

Nested matched case control study for the Japan Fukushima Health Management Survey's first full-scale (second-round) thyroid examination

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Abstract

Since Fukushima nuclear accident in 2011, thyroid ultrasound examinations have been conducted. The first full-scale examination detected 71 thyroid-cancer cases. This study examined whether radiation exposure was associated with thyroid-cancer incidence.

Subjects were participants in the baseline screening and newborns during the 2011 fiscal year. Under nested matched case-control study design, 10 controls per each case were selected by matching the age, sex, baseline screening results, and interval between examinations. With 3 dose levels of external radiation: 1.3 + mSv (upper), 0.8 to 1.3 (middle), and 0.0 to 0.8 (reference), we applied 2 logistic models adjusting for 3 participation-proportions (primary, secondary, and fine-needle aspiratory cytology), overweight, and the B-result of baseline screening (Model 1), and past medical history, family history of thyroid cancer, and frequencies of eating seafood and seaweed in addition to the parameters in Model 1 (Model 2). We examined each model in 3 ways: (a) excluding subjects with a missing radiation exposure dose; and substituting (b1) median or (b2) mean dose of the municipality with missing dose.

Odds ratios (ORs) of middle-dose exposure were (a) 1.35 (0.46–3.94), (b1) 1.55 (0.61–3.96), and (b2) 1.23 (0.50–3.03) for Model 1, and (a) 1.18 (0.39–3.57), (b1) 1.31 (0.49–3.49), and (b2) 1.02 (0.40–2.59) for Model 2. For upper-dose exposure, similar results were obtained. Past medical history was significantly associated (odds ratio = 2.04–2.08) with both (b1) and (b2) in Model 2.

No significant associations were obtained between the external radiation exposure and thyroid-cancer incidence.

Abbreviations: BMI = body mass index, CI = confidence interval, FHMS = the Fukushima Health Management Survey, FNAC = fine-needle aspiratory cytology, OR = odds ratio, SD = standard deviation.

Keywords: nested matched case-control study, odds ratio, the first full-scale thyroid (second-round) examination, the Japan Fukushima Health Management Survey

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1. Introduction

The Great East Japan Earthquake occurred on March 11, 2011, and the subsequent tsunami caused the accident at the Fukushima Daiichi Nuclear Power Plant that released radioactive elements into the surrounding area. The local Fukushima government began the Fukushima Health Management Survey (FHMS) of residents of Fukushima Prefecture (population approx. 2 million) to support the residents' concerns and promote their long-term health. FHMS consists of the basic survey for estimating individual external radiation doses and 4 detailed surveys including thyroid ultrasound examinations.^[1] Because excess emergence of thyroid cancer in children and adolescents in the Chernobyl nuclear power plant disaster in 1986 started 4 years after the accident (4 cases in 1987, 5 in 1988, 6 in 1989, 29 in 1990, and 55 in 1991),^[2,3] the thyroid ultrasound examination was planned as a cohort study design consisting of a baseline screening to reveal the "prevalence" of thyroid cancer in the first 3 years (i.e., the first-round examination done in 2011–2013) and incidence screenings to routinely monitor^[1] for thyroid cancer "incidence" with 2-year intervals for the aged <20 years old and 5-year intervals in those ≥20 years old (the second-round or first full-scale examination in 2014–2015), for all Fukushima Prefecture residents aged ≤18 years at the time of the accident.^[1]

The baseline screening started on October 9, 2011, and ended on April 30, 2014, and it revealed 116 diagnosed or suspected thyroid cancer cases (as of June 30, 2015).^[4] This detection of 116 cases evoked questions regarding whether this amount was excessive or not, why these 116 cases were observed, and whether this finding was caused by over-diagnosis^[5] or was an effect of the radiation.^[6] For the questions, we have described the data^[7] and shown associations were not observed between them by the geographical analysis,^[8–10] and by adjusting 3 factors (common index, creating comparable sample, sensitivity, or detection performance of the examinations) for the even comparison.^[11]

There is thus need of an examination of the cancer "incidence" following the Fukushima nuclear accident, and whether it represented an excess of cases. The objective of the present study was to clarify whether there was an association between the number of detected cases and the external radiation exposure data from the first full-scale examinations conducted between April 2014 and March 2016.

2. Subjects and methods

2.1. Study design

According to the protocol,^[1] the baseline screening is a prevalence study and the full-scale examination is an incidence study. We adopted a nested matched case-control study (with a case-control ratio of 1:10) because the incidence rate of thyroid cancer in Japan is approx. 3 per 1,000,000 people (rare) according to the National Cancer Registry,^[12] and we had a sufficient number of controls, that is, 10 per case.

