Original Article

Analysis of Thyroid Malignant Pathologic Findings Identified During 3 Rounds of Screening (1997-2008) of a Cohort of Children and Adolescents from Belarus Exposed to Radioiodines After the Chernobyl Accident

Lydia B. Zablotska, MD, PhD[1]; Eldar A. Nadyrov, MD[2]; Alexander V. Rozhko, MD, PhD[2]; Zhihong Gong, PhD[3]; Olga N. Polyanskaya, MD[2]; Robert J. McConnell, MD[4]; Patrick O'Kane, MD[5]; Alina V. Brenner, MD, PhD[6]; Mark P Little, PhD[6]; Evgenia Ostroumova, MD[6]; Andre Bouville, PhD[6]; Vladimir Drozdovitch, PhD[6]; Viktor Minenko, PhD[7]; Yuri Demidchik, MD[8]; Alexander Nerovnya, MD[8]; Vassilina Yauseyenka, MS[2]; Irina Savasteeva, MD[2]; Sergey Nikonovich, MD[2]; Kiyohiko Mabuchi, MD, DrPH[6]; and Maureen Hatch, PhD[6]

BACKGROUND: Recent studies of children and adolescents who were exposed to radioactive iodine-131 (I-131) after the 1986 Chernobyl nuclear accident in Ukraine exhibited a significant dose-related increase in the risk of thyroid cancer, but the association of radiation doses with tumor histologic and morphologic features is not clear. **METHODS:** A cohort of 11,664 individuals in Belarus who were aged ≤18 years at the time of the accident underwent 3 cycles of thyroid screening during 1997 to 2008. I-131 thyroid doses were estimated from individual thyroid activity measurements taken within 2 months after the accident and from dosimetric questionnaire data. Demographic, clinical, and tumor pathologic characteristics of the patients with thyroid cancer were analyzed using 1-way analysis of variance, chi-square tests or Fisher exact tests, and logistic regression. **RESULTS:** In total, 158 thyroid cancers were identified as a result of screening. The majority of patients had T1a and T1b tumors (93.7%), with many positive regional lymph nodes (N1; 60.6%) but few distant metastases (M1; <1%). Higher I-131 doses were associated with higher frequency of solid and diffuse sclerosing variants of thyroid cancer ($P<.01$) and histologic features of cancer aggressiveness, such as lymphatic vessel invasion, intrathyroidal infiltration, and multifocality (all $P<.03$). Latency was not correlated with radiation dose. Fifty-two patients with self-reported thyroid cancers which were diagnosed before 1997 were younger at the time of the accident and had a higher percentage of solid variant cancers compared with patients who had screening-detected thyroid cancers (all $P<.0001$). **CONCLUSIONS:** I-131 thyroid radiation doses were associated with a significantly greater frequency of solid and diffuse sclerosing variants of thyroid cancer and various features of tumor aggressiveness. ***Cancer* 2015;121:457-66.** © *2014 American Cancer Society.*

KEYWORDS: thyroid cancer, pathology, morphology, thyroid neoplasms, Chernobyl nuclear accident, papillary carcinoma, radiation, latency.

INTRODUCTION

The Chernobyl nuclear power plant accident in Ukraine on April 26, 1986 released large amounts of radiation, in particular radioactive iodines, into the atmosphere.[1] Children and adolescents living in the contaminated areas in Ukraine and Belarus were exposed to substantial doses of radiation to the thyroid gland from the ingestion of iodine-131 (I-131).[1] At the time, convincing evidence existed of an association between exposure to external x-ray and γ-radiation in childhood

Corresponding author: Lydia B. Zablotska, MD, PhD, 3333 California Street, Suite 280, San Francisco, CA 94118; Fax: (415) 563-4602; E-mail: Lydia.Zablotska@ucsf.edu.

[1]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California; [2]The Republican Research Center for Radiation Medicine and Human Ecology, Gomel, Belarus; [3]Roswell Park Cancer Institute, Buffalo, New York; [4]The Thyroid Center, Columbia University, New York, New York; [5]Radiology Department, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; [6]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; [7]Research Institute for Nuclear Problems, Minsk, Belarus; [8]Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus.

See editorial on pages 339-40, this issue.

The first 2 authors contributed equally to this article.

