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Original Contribution

Risk of Thyroid Follicular Adenoma Among Children and Adolescents in Belarus Exposed to Iodine-131 After the Chornobyl Accident

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Several studies reported an increased risk of thyroid cancer in children and adolescents exposed to radioactive iodines, chiefly iodine-131 (^{131}I), after the 1986 Chornobyl (Ukrainian spelling) nuclear power plant accident. The risk of benign thyroid tumors following such radiation exposure is much less well known. We have previously reported a novel finding of significantly increased risk of thyroid follicular adenoma in a screening study of children and adolescents exposed to the Chornobyl fallout in Ukraine. To verify this finding, we analyzed baseline screening data from a cohort of 11,613 individuals aged ≤18 years at the time of the accident in Belarus (mean age at screening = 21 years). All participants had individual ^{131}I doses estimated from thyroid radioactivity measurements and were screened according to a standardized protocol. We found a significant linear dose response for 38 pathologically confirmed follicular adenoma cases. The excess odds ratio per gray of 2.22 (95% confidence interval: 0.41, 13.1) was similar in males and females but decreased significantly with increasing age at exposure ($P < 0.01$), with the highest radiation risks estimated for those exposed at <2 years of age. Follicular adenoma radiation risks were not significantly modified by most indicators of past and current iodine deficiency. The present study confirms the ^{131}I-associated increases in risk of follicular adenoma in the Ukrainian population and adds new evidence on the risk increasing with decreasing age at exposure.

adenoma; Chornobyl nuclear accident; dose-response relationship; interaction; iodine deficiency; iodine radioisotopes; radiation; thyroid neoplasms

Abbreviations: CI, confidence interval; EOR, excess odds ratio; FNAB, fine-needle aspiration biopsy.

Studies have demonstrated an increased risk of thyroid cancer following exposure to external and internal ionizing radiation in childhood and adolescence (1, 2); there is accumulating evidence also of risk of benign thyroid tumors following external radiation exposure (3), although risks following internal exposure are much less well known. The accident at the Chornobyl (Ukrainian spelling)/Chernobyl (Russian spelling) nuclear power plant in Ukraine in 1986 resulted in the release of large amounts of radionuclides, chiefly iodine-131 (^{131}I), into the atmosphere, leading to radioactive fallout in various regions of Ukraine and neighboring Belarus. We established 2 parallel screening cohort studies in Ukraine and Belarus, referred to as the "UkrAm" and "BelAm" cohort studies, respectively, with each involving about 12,000 subjects who were exposed to radioactive fallout from the Chornobyl accident as children or adolescents (4). The cohorts have undergone periodic standardized screening for thyroid cancer and nonmalignant diseases of the thyroid. The UkrAm (5–7) and BelAm (8) studies have shown a significantly increased risk of thyroid cancer associated with internal exposure to ^{131}I from the radioactive fallout; the estimated risks were similar in magnitude to the risk associated with external radiation exposure (1, 2, 9, 10).

Increased radiation risks of benign thyroid tumors, including nodules, adenomatous goiter, and follicular adenoma, have previously been reported from studies of populations irradiated with x-rays (11–15) or radium and β emitters for medical reasons (16), as well as survivors of the atomic bombings in Japan exposed to γ radiation (17, 18). The magnitude of the risk has not been established because of the great variability in the way these studies were conducted and the endpoints that were used (3). Few studies evaluated radiation risks of thyroid follicular adenoma, a common encapsulated benign tumor of the follicular cells that results from single-cell clonal expansion, as opposed to nonneoplastic thyroid nodules, which result from hyperplastic tissue expansion. Our analysis of thyroid follicular adenoma cases detected 12 years after the Chornobyl accident in the UkrAm cohort suggested for the first time a statistically significant ^{131}I dose response in a systematically screened population (19).

In this report, we present dose-response analyses of follicular adenoma prevalence data from the first screening of the BelAm cohort. All analyses were based on individual radiation doses to the thyroid from ^{131}I that were estimated from subjects' thyroid radioactivity measurements, taken within 2 months after the accident, ecological and biokinetic models, and dietary/lifestyle information (20).