2.2. Study subjects

The initial target population of the thyroid examination included Fukushima Prefecture residents who were aged ≤18 years on the date of the Fukushima Daiichi Nuclear Power Plant accident, that is, March 11, 2011 (born during the period from April 2, 1993, to April 1, 2011) (n=367,649) and the actual participants in the baseline screening (n=299,905) (Fig. 1). The target population of

the first full-scale survey of the thyroid examination was 313,404 individuals, excluding 116 diagnosed or suspected cases of thyroid cancer, 42 subjects who died during the baseline screening period, and 4 unqualified participants from among the baseline screening participants. We added 13,661 children (born during the period from April 2, 2011, to April 1, 2012) to the study population. The total number of subjects in this study was 254,601, as we excluded 27 dead individuals from among the participants of the first full-scale survey (n=254,628). The study subjects were (a) 113,897 subjects whose individual external radiation doses were estimated by the Basic Survey, and those with missing external radiation doses for which were substituted the (b1) median or (b2) mean dose in their municipality. The data used in this study were current as of December 31, 2017.

2.3. External radiation dose estimation

The individual external radiation dose was estimated based on a respondent's self-described "trail of evacuation along which he/she had moved" during the 4 months after the nuclear accident^[13,14] in the Basic Survey, which targeted all of the individuals who were residents (approx. 2,050,000) or visitors to Fukushima Prefecture as of March 11, 2011. The overall effective response proportion for the entire population of Fukushima Prefecture in the Basic Survey was 27.6% (566,680 of 2,055,267 residents) as of March 31, 2017.^[15] Considering the low response proportion of 27.6% in the Basic Survey, we additionally studied the representativeness of the results by comparing mean external doses between respondents and non-respondents, and found no difference, which indicated that the survey results were generalizable to the whole population.^[16] The Basic Survey^[14] showed that 99.8% of the participants were subjected to <5 mSv exposure (Table 1), and the mean and maximum individual external doses were 0.8 and 25 mSv, respectively, excluding both the participants whose estimation period was <4 months and the radiation workers.

2.4. FHMS thyroid examinations

FHMS thyroid ultrasound examinations consisted of a primary complete survey and secondary confirmatory examinations (detailed ultrasound examination and fine-needle aspiratory cytology (FNAC)). In the primary examination, in which ultrasonography was used to examine the thyroid gland, the participants were categorized into Category A, those with test results of A1 (no nodules/cysts) or A2 (nodules ≤5.0 mm or cysts ≤20.0 mm); Category B, those with test results of B (nodules >5.1 mm or cysts >20.1 mm); and Category C, those with test results of C (immediate need for confirmatory examination). Those in Categories B and C were advised or required to take the Confirmatory Examination. Some confirmatory examination participants required FNAC.

2.5. Outcome variable, explanatory variables

The outcome variable was the detection status of thyroid cancer as determined by the thyroid examination (case vs. control). The explanatory variables were:

- (i) external radiation exposure (1.3+, 0.8–1.3, 0.0–0.8);
- (ii) the proportion of the subjects for primary thyroid screening that actually participated in it;