We gratefully acknowledge the late Dr. Jacob Robbins for his important contributions to the study over the years. We thank Drs. Ellen Greenebaum, Eugeny Cherstvoy, Vladimir Gapanovich, Nataliya Kamysh, Vladimir Masyakin, Sergei Petrenko, George Romanov, and Yuri Sidorov; Ms. Liliya Starostenko; and the staff of the Republican Research Center for Radiation Medicine and Human Ecology, Gomel, Belarus, for their dedication and commitment to the success of the study. We express our deep appreciation of the work of the members of the International Pathology Panel of the Chernobyl Tissue Bank and the ad hoc thyroid pathology panels: Drs. Alexander Abrosimov, Tatiana Bogdanova, Ronald Ghossein, Masahiro Ito, Virginia LiVolsi, Alexander Nerovnya, Juan Rosai, Geraldine Thomas, and Dillwyn Williams (Chair). Over the years we have greatly benefited from important advice from the members of the Thyroid Advisory Group: Drs. Oksana Baltarowich, Evelyn Bromet, Maria Demkowicz, Christine Durbak, Shirley Fry, Richard Hornung, Bruce Napier (Chair), Genevieve Roessler, and Arthur Schneider.

DOI: 10.1002/cncr.29073, **Received:** March 15, 2014; **Revised:** May 30, 2014; **Accepted:** June 11, 2014, **Published online** October 28, 2014 in Wiley Online Library (wileyonlinelibrary.com)

and adolescence and an increased risk of thyroid cancer.[2] However, risks from internally deposited radioactive iodines were not well understood.

Previous studies of mostly adult patients who were exposed to I-131 from diagnostic and therapeutic procedures had largely negative findings.[3,4] From 4 to 5 years after the accident,[5] ecologic[6,7] and then analytic epidemiological studies[8,9] reported increased risks of thyroid cancer among those living in Chernobyl-contaminated areas. It was not clear, however, whether the observed increases were caused by radiation doses or by intensive and widespread screening for thyroid abnormalities.[10] These post-Chernobyl thyroid cancers were characterized by a predominance of papillary carcinomas (93%-98% of all post-Chernobyl cases[11,12] compared with 60%-70% in other studies of childhood thyroid cancer[13,14]). The prevalence of solid morphology[15]; high rates of extrathyroidal spread, lymph node involvement,[16] and distant metastases; and changes in histology with time and increasing latency[10] were noted in many early publications. However, it was unknown whether the observed unusual features were because of exposures to Chernobyl-related radiation or to endemic iodine deficiency.[17]

We conducted 2 cohort studies of children and adolescents who lived in territories contaminated by the Chernobyl fallout in Ukraine and Belarus and were systematically screened irrespective of radiation dose.[18] The radiation risks of thyroid cancer were increased significantly in both cohorts.[19,20] Our group previously analyzed the clinical and pathomorphologic features of tumors in 45 patients with screening-detected thyroid cancer from Ukraine.[21] Those patients had a high proportion of cancers with solid structure and intrathyroidal infiltration. However, we did not analyze the correlation between tumor characteristics and radiation dose to the thyroid. Here, we report our findings on the correlation of I-131 thyroid dose and pathomorphologic features in 158 patients who had thyroid cancer detected during 3 sequential screenings in a parallel cohort from Belarus.[18] To compare clinical and pathologic features of screening-detected cancers with cancers identified during routine medical care, we also analyzed 52 cases in this cohort who were diagnosed before the initiation of standardized screening in 1997.

MATERIALS AND METHODS

Study Population

A detailed description of the Belarus-American (BelAm) study population and methods has been published previously.[18,19] In brief, the cohort includes 11,664 individuals who were aged $\leq$18 years at the time of the Chernobyl accident on April 26, 1986. All study participants had thyroid radioactivity measurements taken in Belarus within 2 months after the accident and were screened for the first time during 1997 to 2000.[19] The cohort was screened 2 more times during 2002 to 2004 and 2004 to 2006, and final follow-up was extended to the end of September 2008 to account for patients who were referred for additional biopsies and surgeries.

The study was approved by institutional review boards in Belarus and the United States. Informed consent was provided by the study participants or by accompanying guardians for minors.