METHODS

The cohort

A detailed description of the BelAm Study has been published previously (8). In brief, we identified 38,543 potential cohort subjects who were ≤18 years of age at the time of the Chornobyl accident and had thyroid radioactivity measurements taken within 2 months after the accident. Study subjects were screened at study centers in the cities of Minsk and Gomel or at local medical clinics by visiting mobile screening teams. We traced potential subjects through local and oblast (an administrative subdivision similar to a state or province) address bureaus, departments of education and public health, and medical establishments. A total of 1,804 (5.0%) were ineligible (age >18 years at the time of the accident, died, incarcerated, moved out of the country, and so on), and 20,526 (53.3%) could not be traced. Of the 16,213 individuals who were traced and invited to participate in the study, 11,970 (73.8%) were screened for thyroid diseases. An additional 253 (2.1%) individuals were excluded after screening because of incorrect age (>18 years), incorrect identification, primary thyroid gland aplasia, or prior surgery for benign or malignant thyroid conditions. We also excluded 104 subjects whose doses could not be estimated, leaving a total of 11,613 subjects for analysis. This included 2 subjects who were previously excluded from analysis of thyroid cancer risk in this cohort (8) because their follicular adenoma diagnosis predated their diagnosis of thyroid cancer.

Screening procedures

The first screening was conducted in 1996–2004, with 11,543 of the 11,613 (99.4%) subjects examined between 1997 and 2001. Thyroid screening consisted of palpation and ultrasound examination by an ultrasonographer and clinical examination with independent palpation by an endocrinologist (4). All ultrasound imaging was performed by using 7.5-MHz probes. Most initial examinations were performed by using a Tosbee SSA 240s mechanical sector probe (Toshiba Corporation, Tokyo, Japan) that utilized a dedicated curved array transducer with a built-in water bath. Other studies were done on machines using 7.5-MHz linear probes (Sigma-Aldrich Corporation, St. Louis, Missouri; Logiq 100 or Logiq 200, General Electric Company, Milwaukee, Wisconsin). Discrepancies were resolved by a third examination conducted jointly by both physicians. These evaluations, along with thyroid volume measurements and serum thyroid-stimulating hormone, thyroglobulin, and antibodies to thyroid peroxidase, were used to establish a final diagnosis of thyroid disease or to provide referral for further investigations (see below). At screening, participants were administered questionnaires to ascertain demographic, residential, dietary, and medical history data. Urinary iodine concentrations were measured from spot urine samples.

Identification of cases

Fine-needle aspiration biopsy. The study protocol for identification of thyroid diseases is described in detail by Zablotska et al. (21). In brief, patients were referred to the Minsk or Gomel study center for further evaluation and ultrasound-guided fine-needle aspiration biopsy (FNAB) if they had thyroid nodules detected on palpation or ultrasound during screening that 1) measured at least 10 mm in any dimension or 2) measured 5–10 mm and were sonographically suspicious for malignancy (hypoechoic, indistinct border, calcified inclusions, extension through the thyroid capsule, or suspicious lymph nodes) or if they had diffusely abnormal thyroid tissue accompanied by unexplained cervical lymphadenopathy. Among 595 subjects referred, FNAB was performed for 553 eligible subjects (95.8%).

Histopathology review. Patients were referred for surgery if the cytology was diagnostic or suspicious for malignancy in either a thyroid nodule or a lymph node or for follicular neoplasm in a thyroid nodule. Of the 167 subjects referred for surgery, 152 (91.0%) underwent surgery at the Republican Center for Pathology of the Thyroid Gland in Minsk, Belarus. All cases were reviewed by the International Pathology Panel of the Chernobyl Tissue Bank (www.Chernobyltissuebank.com) or by a specially convened ad hoc international panel of thyroid pathologists (refer to the Acknowledgments) using the World Health Organization classification system (22). An additional 2 follicular adenoma cases were self-reported but could not be confirmed by the panels because of missing pathology specimens and were omitted.

Diagnoses of other thyroid diseases. Patients with confirmed thyroid nodules but negative for malignant cells at FNAB cytology had a final diagnosis of nodular goiter (23). Final diagnosis of diffuse goiter was based on clinical and ultrasound findings of enlarged thyroid gland in a euthyroid or hypothyroid subject with normal or slightly above normal levels of antibodies against thyroid peroxidase. The thyroid volume was calculated on the basis of the volume of an ellipsoid (length × width × depth × 0.479) as described

by Brunn et al. (24). The isthmus was taken into account only if its thickness was more than 5 mm.

Dosimetry

Iodine-l31 thyroid doses, which represented about 92% of the total thyroid dose received after the Chornobyl accident (20), were mainly from consumption of contaminated milk. They were estimated on the basis of 3 sources. The first source was measurements of the γ radiation emitted by the thyroid gland (called "direct thyroid measurements") taken within 2 months after the accident; these measurements were corrected for external and internal contamination of the human body in order to derive the ^{131}I activity in the thyroid at the time of the direct thyroid measurement. The second source was ecological and biokinetic models that were used to assess the temporal variation of ^{131}I activity in the thyroid. The third source was personal interview information on individual dietary and lifestyle habits. Additional data sources used to update the parameters of the dosimetry models included the following: 1) thyroid volume measurements conducted in Belarus by the Sasakawa Memorial Health Foundation (25) to derive age-specific thyroid masses typical for the Belarusian population; 2) measurements of ^{131}I in soil (26) to verify the validity of the calculated ^{131}I deposition density in each settlement; and 3) ^{131}I measurements in soil and grass samples to derive an interception factor of ^{131}I by vegetation.