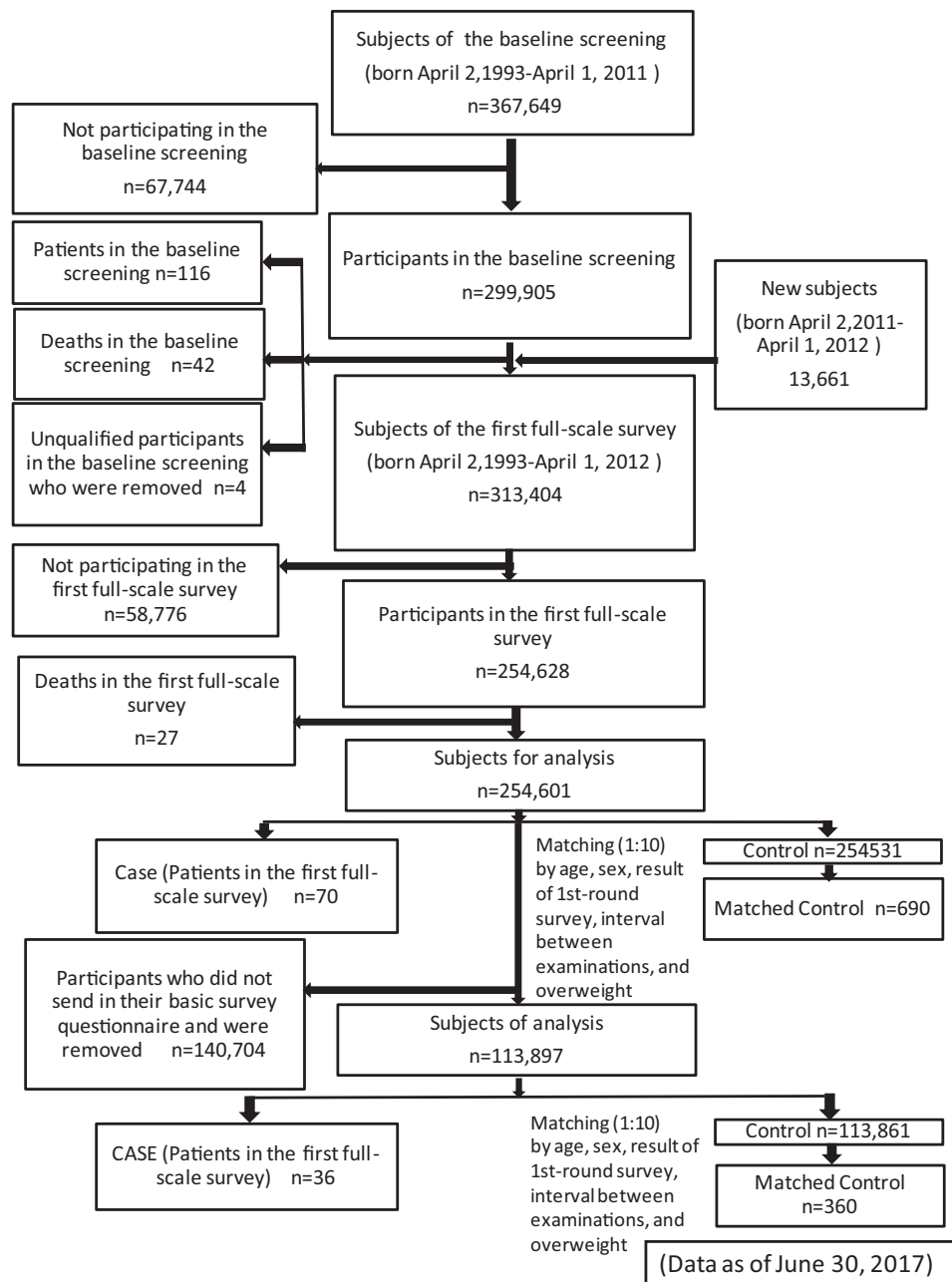


Figure 1. Flowchart of the study's target population.

- (iii) the proportion of the subjects for the secondary confirmation examination that actually participated in it;
- (iv) the proportion of the subjects for the subjects for FNAC that actually participated in it;
- (v) overweight status;
- (vi) the B-result of the baseline screening (b-proportion);
- (vii) the participants' medical history;
- (viii) the family disease history of thyroid cancer;
- (ix) the frequency of eating seafood; and
- (x) the frequency of eating seaweed.

Here, because the childhood body mass index (BMI) might be associated with the future incidence of thyroid cancer,^[17] we

adopted overweight status as an explanatory variable. Overweight was defined as an age- and sex-specific BMI higher than the 85th percentile of all Japanese people in their age group, as recommended by the Japanese Society for Pediatric Endocrinology and the Japanese Association for Human Auxology.^[18] This level corresponded to a BMI >25 at 17.5 years of age.^[18,19]

Three participation-proportions in the examination (for items (ii), (iii), and (vi) above) were obtained for each municipality in which the residents lived at the time of the accident, and the b-proportion was calculated annually in 2011, 2012, and 2013.

To decrease the effect of estimation errors and increase the statistical power, we used 3 levels, each including an equal number of cases. The 33.3% and 66.7% percentiles in the cases

Table 1**Estimated external radiation doses of the study subjects.**

Effective dose (mSv)	Excluding radiation workers (N, %)		Cumulative proportions (%)	
<1	288,736	62.2	93.8	99.8
1–2	147,054	31.7		
2–3	25,664	5.5	5.8	
3–4	1495	0.3		
4–5	505	0.1	0.2	
5–6	389	0.1		0.2
6–7	230	0.0	0.1	
7–8	116	0.0		
8–9	78	0.0	0.0	
9–10	41	0.0		
10–11	36	0.0	0.0	0.0
11–12	30	0.0		
12–13	13	0.0	0.0	
13–14	12	0.0		
14–15	6	0.0	0.0	
>15	15	0.0		0.0
Total	464,420	100.0	100.0	100.0
Max	25 mSv			
Mean	0.8 mSv			
Median	0.6 mSv			

Reprinted partly from the Basic Survey of the Fukushima Management Survey Group (Radiation Dose Estimates) reported on October 23, 2017. <http://fmu-global.jp/download/basic-survey-20/?wpdmdl=3555>.

with an external radiation dose were 0.8 and 1.3 (mSv), respectively. The 33.3% and 66.7% percentiles of the participation-proportions were 70.7% and 74.3% for the primary thyroid screening, 79.1% and 83.4% for the secondary confirmation examination, and 85.8% and 92.9% for FNAC, respectively. The categories for

- (1) overweight status,
- (2) b-proportion,
- (3) participants' medical history, and
- (4) family disease history were yes (=1) versus no (=0), while those of
- (5) the frequency of eating seafood and
- (6) the frequency of eating seaweed were “6 to 7 or 3 to 5/wk”(=1) versus “0 or 1 to 2/wk” (=0), respectively.

