conducted thyroid ultrasonic screening on 4365 children and adolescents 3 to 18 years old at three university hospitals in Aomori, Yamanashi, and Nagasaki, and reported that one thyroid cancer was found.[82] This paper is often quoted as providing evidence that this discovery rate (1/4365) indicates about the same prevalence elsewhere and in Fukushima. However, although the thyroid cancer incidence in children is rare, that is, most recently estimated as 0.54/100,000,[83,84] it entails a prevalence of 10 in 100,000 children aged 1 to 18. Assuming a prevalence of 10 in 100,000 yields a probability as large as 0.354 of observing 1 or more diseased in 4365 children, as was the case in the Hayashida et al study.[82] Therefore, this study does not provide evidence against a background incidence rate in the order of magnitude of 1/200,000. Nevertheless, many people deny the excess thyroid cancers in Fukushima based on just this one single case obviously found by chance in the Hayashida et al study. For comparison, the actual period prevalence[85] in Fukushima is in the order of magnitude of $184/300{,}000*100{,}000 \approx 60$, which is a 6-fold increase compared to normal levels. Consider also that for a stable long-term prevalence of 10 in 100,000 to increase 6-fold in 5 years, the change in the incidence rate must be relatively strong. Shibuya et al[86] and Katanoda et al[45] consider potential 'over-diagnosis' as a cause for the increased thyroid cancer prevalence in Fukushima since they assume rather unrealistic thyroid doses below 3mSv. However, they concede that it is difficult to support 'over-diagnosis' without appropriate control populations for comparison. Moreover, the claim of 'over-diagnosis' would call into question the quality and the reliability of the thyroid cancer diagnostics as well as the validity of surgery.

Tokonami and colleagues measured the equivalent dose to the thyroid by 131-I in 42 people who have been evacuated in April 2011, and they reported an average thyroid equivalent dose of 3.5mSv for 6 children aged 0 to 19 years.[87] In fact, the thyroid equivalent dose of two of the children was 21 and 23mSv. Because the number of subjects was small, Tokonami et al considered the possibility that the thyroid equivalent dose could have been up to 83mSv. In addition, the inhalation exposure by the plume was estimated during 4 hours on March 15, and the thyroid equivalent dose for that 4-hour period was evaluated.

Furuta et al reported the monitoring results of dose-rates, radioactivity concentrations (in air and fallout), and meteorological observations before June 1, 2011 at the Tokai Research and Development Center located about 130 km south of Fukushima. In addition, they estimated the child's thyroid equivalent dose during this period in the range of 20mSv.[88] If the same calculation is applied to the UNSCEAR Report 2013 data set in attachment C-9,[68] not only in the evacuation area, but also in Iwaki, the biggest city in the Fukushima prefecture, the thyroid equivalent doses exceeded 100mSv.

Kim and colleagues published examination results determining the radiation dose of 1080 children aged 0 to 15 in Iwaki City, Kawamata Town, and Iidate Village from March 24 to March 30, 2011 by contacting the thyroid gland with a dosimeter.[73] It was an examination with 0.2 μSv/h as a lower limit at places where the ambient doses were 0.07 to 0.17 μSv/h. It was assumed that 0.2 μSv/h were equivalent to a thyroid dose of 100mSv for a 1-year old child. In later work, Kim et al estimated the rounded 90th percentile values for a 1-year old child to be 30mSv in Futaba town, Itate village, and Iwaki city, which means that theoretically 10% of the children of that age and in these locations may have been exposed to thyroid doses above 30mSv.

Kamada and colleagues estimated external and internal radiation doses for 15 residents who lived approximately 37 km northwest of the FDNPP. Residents were interviewed on their behavior and their diet after the incident. Effective doses up to 54 days after the deposition were calculated. The average cumulative effective dose was 8.4 mSv for adults and 5.1 mSv for children. 131-I was measured in urinary samples of five residents. The equivalent doses for the thyroid gland were 27 to 66 mSv.[89]

Tsuda et al[30] analyzed the prefecture results from the first and the second round up to December 31, 2014 in comparison with the Japanese annual incidence and in comparison with the incidence in a reference area in the Fukushima prefecture. The highest incidence rate ratio, assuming a mean latency period of 4 years, was observed in the central middle district of the prefecture compared with the Japanese annual incidence: incidence rate ratio 50 (25, 90). In the second screening round, even under the assumption that the rest of the examinees were disease free, Tsuda et al found an incidence rate ratio of 12 (5.1, 23.0). They also concluded that the increase was unlikely to be explained by a screening surge. Tsuda et al emphasize that the length of the time-interval between the accident and the screenings should be considered. This is what we have done for the first time and even at the municipality level in the Fukushima prefecture in the present investigation.