Statistical analysis

All analyses were based on the central estimates of thyroid dose from ^{131}I intake. Using a logistic regression model, we estimated odds ratios comparing odds for disease in 4 dose categories with the reference category, <0.25 Gy (27). We also modeled the odds ratio in relation to continuous doses to estimate the excess odds ratio (EOR) per gray, or EOR/Gy, and to evaluate the shape of the dose response. Specifically, the continuous analyses assumed that the odds ratio was given by the following:

$$\lambda(z_0) \times [1 + \delta(\text{dose}, \beta_{\text{dose}})\varepsilon(z_e, \beta_e)],$$

where λ, δ, and ε are functions that describe the background risks, the dose-related risks, and the risk-modifying factors, respectively; z's are possible background (z_0) or risk-modifying (z_e) factors; and β's are dose parameters to be estimated from a linear, log-linear (power), exponential, or quadratic function of dose (β_{dose}). Because of the form of this equation, the possible values of β are limited by the requirement that the corresponding relative risk should not be negative. If the likelihood optimum being sought for a point or bound estimate attempted to converge below this limiting value, the minimum value for β was used, given by $-1/D_{\max}$, where $D_{\max}$ was the maximum dose. To show a linear dose-response pattern, EOR/Gy estimates were plotted on an arithmetic scale of the ordinate axis.

We examined potential confounding variables, such as sex, age at screening, urban/rural status (based on postal code) and oblast of residence at the time of screening, urinary iodine concentration, serum thyroglobulin, presence of screening-detected nodular or diffuse goiter, and self-reported family history of thyroid cancer or nodular goiter using a likelihood ratio test. We retained variables in the model if they significantly improved the model fit or changed the EOR estimate by more than 20%. Possible modifiers of the dose response considered were sex and oblast of residence at the time of the accident in 1986, family history of nodular goiter, and several indicators of past or current iodine deficiency, including screening-detected diffuse goiter or multinodular goiter, thyroid volume on ultrasound, serum thyroglobulin concentration, and urinary iodine concentration. We also evaluated the modifying effects of age at exposure because of known modifications of radiogenic thyroid cancer risk with this variable (2).

All analyses were performed by using the GMBO module of EPICURE statistical software (28). All statistical tests were 2 sided with a 0.05 type I error, and all 95% confidence intervals were likelihood based (29).

RESULTS

There were 38 prevalent cases of histopathologically confirmed follicular adenoma among 11,613 cohort subjects. Fourteen cases had both thyroid cancer and follicular adenoma, and 4 cases could not be classified unambiguously as benign or malignant and were labeled as "follicular tumor of uncertain malignant potential" (30). Three tumors had multiple foci. Iodine-131 thyroid doses in the cohort ranged from 0 to 32.8 Gy with an arithmetic mean of 0.56 (standard deviation, 1.18) Gy; 71% of the cohort had doses of <0.50 Gy, and 30% had doses of <0.10 Gy. Age at screening ranged from 11 years to 33 years (mean/median = 21 years).

Associations with nonradiation factors

After adjustment for thyroid dose, there were no significant differences between follicular adenoma cases and noncases for sex, age, or oblast of residence at screening (Table 1). Follicular adenoma cases were significantly more likely to report family history of nodular goiter (odds ratio = 2.90, 95% confidence interval (CI): 1.31, 6.42) ($P = 0.02$). There was only 1 case of follicular adenoma with family history of thyroid cancer (not shown). Follicular adenoma cases were more likely to come from rural areas than from urban areas (odds ratio = 2.13, 95% CI: 1.01, 4.51) ($P = 0.05$). Sex, age at screening, family history of nodular goiter, and oblast of residence and urban/rural status at the time of screening satisfied the criteria for confounding, and all further analyses were adjusted for these variables.

Associations with radiation dose

The odds ratios for follicular adenoma increased monotonically with increasing ^{131}I dose ($P < 0.01$) (Table 2; Figure 1). Participants with doses of ≥2 Gy (5% of the screened cohort) had the largest (and a significant) increase in risk (odds ratio = 6.93, 95% CI: 2.18, 22.1) for follicular adenoma compared with those with thyroid doses of <0.25 Gy.