2.6. Matching variables, logistic models, and statistical analyses

The matching variables were sex (male=1 vs female=2), age (2, . . . , 24 integer years at the primary examination in the first full-scale survey rounded to the nearest year of age), the results of the baseline screening (A1, A2, B, C),^[1,4] and the interval (months) between the dates of the baseline screening and the first full-scale examinations (0–2, 2–4, . . . , 60–62, 62+).

We applied 2 multivariate logistic regression models. Model 1 had the following explanatory variables:

- (i) radiation exposure,
- (ii) the proportion of participants undergoing primary thyroid screening,
- (iii) the proportion of participants in the secondary confirmation examination,
- (iv) the proportion of participants undergoing FNAC,
- (v) the overweight status, and
- (vi) the b-proportion. Model 2 had the following in addition to the variables of Model 1:

- (vii) the participants' medical history,
- (viii) their family disease history,
- (ix) frequency of eating seafood, and
- (x) frequency of eating seaweed.

For the analysis, we first focused on (a) the subjects for whom estimated external radiation-dose data were available, and (b) the subjects for whom missing dose data were supplied as the estimated (b1) median or (b2) mean dose for their municipality. For all samples, i.e., (a), (b1), and (b2), we tabulated the characteristics of the cases and matched controls, respectively. After matching sex, age, and the interval of the examinations (months), we applied 2 kinds of conditional logistic regression analyses for 3 samples, namely (a), (b1), and (b2). The odds ratio (OR) and 95% confidence intervals (CIs) were estimated in each model.

We used SAS Enterprise Guide Software Version 7.1 and considered a result to be statistically significant if the 95% CI did not contain its reference value for all analyses. This study was approved by the Ethics Committee of Fukushima Medical University (approval no. 1318).

3. Results

For the (a), (b1), and (b2) samples, the estimated external radiation dose of the participants is shown in Table 2. In Table 3, the case and control groups were balanced according to the following matching variables: the average age [17.4 years, standard deviation (SD) 3.3–3.4 years for (a) and 16.6 SD=3.3 for (b1,b2)], the proportion of females [50.0% for (a), 55.7% for (b1,b2)], the results of the baseline screening [A1 (52.8%), A2 (36.1%), B (17.1%) for (a), and 47.1%, 45.7%, 7.1% for (b1, b2)], and the interval between the 1st- and 2nd-round examinations [26.7–27.0 months, SD 5.6–6.2 months for (a) and 27.1–27.3, SD 5.5–5.9 months for (b1,b2)].

Tables 4–6 summarize the results of our examination of the associations between the factors and the incidence using 2

Table 2**Estimated external radiation doses (excluding radiation workers) of the participants in this study.**

Effective dose mSv	(a) Participants for whom estimated radiation dose data were available				(b1) Participants for whom missing radiation-dose data was supplied as the median value of their municipality				(b2) Participants for whom missing radiation-dose data was supplied as the mean value of their municipality			
	n	%	%	%	n	%	%	%	n	%	%	%
<1	66716	58.58	91.36	99.96	149326	58.65	96.01	99.98	151062	59.33	96.01	99.98
1–2	37343	32.79			95118	37.36			93382	36.68		
2–3	9379	8.23	8.55		9698	3.81	3.95		9698	3.81	3.95	
3–4	361	0.32			361	0.14			361	0.14		
4–5	50	0.04	0.07		50	0.02	0.03		50	0.02	0.03	
5–6	25	0.02		0.04	25	0.01		0.02	25	0.01		0.02
6–7	8	0.01	0.02		8	0.00	0.00		8	0.00	0.00	
7–8	6	0.01			6	0.00			6	0.00		
8–9	8	0.01	0.01		8	0.00	0.00		8	0.00	0.00	
9–10	0	0.00			0	0.00			0	0.00		
10–11	0	0.00	0.00	0.00	0	0.00	0.00	0.00	0	0.00	0.00	0.00
11–12	0	0.00			0	0.00			0	0.00		
12–13	0	0.00	0.00		0	0.00	0.00		0	0.00	0.00	
13–14	0	0.00			0	0.00			0	0.00		
14–15	0	0.00	0.00		0	0.00	0.00		0	0.00	0.00	
>15	1	0.00	0.00	0.00	1	0.00	0.00	0.00	1	0.00	0.00	0.00
Total	113,897	100.0	100.0	100.0	254,601	100.0	100.0	100.0	254,601	100.0	100.0	100.0
Max		18.0 mSv				18.0 mSv				18.0 mSv		
Median		0.70 mSv				0.60 mSv				0.69 mSv		
Mean		0.91 mSv				0.83 mSv				0.86 mSv		