Screening Procedures

The details of the screening are presented in Figure 1. The majority of study participants resided in Minsk and Gomel oblasts (an oblast is an administrative subdivision similar in size to a state or province) and were screened at study centers in the cities of Minsk and Gomel or at local medical clinics by visiting mobile screening teams. Thyroid screening consisted of ultrasound examination and palpation by a sonographer and a clinical examination with independent palpation by an endocrinologist.[18] Any discrepancies were resolved by a third examination conducted jointly by both physicians. At the time of screening, participants were administered questionnaires to ascertain demographic, residential, dietary, and medical history. Individual estimates of I-131 dose to the thyroid were assigned to each participant based on their thyroid radioactivity measurement taken in 1986, the interview data on factors contributing to dose (residential locations, diet), and radioecologic models of the environmental transfer of I-131.[22]

Patients who had 1) thyroid nodules detected either on palpation or sonogram that measured $>$10 mm in greatest dimension and 2) nodules that measured between 5 and 10 mm and were sonographically suspicious for malignancy (hypoechoic, indistinct borders, calcified inclusions, extension through the thyroid capsule, or suspicious lymph nodes) or diffusely abnormal thyroid tissue accompanied by unexplained cervical lymphadenopathy were referred to study centers for further evaluation and ultrasound-guided fine-needle aspiration biopsy (FNAB). Patients were further referred for surgery if cytology was diagnostic or suspicious for malignancy in either a nodule or a lymph node or for a follicular neoplasm in a nodule.

When the intraoperative frozen-section diagnosis was carcinoma, the patient underwent a total or near total thyroidectomy, which was followed by the usual standard

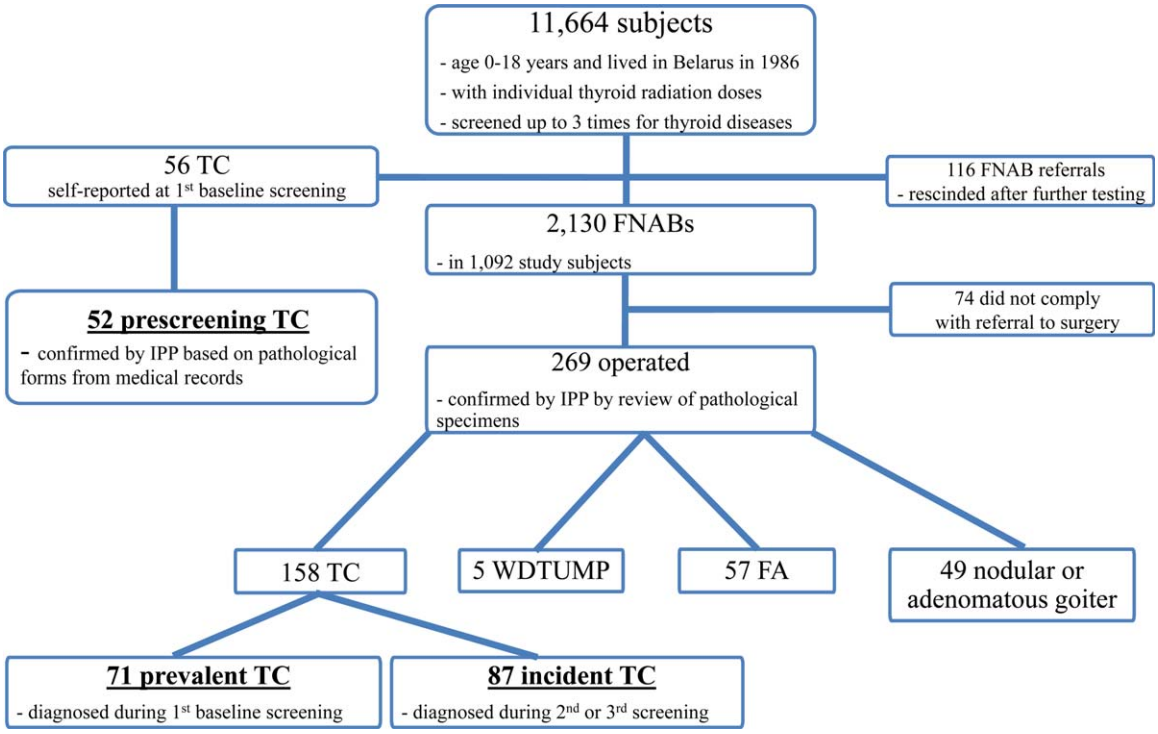

Figure 1. This Consolidated Standards of Reporting Trials (CONSORT) diagram illustrates the flow of Belarus-American study participants through each stage of systematic screening. FA, follicular adenoma; FNAB, fine-needle aspiration biopsy; IPP, International Pathology Panels; TC indicates thyroid cancer; WDTUMP, well differentiated tumors of uncertain malignant potential.