A linear model provided a good fit to the dose data ($P < 0.001$), with an estimated EOR/Gy of 2.22 (95% CI: 0.41, 13.1) (Table 3). Tests for quadratic, exponential, or power departures from linearity were not significant ($P = 0.42$,

Table 1. Odds Ratios for Prevalent Thyroid Follicular Adenoma by Selected Background Risk Factors, Belarus, 1996–2004

Variable and Subcategory	Cases		Noncases		OR[a]	95% CI	df	*P* Value[b]
	No.	%	No.	%				
Sex								0.10
Male	14	36.8	5,626	48.6	1.00	Referent	1	
Female	24	63.2	5,949	51.4	1.74	0.89, 3.39		
Age at screening, years								0.20
10–14	12	31.6	1,382	11.9	1.00	Referent	3	
15–19	10	26.3	3,503	30.3	0.49	0.21, 1.16		
20–24	11	28.9	3,241	28.0	0.76	0.31, 1.82		
25–33	5	13.2	3,449	29.8	0.36	0.12, 1.10		
Family history of nodular goiter								0.02
No	30	78.9	10,688	92.3	1.00	Referent	1	
Yes	8	21.1	887	7.7	2.90	1.31, 6.42		
Oblast of residence at screening								0.17
Minsk	11	28.9	3,153	27.2	1.00	Referent	2	
Gomel	25	65.8	7,147	61.7	0.50	0.23, 1.11		
Other[c]	2	5.3	1,275	11.0	0.33	0.07, 1.51		
Urban/rural status at screening								0.05
Urban	14	36.8	7,033	60.8	1.00	Referent	1	
Rural	24	63.2	4,542	39.2	2.13	1.01, 4.51		

Abbreviations: CI, confidence interval; df, degrees of freedom; OR, odds ratio.
[a] Adjusted for thyroid dose and other variables in the table.
[b] *P* value from the likelihood ratio test for significance of adding corresponding variables to the model.
[c] Includes Brest, Grodno, Mogilev, and Vitebsk.

$P = 0.18$, and $P = 0.21$, respectively) (Figure 1); when we repeated our analyses excluding subjects with doses greater than 4 Gy (35 follicular adenoma cases and 11,388 noncases), tests for quadratic, exponential, or power departures from linearity remained not significant ($P = 0.40$, $P = 0.42$, and $P = 0.27$, respectively). Significant dose-response results were essentially unchanged when we excluded 4 cases with follicular tumor of uncertain malignant potential ($P < 0.001$) and the 3 cases with multiple foci ($P = 0.001$) or when we included the 2 self-reported cases ($P < 0.001$) (not shown). The EOR/Gy did not differ significantly by the largest dimension of follicular adenoma as determined at thyroid pathology ($P = 0.17$, not shown).

Effect modifiers of the radiation dose response

The EOR/Gy was similar for males and females but decreased significantly as age at exposure increased ($P < 0.01$),

Table 2. Odds Ratios for Prevalent Thyroid Follicular Adenoma by Thyroid Dose Category, Belarus, 1996–2004

Dose Category, Gy	Mean Dose, Gy	Cases		Noncases		OR[a,b]	95% CI
		No.	%	No.	%		
0.00–0.24	0.10	7	18.4	6,031	52.1	1.00	Referent
0.25–0.49	0.36	7	18.4	2,179	18.8	2.70	0.92, 7.93
0.50–0.99	0.70	8	21.1	1,702	14.7	3.58	1.24, 10.3
1.00–1.99	1.37	9	23.7	1,054	9.1	5.92	2.05, 17.1
2.00–32.8	4.12	7	18.4	609	5.3	6.93	2.18, 22.1
Total	0.56	38	100.0	11,575	100.0		

Abbreviations: CI, confidence interval; df, degrees of freedom; OR, odds ratio.
[a] $P_{\text{linear trend}} < 0.01$ (df = 1).
[b] Model adjusted for sex, age at risk, family history of nodular goiter, oblast of residence, and urban/rural status at the time of screening.