4.4. Dose-response analyses concerning Fukushima

On the grounds that thyroid cancer patients had external exposure estimates of below 2.2mSv during the first 4 months, and that there was no significant difference in the prevalence between the evacuated and the non-evacuated areas, Suzuki et al explain the thyroid cancer increases in Fukushima by a screening effect.[42,43] Ohira and colleagues classified the Fukushima prefecture into groups based on the same dose data employed by Suzuki et al: highest, middle, and lowest dose areas. As a result of comparing the prevalence ORs between the groups, they also concluded that there was no dose-response relationship between thyroid cancer and radiation dose.[90] In a more recent letter, Ohira et al classified the FHMS participants into quintiles according to individual radiation doses. They employed an indirect exposure criterion, namely the proportions of persons in the municipalities with external doses above 1.0mSv. The odds ratios (ORs) and 95%-confidence intervals of thyroid cancer were calculated using logistic regression models adjusted for age, sex, and the duration from the accidents to the examinations. Ohira et al concluded "*regional and individual differences in external radiation dose were not associated with thyroid cancer prevalence among children in the 4 years after the nuclear power plant accident*".[91] In their response, Tsuda et al criticize, among others, that Ohira et al considered only 1st screening round data.[92] What is common to those papers and letters is the utilization of a questionnaire-based individual radiation dose ascertainment (with 27% response rate) for the assessment of possible thyroid cancer prevalence differences between 3 to 5 groups of the 59 municipalities. Therefore, all these approaches do not exhaust the available quantitative spatiotemporal exposure-effect information.

4.5. Questionnaire-based assessment of the individual external radiation dose

Employing a questionnaire-based method, the Fukushima Health Management Survey estimated the distribution of the external individual radiation doses in each municipality (see http://www.pref.fukushima.lg.jp/uploaded/attachment/201726.pdf). Although the response rate was as low as ca. 27%, this dose distribution takes into account that no or only few residents remained in the evacuation areas.[93] The eight municipalities with average dose-rates above 1.5 μSv/h Naraha Machi(1.6), Minamisoma Shi(1.7), Katsurao Mura(4.5), Iitate Mura(6.6), Tomioka Machi(6.9), Namie Machi(13.8), Okuma Machi(16.1), and Futaba Machi(17.7) comprise areas that have been evacuated (partially or completely) within a few days to a few weeks after the nuclear power plant accidents. It is, therefore, of interest to set the average municipality-specific MEXT/UNSCEAR dose-rates [μSv/h] employed in our study in perspective to the average FHMS questionnaire-based cumulative doses [mSv] in the municipalities during the 4 months period from March 11 to July 11, 2011. Figure 9 reflects a plausible and relatively strong association between the two dose concepts in the 51 essentially non-evacuated municipalities. However, a restricted resolution of the FMHS dose-system below 0.4 μSv/h becomes apparent, which is due to the (reported) coarse 1.0mSv-steps of the dose distributions in the municipalities and the low participation rate. This low resolution can be considered an additional disadvantage of the questionnaire-based approach. Table 3 summarizes and compares the thyroid cancer detection rate ratios (DRR) for the single and the combined screenings stratified by the two different dose concepts and by the data ranges: < 1.5, < 2.0, and < 20.0 μSv/h, respectively. It becomes