Table 3**Basic characteristics of the subjects in the first full-scale survey of thyroid examination in the Fukushima Health Management Survey, 2014–2015.**

Characteristic	(a) Cases for whom estimated radiation-dose data were available				(b1) Cases for whom missing radiation-dose data were supplied as the median value of their municipality				(b2) Cases for whom missing radiation-dose data were supplied as the mean value of their municipality			
	Cases		Matched control		Cases		Matched control		Cases		Matched control	
	N = 36	N = 360	N = 70	N = 700	N = 70	N = 700	N = 70	N = 700				
Age, SD, (yr)	17.4	3.4	17.4	3.3	16.6	3.3	16.6	3.3	16.6	3.3	16.6	3.3
Female, n, %	18	50.0	180	50.0	39	55.7	390	55.7	39	55.7	390	55.7
Examination results in the first-round survey, n, %												
A1	19	52.8	190	52.8	33	47.1	330	47.1	33	47.1	330	47.1
A2	13	36.1	130	36.1	32	45.7	320	45.7	32	45.7	320	45.7
B	4	17.1	40	11.1	5	7.1	50	7.1	5	7.1	50	7.1
Interval between the baseline and the full-scale survey of thyroid examinations, months, SD	26.7	6.2	27.0	5.6	27.1	5.9	27.3	5.5	27.1	5.9	27.3	5.5
External radiation exposure (mSv), n, %												
0.0–0.8	11	30.6	181	50.3	27	38.6	329	47.0	27	38.6	325	46.4
0.8–1.3	11	30.6	82	22.8	12	17.4	85	12.1	22	31.4	170	24.3
1.3+	14	38.9	97	26.9	31	44.3	286	40.9	21	30.0	205	24.3
Past medical history (yes)	8	22.2	44	12.3	15	21.7	96	13.9	15	21.7	96	13.9
Family history of thyroid cancer (yes), n, %	3	8.3	31	8.6	4	5.7	51	7.3	4	5.7	51	7.3
Frequency of eating seafood (FESF) per week, n, %												
0 or 1–2	29	80.6	285	79.6	56	80.1	547	79.4	56	80.1	547	79.4
3–5 or 6–7	7	19.4	73	20.4	14	20.0	142	20.6	14	20.0	142	20.6
Frequency of eating seaweed (FESW) per week, n, %												
0 or 1–2	28	77.8	286	79.9	60	85.7	548	79.7	60	85.7	548	79.7
3–5 or 6–7	8	22.2	72	20.1	10	14.3	140	20.4	10	14.3	140	20.4
Overweight*	4	11.1	29	8.1	12	17.1	90	12.9	12	17.1	90	12.9

* Overweight was defined as an age- and sex-specific BMI higher than the 85th percentile of all Japanese in their age group, as recommended by the Japanese Society for Pediatric Endocrinology and the Japanese Association for Human Auxology. (<http://jspe.umin.jp/medical/taikaku.html>).

Table 4
Conditional logistic regressions (for cases in which estimated external radiation-dose data were available).

	Logistic regression Model 1 [‡]		Logistic regression Model 2 [†]	
	OR	95%CI	OR	95%CI
External radiation exposure (ERE) (mSv)				
0.0–0.8	1.00	–	1.00	–
0.8–1.3	1.35	0.46–3.94	1.18	0.39–3.57
1.3–∞	1.69	0.55–5.18	1.69	0.55–5.20
Proportion participating in the examination (primary examination) (PP1) [‡] , %				
0.0–70.7	1.00	–	1.00	–
70.7–74.3	1.36	0.27–6.90	1.39	0.27–7.10
74.3–100.0	1.68	0.53–5.34	1.62	0.51–5.12
Proportion participating in the examination (secondary examination) (PP2) [‡] , %				
0.0–79.1	1.00	–	1.00	–
79.1–83.4	0.48	0.12–1.91	0.55	0.14–2.24
83.4–100.0	0.40	0.09–1.69	0.47	0.11–2.06
Proportion participating in the examination (FNAC) (PP3) [‡] *c, %				
0.0–85.8	1.00	–	1.00	–
85.8–92.9	0.94	0.19–4.68	0.82	0.16–4.24
92.9–100.0	2.11	0.53–8.43	2.15	0.53–8.83
Overweight				
No	1.00	–	1.00	–
Yes	1.60	0.47–5.49	1.74	0.49–6.13
B proportion in the first-round survey:	0.82	0.71–0.95	0.81	0.70–0.94
Past medical history (PMH):				
No	–	–	1.00	–
Yes	–	–	2.17	0.81–5.80
Family history of thyroid cancer (FTC):				
No	–	–	1.00	–
Yes	–	–	0.90	0.23–3.59
Frequency of eating seafood (FESF), /wk				
0 or 1–2	–	–	1.00	–
3–5 or 6–7	–	–	0.94	0.34–2.64
Frequency of eating seaweed (FESW), /wk:				
0 or 1–2	–	–	1.00	–
3–5 or 6–7	–	–	0.99	0.37–2.65

* Model 1: Explanatory variables were ERE+ PP1+PP2+PP3+Overweight.