of care. When the frozen-section diagnosis was follicular neoplasm, the patient underwent a hemithyroidectomy, which was followed by a completion thyroidectomy when indicated. All specimens were fixed in 10% neutral buffered formalin and embedded in serial 3-mm to 4 mm paraffin blocks; 4-μm-thick sections were stained with hematoxylin and eosin for histologic examination. Pathologic specimens from all patients were reviewed and thyroid cancer diagnoses were confirmed by the International Pathology Panels (IPP), which were established initially in the framework of the Chernobyl Tissue Bank[23] and later were convened specifically for this study. Panel members were unaware of the patients' thyroid radiation doses.

Cancers were staged according to the *TNM Classification of Malignant Tumors* (fifth edition), and staging was converted later to the sixth edition classification.[24] Papillary thyroid cancers (PTCs) were subdivided into several different variants, depending on the dominant structural component: papillary, follicular, or solid when >80% of the surface of the slides had the corresponding structure.[25] Similar to several recent publications by members of the IPP,[21,26] we classified PTCs as mixed when they were composed of a combination of 2 patterns (papillary-follicular, papillary-solid, or solid-follicular) at a ratio of 50%:50%, 50%:40%, or 60%:30%, respectively, allowing for a third pattern in <10% of the tumor. Screening-detected thyroid cancers were further subdivided into prevalent cancers (cancers surgically removed within 3 years of initial screening and located within the same area of the thyroid gland where thyroid pathology was identified during initial screening) and incident cancers (all others) (Fig. 1).

Prescreening Cancers

Prescreening thyroid cancers were defined as cancers that were diagnosed after the accident and were reported by patients in the cohort at their initial screening in 1997. The route to diagnosis for the prescreening cancers was primarily through an ultrasound-detected or palpation-detected thyroid nodule during routine medical care or through 1 of the screening programs instituted in Belarus by national or international organizations. Pathology reports for self-reported cancers were retrieved from the medical records and reviewed by the IPP, as described above.

Statistical Analysis

We examined means and distributions of demographic, clinical, and pathologic characteristics across 3 groups of

thyroid cancers diagnosed in the BelAm cohort (screening-detected prevalent and incident cases and prescreening cases) and tested for statistically significant associations using 1-way analysis of variance for continuous variables and chi-square tests or Fisher exact tests for categorical variables. Thyroid radiation dose was log-normally distributed. Therefore, all further univariate tests were done using a Wilcoxon-Mann-Whitney test. Correlations of thyroid radiation dose with other continuously distributed variables were evaluated using the Spearman rank correlation test.

Adjusted unconditional logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of radiation doses with various tumor properties. For screening-detected cancers, latency was defined as the time from exposure to surgery.

All statistical tests were 2-sided and were considered statistically significant for $P < .05$. Statistical analyses were conducted using SAS software (SAS Institute Inc., Cary, NC).[27]

RESULTS

Screening-Detected and Prescreening Thyroid Cancers

Over the 3 cycles of screening in 11,664 individuals, 2130 FNABs were completed in 1092 individuals (of 2246 referrals; 94.8%) (Fig. 1). After FNAB, 343 patients were referred for surgery, and 269 (78.4%) complied. In total, the expert IPP reviewed surgical specimens and agreed on the diagnoses of thyroid cancer for 158 patients (157 papillary and 1 follicular), follicular adenoma for 57 patients and nodular or adenomatous goiter for 49 patients. The IPP was not able to classify 5 cases as definitely benign or malignant and labeled them as *well differentiated tumors of uncertain malignant potential*.[26] Patients with these results were not included in subsequent analyses.

The IPP used pathology reports extracted from medical records to confirm thyroid cancer diagnoses for 52 (all papillary type) of 56 thyroid cancers reported during interview at the initial screening. The pathology report was missing for 1 patient, and diagnoses were not confirmed for 3 patients with self-reported cancers.