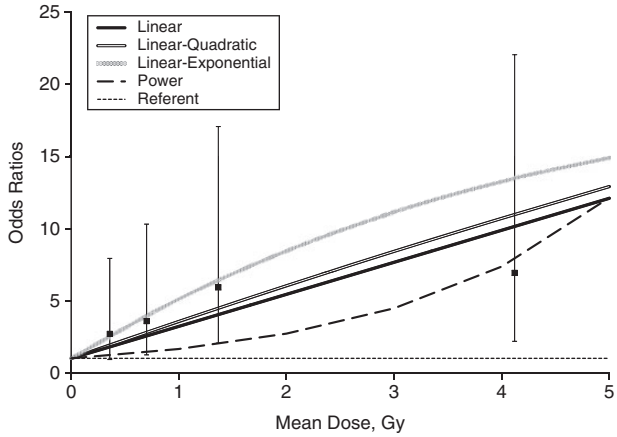

Figure 1. Odds ratios for prevalent thyroid follicular adenoma by mean dose for each of 5 dose categories and fitted dose-response curves constructed via maximum likelihood, BelAm Study, Belarus, 1996–2004. All odds ratios were calculated relative to <0.25 Gy; the referent odds ratio is 1.0; horizontal bars represent 95% confidence intervals.

with those exposed at age <2 years having the highest risks (EOR/Gy = 6.10, 95% CI: <0, 46.0) (Table 3). Although individuals with a family history of nodular goiter had a lower EOR/Gy compared with individuals without a family history, the difference in dose-response slopes between the 2 groups was not statistically significant ($P = 0.50$).

We examined possible modifying effects of past or current iodine deficiency using several indicators (Table 3). The EOR/Gy did not vary significantly by oblast of residence at the time of the Chornobyl accident in 1986 ($P = 0.88$). Also, the EOR/Gy estimates did not differ by diffuse goiter diagnosis at screening ($P = 0.51$) or across categories of thyroid volume ($P = 0.92$) or urinary iodine concentration during screening ($P = 0.81$). We observed a significantly higher dose-response estimate for those with only 1 nodule detected during ultrasound screening compared with those with ≥2 nodules ($P = 0.02$). Although the EOR/Gy was noticeably higher for those with high serum thyroglobulin levels, the difference was not statistically significant ($P = 0.51$).

Dose response for a combined category of thyroid neoplasia

During the first screening of the BelAm cohort, 112 study subjects (108 with doses less than 5 Gy) had diagnoses of thyroid neoplasia (thyroid cancer or follicular adenoma) confirmed by the pathology panels. The EOR/Gy estimate for this combined category increased monotonically with dose (EOR/Gy = 2.64, 95% CI: 1.08, 6.49) ($P < 0.001$) (Table 4). We estimated an EOR/Gy of 2.75 (95% CI: 1.38, 5.64) ($P = 0.04$) for 98 cases with thyroid cancer alone or follicular adenoma alone, while the EOR/Gy for 14 patients with concomitant diagnoses of follicular adenoma and thyroid cancer was 0.26 (95% CI: <0, 3.02) (not shown).

DISCUSSION

In this paper, we present results of the first analysis of follicular adenoma in the BelAm cohort of individuals exposed to ^{131}I as children or adolescents after the Chornobyl accident. Our findings confirm the previous report on the ^{131}I-related risk of follicular adenoma in the parallel UkrAm cohort (19). We found a significant linear ^{131}I dose response for follicular adenoma in Belarus. The estimated EOR/Gy of 2.22 for follicular adenoma was similar in magnitude to the EOR/Gy of 2.15 (95% CI: 0.81, 5.47) for thyroid cancer in the same Belarusian cohort (8) and also comparable with that of 2.07 (95% CI: 0.28, 10.31) for follicular adenoma in the Ukrainian cohort (19).

The Belarusian and Ukrainian cohorts are similar in size (about 12,000 each) and were similar in age at the time of the accident. Prevalent follicular adenoma cases were detected during the first screening, conducted a little over a decade (11–15 years in Belarus and 12–14 years in Ukraine) after the Chornobyl accident. In the Belarusian cohort, we also found that the radiation-related risk of follicular adenoma increased significantly with decreasing age at exposure. This age-at-exposure pattern was driven by the especially high EOR/Gy for those who were exposed very early in life, that is, <2 years of age. The UkrAm Study presented no clear modifying effects of age at exposure on the radiation risks of follicular adenoma, but this may have been due in part to the smaller number of cases, especially those exposed at very young ages (19). We found the ^{131}I-related risks of follicular adenoma to be similar for males and females. The UkrAm Study showed a significantly higher ^{131}I-related risk for females than for males, although based on a very small number of male cases (19).

Studies of populations with medical exposures to x-rays or radium and β emitters have also reported an increased risk of follicular adenoma, but the risk has varied widely in magnitude, with the estimated EOR/Gy ranging from about 3 (in childhood cancer survivors) to 6–14 (in those treated for head and neck conditions (Table 4) (11, 12, 14, 16). The higher EOR/Gy values were found in patients who were irradiated in infancy (12) or in early childhood (16), and they are consistent with the higher EOR/Gy among those exposed at <2 years of age in the present study. As for the sex differences, most studies (11, 12, 15–18), but not all (13), reported similar radiation risks for males and females (Table 4).