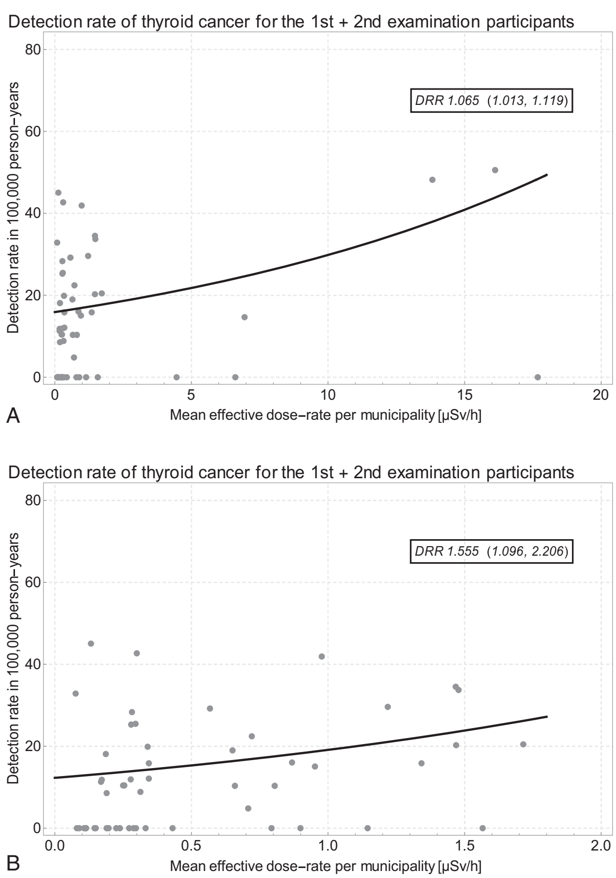

Figure 8. A. Thyroid cancer detection rate by dose-rate and Poisson regression line (Preliminary Baseline Screening and First Full-Scale Screening Programs combined) in all 59 municipalities; B. data restricted to 53 municipalities with dose-rate < 2.0 μSv/h; one outlying data point not shown for prefecture No. 10 Kawauchi Mura with 1 TC in 280 1st round participants and no TC in 213 2nd round participants.

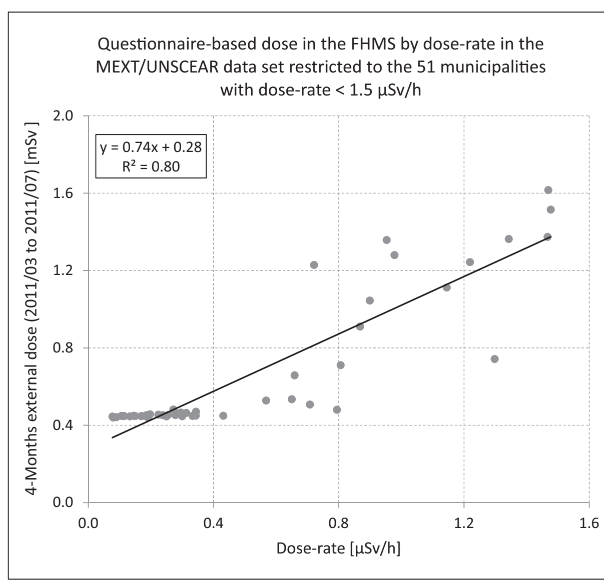

Figure 9. Comparison of the MEXT/UNSCEAR dose-rate and the questionnaire-based FHMS dose in 51 Fukushima municipalities with dose-rate < 1.5 μSv/h,[68,93] see also Table 3 and http://www.pref.fukushima.lg.jp/uploaded/attachment/201726.pdf.

Table 3

Detection rate ratios (DRR), 95%-confidence intervals, and p-values for the Poisson regression of the thyroid cancer detection rate on dose in the FHMS by dose concept, data range, and screening rounds; see Figure 9.

				Dose concept					
				MEXT/UNSCEAR [μSv/h]			questionnaire-based 4-months [mSv]		
Data range	Screening	Cancer cases	Person-years	DRR	95%-CI	*P* value	DRR	95%-CI	*P* value
< 1.5 μSv	1st	109	510,895	1.847	(1.122, 3.040)	.0158	1.622	(1.042, 2.524)	.0321
	2nd	61	976,431	2.714	(1.413, 5.212)	.0027	2.707	(1.473, 4.973)	.0013
	combined	170	1,020,505	1.726	(1.155, 2.579)	.0078	1.615	(1.132, 2.304)	.0082
< 2.0 μSv	1st	111	520,383	1.672	(1.062, 2.631)	.0263	1.624	(1.045, 2.526)	.0312
	2nd	65	1,007,554	2.498	(1.446, 4.315)	.0010	2.554	(1.416, 4.607)	.0018
	combined	176	1,053,236	1.555	(1.096, 2.206)	.0134	1.611	(1.132, 2.293)	.0081
< 20.0 μSv (all data)	1st	115	527,734	1.086	(1.012, 1.165)	.0213	1.505	(1.013, 2.235)	.0429
	2nd	69	1,032,817	1.101	(1.031, 1.176)	.0043	1.865	(1.228, 2.833)	.0035
	combined	184	1,079,786	1.065	(1.013, 1.119)	.0130	1.416	(1.052, 1.904)	.0217

obvious that the two dose-concepts yield consistent and significant results especially in most of the data, that is, excluding the partly or completely evacuated areas. Therefore, the two dose concepts mutually corroborate each other and support each a distinct significant association between radiation-exposure and subsequent thyroid cancer detection.