Demographic and Clinical Characteristics of Patients With Thyroid Cancer

The demographic characteristics of the total screened study population (n = 11,664) were published previously.[19] In brief, men and women were equally represented in the cohort, approximately 70% were screened after age 18 years, and approximately 2% each had a history of diffuse or nodular goiter before screening. At the time of first screening in 1997 to 2000, the majority of study participants (65%) had urinary iodine concentrations <100 μg/L, which has been defined by the World Health Organization as iodine deficiency.[28]

Compared with the patients who had prevalent and incident screening-detected cancers (n = 158), the patients who had prescreening cancers (n = 52) were significantly younger at the time of the accident ($P < .01$), significantly younger at the time of surgery ($P < .0001$), and significantly more likely to have lived in rural areas at the time of the accident ($P = .02$) (Table 1). Patients with prescreening cancers were significantly more likely to have a more advanced tumor stage at histology (71% had ≥T3 tumors), whereas the majority (94%) of patients who had screening-detected cancers had tumors in less advanced stages (T1a and T1b; $P < .0001$) (Table 1). There were no differences between patients with prescreening and screening-detected cancers or between patients with prevalent and incident cancers in the stage of regional lymph node or distant metastases.

Histopathologic Features of Thyroid Cancer Cases

Although screening and prescreening patients overall had a similar proportion of tumors measuring >10 mm at pathology ($P = .92$) (Table 2), prevalent tumors were significantly more likely to measure >10 mm compared with incident tumors ($P = .04$). Prescreening cancers were more likely to be multifocal compared with cancers that were detected during serial screenings of the cohort ($P = .06$). At the same time, compared with prescreening cancers, screening-detected cancers more frequently had noncancer thyroid nodular pathology, such as hyperplastic nodules, follicular adenomas, and adenomatous goiter, diagnosed along with cancer ($P < .01$); had a significantly higher proportion of the solid histopathologic variant of PTC; and were less likely to be a papillary variant ($P < .0001$). There were no patients with the classic papillary variant among the prescreening cancers, but histopathologic features were unknown for about 31% of cancers. Patients with prescreening cancers also were significantly more likely to have thyroid capsule invasion and extrathyroidal spread than patients with screening-detected cancers (both $P < .0001$). However, there was no significant difference in intrathyroidal infiltration between prescreening and screening cancers ($P = .13$).

TABLE 1. Demographic and Clinical Characteristics of Patients With Thyroid Cancer

Characteristic	Prescreening Cases	Screening-Detected Cases		P[a]	
		Prevalent	Incident	Prescreening vs Screening	Prevalent vs Incident
Total no. (%)	52 (100)	87 (100)	71 (100)		
Age at time of the accident, years					
Mean ± SD	5.4 ± 3.7	8.7 ± 5.4	6.4 ± 5.11		
<7	38 (73.1)	35 (40.2)	41 (57.8)	<.01	.07
7-12	12 (23.1)	29 (33.3)	19 (26.8)		
13-18	2 (3.8)	23 (26.5)	11 (15.4)		
Age at surgery, years					
Mean ± SD	15.0 ± 4.4	23.0 ± 5.9	24.4 ± 6.1		
<15	27 (51.9)	9 (10.3)	3 (4.2)	<.0001	.18
15-19	17 (32.7)	21 (24.1)	14 (19.7)		
20-24	8 (15.4)	19 (21.8)	25 (35.2)		
25-38	0 (0)	38 (43.7)	29 (40.9)		
Sex				.42	.17
Male	28 (53.8)	37 (42.5)	38 (53.5)		
Female	24 (46.2)	50 (57.5)	33 (46.5)		
Place of residence at time of the accident				.02	.21
Urban	16 (30.8)	39 (44.8)	39 (54.9)		
Rural	36 (69.8)	48 (55.2)	32 (45.1)		
Oblast of residence at time of the accident				.28	.15
Gomel oblast	46 (88.5)	78 (89.7)	62 (87.3)		
Minsk city/oblast	6 (11.5)	4 (4.6)	8 (11.3)		
Other	0 (0)	5 (5.7)	1 (1.4)		
Family history of thyroid cancer				0.26	0.99
Yes	2 (4.0)	1 (1.2)	1 (1.4)		
No	50 (96.0)	86 (98.8)	70 (98.6)		
Tumor classification				<.0001	.28
T1a: ≤10 mm	11 (21.2)	53 (60.9)	52 (73.2)		
T1b: 11-20 mm	4 (7.7)	28 (32.2)	15 (21.1)		
T2	0 (0)	5 (5.8)	4 (5.6)		
T3	35 (67.3)	1 (1.1)	0 (0)		
T4a	2 (3.8)	0 (0)	0 (0)		
T4b	0 (0)	0 (0)	0 (0)		
Metastases to regional lymph nodes				.06	.25
N0	13 (25.0)	30 (34.5)	31 (43.7)		
N1	39 (75.0)	55 (63.2)	39 (54.9)		
Unknown	0 (0)	2 (2.3)	1 (1.4)		
Distant metastases				.43	.45
M0	50 (92.3)	87 (100)	70 (98.6)		
M1	1 (5.8)	0 (0)	1 (1.4)		
Unknown	1 (1.9)	0 (0)	0 (0)		