Other than post-Chornobyl studies, there are few studies on the associations of environmental exposures to radioactive iodines with follicular adenoma risk. The most notable of these are the Nevada Test Site Study and the Hanford Thyroid Disease Study (31, 32), both of which relied on retrospective dose reconstruction from residential and dietary history data obtained decades after exposures had occurred. Radiation risk estimates in these studies were provided for a broad group of thyroid neoplasia, which included thyroid cancer and follicular adenoma, and they were compatible with risk estimates in the BelAm and UkrAm studies (Table 4).

What distinguishes the Belarusian and Ukrainian data from other published studies is that the ascertainment of follicular adenoma was based on standardized screening and diagnostic review to minimize the potential bias related to radiation dose. In most other studies, follicular adenoma cases were

Table 3. Excess Odds Ratio per Gray for Prevalent Thyroid Follicular Adenoma Within Categories of Various Effect-Modifying Factors, Belarus, 1996–2004

Effect-Modifying Factor	Cases		Noncases		EOR/Gy[a]	95% CI	df	*P* Value[b]
	No.	%	No.	%				
All cases	38	100	11,575	100	2.22	0.41, 13.1	1	<0.001[c]
Sex								
Male	14	36.8	5,626	48.6	2.01	<−0.03, 156	1	0.94
Female	24	63.2	5,949	51.4	2.26	0.36, 14.6		
Age at exposure, years								
0–1	13	34.2	1,424	12.3	6.12	<−0.04, 46.0	1	<0.01
2–7	14	36.8	4,442	38.4	1.94	<−0.03, 17.1	2	0.12
8–18	11	28.9	5,709	49.3	0.81	<−0.07, 7.29		
Family history of nodular goiter								
No	30	78.9	10,688	92.3	2.72	0.46, 20.4	1	0.50
Yes	8	21.1	887	7.7	0.95	<−0.06, 24.9		
Indicators of past iodine deficiency								
Oblast of residence in 1986[d]								
Gomel	34	89.5	8,513	73.8	2.19	0.41, 13.0	1	0.88
Other	4	10.5	3,030	26.2	2.72	0.46, 20.4		
Diffuse goiter diagnosed at screening								
No	18	47.4	9,405	81.3	1.09	−0.08, 8.39	1	0.51
Yes	20	52.6	2,170	18.7	2.70	<−0.05, 675		
Thyroid volume on ultrasound at screening, cm^3 [e]								
0–10.99	13	34.2	4,279	37.2	0.85	<−0.03, 15.0		
11.00–13.99	13	34.2	3,237	28.1	4.37	0.49, 1,072	1	0.92
14.00–89.7	12	31.6	3,993	37.5	2.58	<−0.06, 1,538	2	0.57
Urinary iodine concentration at screening, μg/L[f]								
0–19	8	21.1	1,268	11.1	8.05	<−0.04, 5,255	1	0.81
20–99	21	55.3	6,253	54.7	1.78	<−0.03, 18.3	2	0.66
100–2,120	9	23.7	3,901	34.2	0.93	<−0.05, 34.3		
No. of nodules on ultrasound at screening								
0	0	0.0	10,675	92.2				
1	29	76.3	652	5.6	4.45	<−0.04, 553	1	0.02
≥2	9	23.7	248	2.1	1.19	<−0.03, 14.8		
Serum TG, ng/mL[g]								
0–69	32	86.5	11,336	98.6	1.56	0.20, 10.4	1	0.51
70–6,000	5	13.5	166	1.4	5.39	<−0.11, 493		

Abbreviations: CI, confidence interval; df, degrees of freedom; EOR, excess odds ratio; TG, thyroglobulin.

[a] Model adjusted for sex, age at risk, family history of nodular goiter, oblast of residence, and urban/rural status at the time of screening. Models additionally adjusted for variables investigated for possible interaction effects.

[b] *P* value from the likelihood ratio test for interaction effects, unless otherwise stated.

[c] *P* value for departure of EOR/Gy from 0.

[d] Among 11,581 subjects with known oblast of residence in 1986.

[e] Among 11,547 subjects with measurements of thyroid volume on ultrasound.

[f] Among 11,460 subjects with urinary iodine tests.