4.6. Non-linearity of the dose-response association

In the 3 analysis variants (first, second, and both rounds combined), the DRRs based on doses below 2 μSv/h are considerably larger than the *DRRs* based on the full dose range below 20 μSv/h. This is consistent by trend with an observation by Zablotska et al "*The excess odds ratio per gray (EOR/Gy) was modelled using linear and linear-exponential functions. For thyroid doses <5Gy, the dose-response was linear (n=87 EOR/Gy=2.15, 95% confidence interval: 0.81–5.47), but at higher doses the excess risk fell*".[19] One may speculate that this is an artifact of better protection (such as evacuation), some other biases in the highly exposed sub-populations, or an intrinsic biological nonlinearity. A possible explanation for this nonlinear behavior might be that high doses or dose-rates of 131-I destroy thyroid tissue and thus reduce the risk of developing cancer.[94–96] To cope with this disproportionate behavior of the association between the widely scattered dose-rate and the detection rate, it might be interesting to consider the log transformed dose-rate. Figure 10 shows the Poisson regression of the thyroid cancer detection rate on the natural log of the mean dose-rates in the decile categories. A less scattered (compared to Figs. 6–8) and monotone increasing association between the log-transformed dose-rate and the thyroid cancer detection rate becomes evident. The association is described by a DRR per log (μSv/h) of 1.281 (1.088, 1.508), *P* value .0030. See Table 4 for the corresponding decile-based data and the according point estimates and interval estimates.

4.7. Dependence of the detection rate on the participation rate

The participation rate per municipality (participants / target population, see Table 1) increases from 58% to 93% in the first screening round, and from 54% to 78% in the second screening round. The highest participation rate (93%) is found in Date Shi in the first screening and the lowest rate is observed in the second round in Futaba Machi (54%), which is the highest contaminated and evacuated municipality (17.7 μSv/h). It is true that the higher the participation rate the more cancer cases can be detected, which increases the numerator, but at the same time more participants increase the person-years in the denominator. Thus, theoretically, there is no (intrinsic) association between the participation rate and the detection rate. Hence, there is no need

Table 4

Data and results of the decile-based Poisson regression analysis for the 1st and the 2nd rounds combined; data is obtained by calculating the dose-rate deciles and by totaling the thyroid cancers and the person-year counts in Tables 1 and 2 for the 10 strata (categories) defined by those deciles; see Figure 10.

Decile of dose rate \ upper boundary	Count of municipalities	Municipality No. in decile category (see Table 1)	Mean dose rate in decile category [μSv/h]	Log (mean dose rate in decile category)	Thyroid cancers	Person-years	DR 10^5 PY observed	DR 10^5 PY expected	95%-CI DR 10^5 PY expected
10 \ 0.114	5	43,44,45,48,50	0.093	−2.372	1	15,215	6.6	10.5	(7.3, 15.1)
20 \ 0.186	6	34,46,49,51,57,58	0.147	−1.917	12	102,328	11.7	11.8	(8.7, 15.8)
30 \ 0.250	6	35,38,39,47,53,55	0.204	−1.589	2	26,863	7.4	12.8	(9.9, 16.4)
40 \ 0.288	6	24,31,33,40,52,56	0.269	−1.312	5	41,279	12.1	13.7	(11.0, 17.0)
50 \ 0.340	6	32,36,41,42,54,59	0.304	−1.190	3	27,567	10.9	14.1	(11.5, 17.2)
60 \ 0.659	6	6,22,26,29,30,37	0.446	−0.808	46	272,151	16.9	15.5	(13.1, 18.2)
70 \ 0.899	6	7,18,23,25,27,28	0.759	−0.276	52	285,630	18.2	17.6	(15.3, 20.4)
80 \ 1.343	6	5,10,14,17,20,21	1.082	0.079	34	189,973	17.9	19.3	(16.4, 22.6)
90 \ 4.463	6	1,4,8,15,16,19	1.506	0.410	21	92,233	22.8	20.9	(17.3, 25.2)
100 \17.68	6	2,3,9,11,12,13	10.939	2.392	8	26,547	30.1	34.1	(21.4, 54.4)
Total or mean	**59**		**1.575**	**0.454**	**184**	**1,079,786**	**17.0**	**17.0**	**(14.7, 19.7)**