† Model 2: Explanatory variables were ERE+ PP1+PP2+PP3+Overweight+PMH+FTC+FESF+FESW.

‡ The proportion participating in the examination was calculated for each municipality.

The values of the cases and controls were calculated using the proportion participating in each municipality.

multivariate conditional logistic regressions (Model 1 and Model 2) for the (a), (b1), and (b2) samples, respectively.

For the subjects (a) for whom external radiation-dose data were available (Table 4), the ORs of the middle-level external radiation exposure were 1.35 (0.46–3.94) for Model 1 and 1.18 (0.39–3.57) for Model 2, and the ORs of the upper-level external radiation exposure were 1.69 (0.55–5.18) and 1.69 (0.55–5.20), respectively. All ORs showed no significance.

For the subjects (b1) in whom the median was substituted for missing values (Table 5), the middle level ORs were 1.55 (0.61–3.96) for Model 1 and 1.31 (0.49–3.49) for Model 2, and the upper-level ORs were 1.10 (0.45–2.67) for Model 1 and 1.01 (0.41–2.50) for Model 2. All ORs showed no significance.

For the subjects (b2) in whom the mean was substituted for missing values (Table 6), the middle level ORs were 1.23 (0.50–3.03) for Model 1 and 1.02 (0.40–2.59) for Model 2, and the upper-level ORs were 1.07 (0.44–2.60) for Model 1 and 0.98 (0.39–2.44) for Model 2. All ORs showed no significance.

For the (b1) and (b2) samples, the subjects' past medical history showed significant ORs, 2.04 (1.06–3.92) and 2.08 (1.08–3.99) for Model 2, respectively.

4. Discussion

We showed that the associations between external exposure and cancer incidence was not statistically significant for exposure at either the middle or upper level for either 2 models (Model 1 and Model 2) in all 3 ways of radiation estimations using a nested matching case-control study design. This is the first study to apply individual data from the first full-scale survey of the FHMS thyroid examination for both the external radiation dose and thyroid cancer incidence. Fortunately, we were able to apply 10 controls per case in our analysis, which raised its statistical power. Our finding that there was no association between external radiation exposure and thyroid cancer incidence following the Fukushima disaster is thus more accurate than those of previous ecological studies.

In the FHMS, it was difficult to analyze data because 2 factors could distort the true association. One factor was the violation of uniqueness in the percentage participation of thyroid examinations both among municipalities and during the survey period, which directly influenced the detection of thyroid cancer. The other factor was individual confounders such as sex, age, overweight, medical history, family history of thyroid cancer, the

Table 5
Conditional logistic regressions (in participants for whom the median external radiation dose in the municipality was substituted for a missing dose).

	Logistic regression Model 1*		Logistic regression Model 2†	
	OR	95%CI	OR	95%CI
External radiation exposure (ERE) (mSv)				
0.0–0.8	1.00	–	1.00	–
0.8–1.3	1.55	0.61–3.96	1.31	0.49–3.49
1.3–∞	1.10	0.45–2.66	1.01	0.41–2.50
Proportion participating in the examination (primary examination) (PP1)‡, %				
0.0–70.7	1.00		1.00	
70.7–74.3	1.25	0.36–4.35	1.35	0.38–4.83
74.3–100.0	1.11	0.47–2.61	1.28	0.54–3.08
Proportion participating in the examination (secondary examination) (PP2)‡, %				
0.0–79.1	1.00		1.00	
79.1–83.4	0.91	0.35–2.38	1.02	0.37–2.80
83.4–100.0	0.90	0.35–2.35	0.87	0.32–2.37
Proportion participating in the examination (FNAC) (PP3)*c, %				
0.0–85.8	1.00		1.00	
85.8–92.9	0.75	0.24–2.36	0.64	0.19–2.13
92.9–100.0	1.06	0.41–2.72	0.93	0.34–2.51
Overweight				
No	1.00		1.00	
Yes	1.54	0.77–3.08	1.62	0.80–3.28
B proportion in the first-round survey:	0.95	0.87–1.03	0.94	0.86–1.03
Past medical history (PMH):				
No	–	–	1.00	
Yes	–	–	2.04	1.06–3.92
Family history of thyroid cancer (FTC):				
No	–	–	1.00	
Yes	–	–	0.77	0.26–2.27
Frequency of eating seafood (FESF), /wk				
0 or 1–2	–	–	1.00	
3–5 or 6–7	–	–	1.18	0.59–2.36
Frequency of eating seaweed (FESW), /wk:				
0 or 1–2	–	–	1.00	
3–5 or 6–7	–	–	0.58	0.27–1.28

* Model 1: Explanatory variables were ERE+ PP1+PP2+PP3+Overweight.