Abbreviations: SD, standard deviation.
[a] P values were calculated using 1-way analyses of variance for continuous variables and chi-square test or Fisher exact tests of heterogeneity for categorical variables.

Association of Histopathologic Features of Screening-Detected Thyroid Cancers With Thyroid Radiation Dose

The distribution of thyroid cancers by individual thyroid doses is presented in Figure 2. Overall, in analyses that were adjusted for age at exposure, thyroid I-131 doses in prescreening cancers were similar to the doses in screening-detected cancers ($P = .61$; data not shown). The median thyroid dose for screening-detected cancers was 529 mGy (mean, 1296 mGy; range, 1-17,472 mGy; data not shown).

Table 3 indicates that the frequency of lymphatic invasion ($P = .03$) and intrathyroidal infiltration ($P = .02$) increased significantly with increasing radiation doses among screening-detected cancers; however, other invasive properties of thyroid cancer, such as the presence of tumor capsule and vascular invasion, thyroid capsule invasion, and extrathyroidal spread, were not associated with radiation dose. Patients in the highest dose category of ≥950 mGy were almost 5 times more likely to have more than 1 distinct cancer at pathology compared with patients who had received doses

TABLE 2. Histopathologic Features of Thyroid Cancer Cases.

Feature	Prescreening Cases	Screening-Detected Cases		P[a]	
		Prevalent	Incident	Prescreening vs Screening	Prevalent vs Incident
Total no. (%)	52 (100)	87 (100)	71 (100)		
Tumor size at pathology, mm				.92	.04
≤10	31 (59.6)	45 (51.7)	48 (67.6)		
11-47	21 (40.4)	42 (48.3)	23 (32.4)		
Multifocality[b]				.06	.54
No	35 (67.3)	72 (82.8)	56 (78.9)		
Yes	16 (30.8)	15 (17.2)	15 (21.1)		
Unknown	1 (1.9)	0 (0)			
TC with other nodular pathology[c]				<.01	.75
No	49 (94.2)	63 (72.4)	53 (74.6)		
Yes	3 (5.8)	24 (27.6)	18 (25.4)		
Histopathologic variant of PTC[d]				<.0001	.72
Follicular	10 (19.2)	21 (24.4)	20 (28.2)		
Papillary	0 (0)	23 (26.7)	23 (32.4)		
F-P mixed[e]	4 (7.7)	17 (19.8)	11 (15.5)		
Solid[f]	18 (34.6)	24 (27.9)	17 (23.9)		
Diffuse sclerosing	4 (7.7)	1 (1.2)	0 (0)		
Unknown	16 (30.8)	0 (0)	0 (0)		
Intrathyroidal infiltration				.13	.48
No	22 (42.3)	25 (28.7)	24 (33.8)		
Yes	29 (55.8)	61 (70.1)	46 (64.8)		
Unknown	1 (1.9)	1 (1.2)	1 (1.4)		
Thyroid capsule invasion				<.0001	.84
No	16 (30.8)	76 (87.4)	62 (87.3)		
Yes	36 (69.2)	10 (11.5)	9 (12.7)		
Unknown	0 (0)	1 (1.1)	0 (0)		
Extrathyroidal spread				<.0001	.81
No	40 (76.9)	83 (95.4)	68 (95.8)		
Yes	12 (23.1)	3 (3.5)	3 (4.2)		
Unknown	0 (0)	1 (1.1)	0 (0)		

Abbreviations: F-P, follicular-papillary; PTC, papillary thyroid cancer; TC, thyroid cancer.
[a] P values were calculated using chi-square tests or Fisher exact tests of heterogeneity for categorical variables.
[b] These were patients who had TC with more than 1 carcinoma at pathology.
[c] These were patients who had TC with 1 or more thyroid follicular adenoma, nodular goiter, or adenomatous goiter.
[d] One patient with prevalent TC was identified with the follicular subtype; all other patients in the prescreening and screening populations had the papillary subtype.
[e] These include follicular-papillary and papillary-follicular histopathologic variants.
[f] These include solid variants and any mixed variants with solid component.