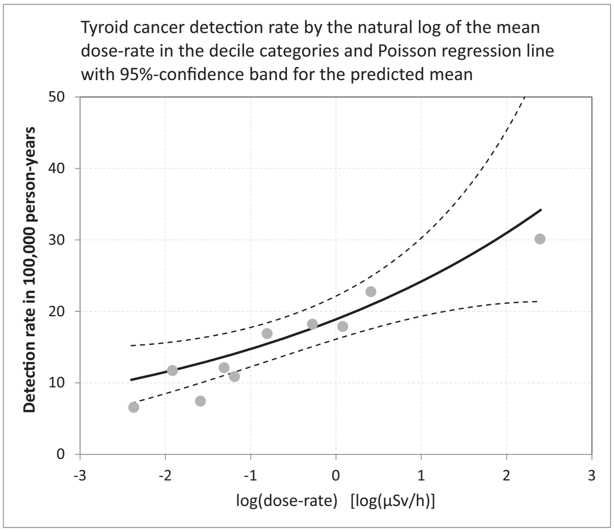

Figure 10. Thyroid cancer detection rate in 100,000 person-years (1st and 2nd screening rounds combined) by the natural log of the mean dose-rate in the 10 decile categories and Poisson trend with 95%-prediction bands for the mean; see Table 4.

to adjust for the participation rate, which adjustment could lead to over-fitting and variance inflation decreasing the precision of the Poisson regression models.

4.8. Limitations

The precise (anonymized) individual data on where the participants lived, when the screenings were carried out, and when the diagnoses were established, have not yet been released. We requested this information from one of the directors of the Fukushima Medical University to carry out independent investigations and to publish epidemiological studies. Unfortunately, this data was not provided or made public. Note, the concealment of these data is partly due to restrictions outlined in the informed consent by the FHMS participants.[97] Therefore, we estimated the corresponding proxy information from the published screening schedule tables, the number of the municipality-specific cumulative examination participants, and the thyroid cancer cases in each municipality. This data was announced approximately once every three months, which is why we assumed that the date when an individual had been examined can be estimated up to a precision of 90 days. For more accurate analyses, it is required to provide open access to the (anonymized) information as to where any participating person lived and when he or she was examined and diagnosed. With this more precise data, our analyses can easily be replicated. Since our approach inevitably entails spatial-temporal non-differential misclassification, it is likely that ‘true’ effects based on individual location and individual exposed person-time observed will turn out to be stronger and more precise compared to the results reported in the present paper. From this point of view, our quantitative estimates may be considered conservative.

There are few data, if any, which allow estimating validly the internal thyroid exposure after the FDNPP accidents for larger numbers of residents. It is a disadvantage of our study that information on the external dose resulting from the initial plume, the inhalation, and the diet contamination could not be assessed directly. However, such information cannot be obtained by simple physical measurement; exposure measures are rather dependent on various conversion coefficients and many other factors that introduce considerable uncertainty.

It was not possible to analyze the data by comparing the radiation dose-rate between the individuals that developed thyroid cancer and the individuals that remained healthy. In other words, we were not able to carry out a case-control study, which is a powerful epidemiological instrument. The reason is that the geographical locations where the thyroid cancer cases and the healthy participants lived as well as the date when the participants were examined or diagnosed have not yet been made available. The confounding factors age and sex at the municipality level have not been disclosed by the Fukushima Health Management Survey as yet. So, it is not possible to adjust our analyses for age and sex. We are also not aware of representative BMI data and iodine intake statistics at the municipality level that could be used for our study. Nevertheless, we think that our approach and our analyses are valid and important and that our work may motivate more refined and better adjusted analyses in the future.

5. Conclusions

We suggest an innovative statistical technique to determine the municipality-specific average exposed person-time of the participants in the ’Fukushima Health Management Survey’. The knowledge of the exposed person-time enables the assessment of the association between the radiation dose rate and the thyroid cancer detection rate more precisely than in previous studies. The thyroid cancer detection rate and the radiation dose-rate in the 59 municipalities in the Fukushima prefecture show statistically significant dose-response relationships. The detection rate ratio per μSv/h was 1.065 (1.013, 1.119) based on all data in both examination rounds combined. In the 53 municipalities subjected to less than 2 μSv/h, the detection rate ratio was considerably higher: 1.555 (1.096, 2.206). Therefore, it became evident that the radiation contamination due to the Fukushima nuclear power plant accidents is positively associated with the thyroid cancer detection rate in children and adolescents. This corroborates previous studies providing evidence for a causal relation between nuclear accidents and the subsequent occurrence of thyroid cancer.

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