† Model 2: Explanatory variables were ERE+ PP1+PP2+PP3+Overweight+PMH+FTC+FESF+FESW.

‡ The proportion participating in the examination was calculated for each municipality.

The values of the cases and controls were calculated using the proportion participating in each municipality.

frequency of eating seafood, and those of eating seaweeds after the accident. In this analysis, we adjusted 3 participation-proportions of thyroid examinations (primary thyroid screening, secondary confirmation examination, and FNAC) and the B-result of the baseline screening as the behavioral factors, which were considered as essential.

On the other hand, we examined only the external radiation exposure, which would have underestimated the association based on the total radiation exposure. Thus, the estimation of internal exposure and natural background radiation exposure is important. For the internal exposure, Hayano and colleagues^[20] estimated that the dose received by school children in the town of Miharu (in Fukushima Prefecture) in the fall of 2012 was below the detection limit of 300Bq/body using extensive individual whole body counter data (n=32,811). They also estimated that the internal radiation dose of the school children (using the whole body counter as the upper intake limit) was 1 Bq/day for Cs-137 for four consecutive years from 2011 to 2014.^[21] The dose of 1 Bq/day for 4 years (in Miharu) was calculated as $365 \times 4 \times 1.3 \times$

$10^{-5} = 0.019$ mSv, which was much lower than the mean and median external doses of 0.8 mSv and 0.6 mSv, respectively. On the other hand, there was another estimation by Kim et al showing that the 90th percentile of the internal thyroid dose for the residents of the Fukushima municipalities ranged from ≤ 10 to 30 mSv for 1-year-olds and from ≤ 10 to ≤ 20 mSv for adults, with a high level of uncertainty.^[22] The natural background radiation was calculated to have a median value of 0.04 μ Gy/h (with 0.03 μ Sv/h as the effective dose rate) in our Basic Study, which corresponds to a 4-month effective dose of 0.05 mSv under the assumption of a shielding factor and a daily time-budget.^[14] Since the variation of background radiation is considered to be within the range of uncertainty, it has little effect.

For the effect of radiation exposure, a pooled analysis of 9 cohorts by Lubin et al^[23] showed that

- (i) the relative rate non-linearly increased with the thyroid dose of < 0.2 Gy (increase: $P < .01$, linearity: $P = .77$) and < 0.1 Gy ($P < .01$, $P = .66$), and

Table 6
Conditional logistic regressions (in participants for whom the mean external radiation dose in the municipality was substituted for a missing dose).

	Logistic regression Model 1*		Logistic regression Model 2†	
	OR	95%CI	OR	95%CI
External radiation exposure (ERE) (mSv)				
0.0–0.8	1.00	–	1.00	–
0.8–1.3	1.23	0.50–3.03	1.02	0.40–2.59
1.3–∞	1.07	0.44–2.60	0.98	0.39–2.44
Proportion participating in the examination (primary examination) (PP1)‡, %				
0.0–70.7	1.00	–	1.00	–
70.7–74.3	1.23	0.37–4.12	1.37	0.40–4.76
74.3–100.0	1.15	0.50–2.69	1.34	0.56–3.18
Proportion participating in the examination (secondary examination) (PP2)‡, %				
0.0–79.1	1.00	–	1.00	–
79.1–83.4	0.91	0.34–2.43	1.00	0.36–2.81
83.4–100.0	0.93	0.35–2.48	0.87	0.31–2.41
Proportion participating in the examination (FNAC) (PP3)*c, %				
0.0–85.8	1.00	–	1.00	–
85.8–92.9	0.76	0.24–2.40	0.65	0.19–2.16
92.9–100.0	1.08	0.41–2.80	0.94	0.34–2.56
Overweight				
No	1.00	–	1.00	–
Yes	1.55	0.78–3.09	1.63	0.81–3.29
B proportion in the first-round survey:	0.94	0.86–1.03	0.94	0.85–1.03
Past medical history (PMH):				
No	–	–	1.00	–
Yes	–	–	2.08	1.08–3.99
Family history of thyroid cancer (FTC):				
No	–	–	1.00	–
Yes	–	–	0.79	0.27–2.32
Frequency of eating seafood (FESF), /wk				
0 or 1–2	–	–	1.00	–
3–5 or 6–7	–	–	1.20	0.60–2.39
Frequency of eating seaweed (FESW), /wk:				
0 or 1–2	–	–	1.00	–
3–5 or 6–7	–	–	0.59	0.27–1.29

* Model 1: Explanatory variables were ERE+ PP1+PP2+PP3+Overweight.