[g] Among 11,539 subjects with serum TG tests.

identified by self-reporting by questionnaires, linkage to tumor registries, review of medical records, and so on, which are prone to reporting or detection bias (Table 4) (11–14, 16). Follicular adenomas are often difficult to distinguish from follicular carcinomas or benign nodules of the thyroid, and some studies examined radiation risks for all benign

Table 4. Radiation-Related Risks of Thyroid Follicular Adenoma or Other Thyroid Nodule Groupings and Modifying Effects of Sex and Age at Exposure, Studies of External and Internal Radiation Exposures[a]

First Author, Year (Reference No.)	Location	Study Population	Type of Radiation	Mean Thyroid Dose, Gy	Age at Exposure, years	Method of Ascertainment	Thyroid Nodule			Effect Modification	
							No.	ERR/Gy	95% CI	Sex	Age at Exposure
							Follicular Adenoma				
Zablotska, 2015 (current study)	Belarus	BelAm Chornobyl cohort	^{131}I	0.56	0–18	Standardized screening and pathology	38	2.22	0.41, 13.1	No	Yes[b]
Zablotska, 2008 (19)	Ukraine	UkrAm Chornobyl cohort	^{131}I	0.77	0–18	Standardized screening and pathology	23	2.07	0.28, 10.31	Yes[b]	No
Shore, 1993 (12)	Rochester, New York	Thymus enlargement cohort	X-rays, chronic	1.36[c]	0–34 weeks	Questionnaire, medical records	97	6.3[d]	3.7, 11.2	No	NA[d]
Ron, 1989 (11)	Israel	Tinea capitis cohort	X-rays, chronic	0.09[c]	1–15	Tumor registries, pathology reports	43	14.4	2.9, 35.0	No	Yes
Shore, 2003 (13)	New York, New York	Tinea capitis cohort	X-rays, chronic	0.06[c]	1–15	Questionnaire, medical records	12	93	1.7, 647	Yes	No
Haddy, 2009 (16)	France	Hemangioma cohort	Radium and β emitters, chronic; x-rays, chronic (11%)	0.04[c]	0–>15; 74% < 1	Questionnaire, pathology reports	44	5.7	0.7, 19.4	No	No
Haddy, 2012 (14)	France	Childhood survivors of solid cancers	X-rays, chronic	5.8[c]	0–16	Questionnaire, pathology reports	71	2.8	1.2, 6.9[e]	NE	Yes[f]
							Other Thyroid Nodule Groupings				
Imaizumi, 2006 (17)	Japan	Atomic bomb survivors[g]	γ, acute	0.25	0–>90	Screening, tumor registries	156[h]	1.53	0.76, 2.67	No	Yes[b]
Imaizumi, 2015 (18)	Japan	Atomic bomb survivors[i]	γ, acute	0.18	0–10	Screening, tumor registries	186[h]	2.07	1.16, 3.39	No	No
Schneider, 1993 (15)	Chicago, Illinois	Head and neck cancer patients	X-rays, chronic	0.58	0–15	Screening, pathology reports	549[j]	8.2	3.0, 37.0	No	No
Zablotska, 2015 (current study)	Belarus	BelAm Chornobyl cohort	^{131}I	0.48	0–18	Standardized screening and pathology	108[k]	2.64[l]	1.08, 6.49	No	No
Zablotska, 2008 (19)	Ukraine	UkrAm Chornobyl cohort	^{131}I	0.77	0–18	Standardized screening and pathology	58[k]	4.39	1.67, 13.28	No	No
Lyon, 2006 (32)	Nye County, Nevada	Nuclear weapons test site	^{131}I	0.12	12–18	Screening, pathology reports	20[k]	13.0	2.7, 68.7	No	NE
Davis, 2004 (31)	Hanford, Washington	Nuclear site	^{131}I	0.17	0–18	Screening, pathology reports	33[k]	0.1	<−0.3, 2.2	NE	NE

Abbreviations: CI, confidence interval; ERR, excess relative risk; NA, not applicable; NE, not examined.

[a] Adapted from Ron and Brenner (38) with additions and modifications.

[b] $P < 0.01$.

[c] Among exposed.

[d] All subjects were infants.

[e] Ninety percent CI.

[f] $P = 0.02$.

[g] Study subjects examined for the first time 55–58 years after radiation exposure (in 2000–2003).

[h] Benign nodules, including follicular adenoma, adenomatous goiter, and cytologically benign nodules.

[i] Seventy-three percent of study subjects examined for the first time 62–66 years after radiation exposure (in 2007–2011).

[j] Benign nodules, including multinodular thyroids and colloid nodules in patients who did not develop thyroid cancer.

[k] Thyroid neoplasia, including thyroid cancer and follicular adenoma.