† Model 2: Explanatory variables were ERE+ PP1+PP2+PP3+Overweight+PMH+FTC+FESF+FESW.

‡ The proportion participating in the examination was calculated for each municipality.

The values of the cases and controls were calculated using the proportion participating in each municipality.

(ii) estimates of the threshold dose ranged from 0.0 to 0.03 Gy with a 95% CI of 0.0 to 0.04 (Gy). The usual transformation formula $1 \text{ Gy} = 1 \text{ Sv}$ gives a threshold range of 0 to 30 mSv. According to the finding that 99.8% of the participants had an exposure of <5 mSv (Table 1) and Kim's estimation, their exposures were considered to be within the threshold range. Ivanov et al^[24] reported that in the population of the most contaminated territories of Bryansk, Kaluga, Oryol, and Tula Oblast affected by the Chernobyl nuclear power plant accident, the excess relative risk per 1 Gy (ERR/Gy) was significant for children and adolescents (0–17 years of age): $\text{ERR/Gy} = 3.22$ with a 95%CI of 1.56 to 5.80. In their study, the average thyroid dose was 0.19 Gy for the younger portion of the population (0–17 years in 1986) and 0.04 Gy for the older portion (18 years old in 1986). The transform formula gives their average exposure as 185 mSv for 0- to 17-year-olds and 38 mSv for ≥ 18 -year-olds.

The averaged external dose in our study was 0.8 mSv, which was much smaller than the Chernobyl doses. Their Figure 1^[24]

showed no cases with an exposure of 0.8 mSv in their cohort, which implies that the external radiation dose in the Fukushima disaster was outside the range of their studies. These results supported our finding that there was no statistically significant association between the external radiation dose and the thyroid cancer incidence.

When interpreting the results of a cohort study, generally, it is important if the real observed time in person-years includes a sufficient span of time to the cancer incidence (latent period). In our case-control study, however, this was not a concern because the controls were selected at the point when the case was detected, that is, each case and its corresponding 10 controls have the same number of person-years.

It is possible that baseline screening might not find all of the prevalent cases.^[11] If some cases were not detected by the baseline screening but were found in the first full-scale survey, this would reduce the OR and strengthen the certainty that there was no association in the first full-scale survey.

With regard to the result that past medical history was statistically significantly associated with the incidence status of thyroid cancer in samples (b1) and (b2) in Model 2 (Tables 5 and 6, respectively) but not in sample (a) in Model 1, we consider that this was caused by there being more cases and controls in (b1) and (b2) than in (a), which shrank the length of the CI of the OR.

To obtain robust results, we categorized the external radiation dose values into 3 levels. We used 33.3% and 66.7% of the external dose received by the cases as the cutoffs in order to increase the statistical power (because of the small number of cases).

There is also a way of thinking that 3 populations participating thyroid examination should be treated as random effect not but explanatory variables. We applied generalized linear mixed model with binary outcomes and logit link, and obtained similar results that radiation exposures were not associated. (See Table S1~S3, Supplemental Content, <http://links.lww.com/MD/E344>, <http://links.lww.com/MD/E345>, <http://links.lww.com/MD/E346>).

Concerning to study design, case-cohort study is another option in this situation, which is more efficient in the sense enabling us to study several disease outcomes. And longer follow-up would be necessary to confirm the results.

4.1. Limitations

First, we did not apply the individual internal dose or natural radiation dose in this study, which could have caused us to underestimate the association. However, we carefully discussed the estimated effect of the individual internal dose based on previous studies, and showed that it would be included in the threshold range of the association.

Second, when children graduate from high school, many of them tend to move to other prefectures to enter university or to work, which lowers the examination-participation proportions of residents who are ≥ 18 years old. Though we adjusted our analyses by including the proportions as explanatory variables in the models, we could not fully adjust for the missing information and this may have caused a bias.

Third, we could not adjust for either non-preventable effects that occurred during the residents' evacuation or the effects of the diagnoses of latent and non-progressive cancers.

5. Conclusion

We conducted a nested matched case-control study of the FHMS cohort to explore the association between external radiation exposure and thyroid cancer incidence in children and adolescents in Fukushima Prefecture, Japan. No significant associations between the external radiation exposure and the incidence of thyroid cancer were found.

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Author contributions

H. Takahashi: contributed to make research questions, formulated the analysis plan, analyzed data, discussed the study results with co-authors, and wrote the manuscript.

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