[l] Based on 11,493 subjects with thyroid doses of <5 Gy.

thyroid nodules (15, 17, 18) or for a combined category of thyroid neoplasia (31, 32). It is not possible to differentiate follicular adenoma from thyroid cancer on the basis of cytology, and current treatment guidelines for both conditions include thyroid gland removal and lifelong treatment with thyroid hormones (33). Given this background, a major concern in epidemiologic studies of radiation-related risks of follicular adenoma relates to a potential bias that may occur because of varying methods of case ascertainment (e.g., identification of nodules by palpation vs. ultrasound vs. surgically removed nodules, selection of cases for FNAB, and subsequent histopathology). The 2 parallel screening studies in Belarus and Ukraine were set up to overcome this potential ascertainment bias by providing standardized screening and pathology review of all potential cases.

Some post-Chornobyl studies (8, 34), but not all (6), have reported that iodine deficiency can modify the ^{131}I dose response for thyroid cancer. Radiation-related risks of thyroid cancer in the BelAm cohort were significantly increased among those with diffuse goiter or an enlarged thyroid volume detected during screening (8). However, in the present study, we found little evidence of the radiation effect of follicular adenoma being modified by any of the measures of past iodine deficiency, although the EOR/Gy tended to be higher in individuals more likely to be iodine deficient (i.e., among those with diffuse goiter diagnosis, larger thyroid volume, higher serum thyroglobulin, or lower urinary iodine). As there were reportedly regional differences in iodine intake at the time of the Chornobyl accident (35, 36), we also used oblast of residence in 1986 as a surrogate indicator of iodine intake, but it did not modify the radiation-related risk of follicular adenoma. Our findings are also consistent with those of the UkrAm Study, which showed no modifying effects of iodine deficiency, as measured by history of thyroid diseases, current iodine excretion, or oblast of residence (19). Multinodularity has been reported as a possible indicator of iodine deficiency (37), but in our study radiation risks of follicular adenoma were significantly lower in those with ≥2 nodules on ultrasound compared with those with only 1 nodule.

Some limitations should be considered. BelAm Study cohort recruitment was based on a roster of direct thyroid measurements taken in 1986 when subjects were ≤18 years of age (4). Because subjects could have moved out of the study areas or married and changed last names, 53.3% of potential study subjects with direct thyroid measurements could not be located. However, because screening personnel were blinded to radiation dose estimates and we adjusted for a variety of potential confounders, bias in risk estimates is likely to be minimal. Furthermore, of those traced and invited to participate in the study, 73.8% complied and underwent full screening. Our protocol for identification of thyroid diseases (21) was done without regard to thyroid dose and required referral of all patients with cytology of thyroid nodules diagnostic or suspicious for malignancy or follicular neoplasm to surgery and would be unlikely to miss any potential follicular adenoma cases. Study participants were not aware of their ^{131}I doses, and 91% of patients complied with a referral for surgery. Because most patients with benign cytology do not come to surgery, it is possible that follicular adenomas with a benign FNAB could have been missed. However, in our study, all subjects with thyroid nodules diagnosed as benign on FNAB during screening were recalled every 3 or 6 months for follow-up. Any changes in nodule characteristics or appearance of new clinical characteristics suspicious of cancer would have precipitated a new referral for FNAB and subsequent diagnosis at follow-up.

Our analysis used the central estimate of thyroid dose from ^{131}I intake and did not account for uncertainties in dosimetry. Recent analysis of the effects of uncertainties in thyroid dose assessment on thyroid cancer risk estimates in the Ukrainian cohort indicated comparatively modest changes (ranging from −11% to 7%) in regression parameters after adjustment for a mixture of Berkson and classical form errors (7). Because ^{131}I on average contributed about 92% of the thyroid dose (20), contributions of other exposure pathways, mainly external exposure and intake of short-lived radioiodine isotopes and tellurium 132 (^{132}Te), are unlikely to produce sizeable changes in risk estimates.

In summary, the present study in the Belarusian population provides an important confirmation of the previous novel finding of significantly increased risk of thyroid follicular adenoma following childhood and adolescent exposures to ^{131}I from the Chornobyl accident in the Ukrainian population, and it adds evidence on the importance of young age at exposure as a modifier of this risk. The consistency in the results obtained from the 2 cohorts, in which follicular adenomas were ascertained by standardized examinations and pathology reviews, strengthens the evidence of the radiation risks of this benign tumor. The ^{131}I-related risk of follicular adenoma is similar in magnitude to that of thyroid cancer in the same Belarusian cohort. Continuing follow-up of the 2 screening cohorts in Belarus and Ukraine will enable us to clarify the clinical consequences of screening-detected tumors and the temporal pattern of the ^{131}I risk as affected by age and other factors.

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