<200 mGy (relative risk, 4.86; 95% CI, 1.30-18.1; $P = .02$) (Table 3). In addition, patients who had received higher doses were significantly more likely to be diagnosed with a solid or diffuse sclerosing variant of PTC than with any of the other variants combined ($P < .01$). Thyroid cancers that were associated with high radiation doses were more likely to have other nodular pathology, although the association was not significant ($P = .44$).

Nine patients with screening-detected thyroid cancers had tumors that could be classified as occult (5 were referred for surgery because of suspicion for follicular adenoma, and 4 were detected in 1 of many suspicious nodules). Results from the analyses with and without these patients generally were similar.

Associations With Other Factors

Urinary iodine concentrations during baseline screening were not associated with tumor size or aggressiveness of incident thyroid cancers (all $P > .10$; data not shown). The mean ± standard deviation (SD) latency period for screening-detected, prevalent and incident cancers was 14.2 ± 1.4 years and 18.1 ± 2.4 years, respectively (results not shown). Latency was not correlated with thyroid dose (Spearman r, −0.12; $P = .15$; results not shown).

DISCUSSION

In a large, prospective cohort study of children and adolescents from Belarus who were exposed to I-131 after the Chernobyl accident, we observed that, among 158 patients who had screening-detected thyroid cancers, higher radiation

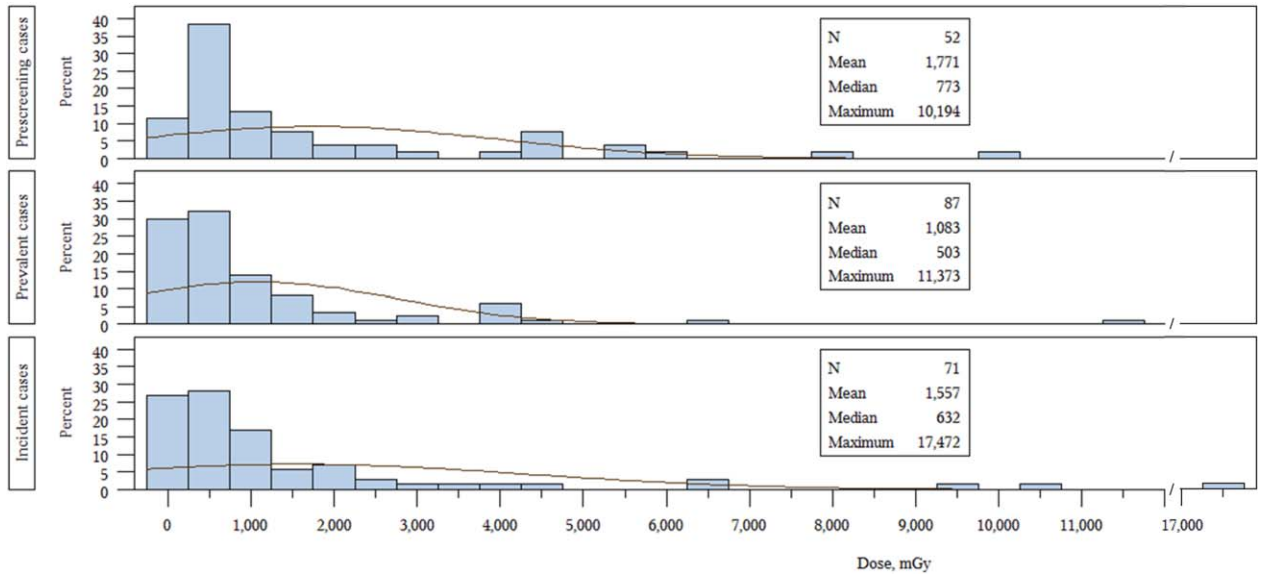

Figure 2. Thyroid doses of radioactive iodine-131 are compared for prescreening, prevalent, and incident thyroid cancer cases in the Belarus-American cohort. mGy indicates milligrays.

doses were associated with a significantly higher frequency of solid variant PTC and with several histopathologic features of tumor aggressiveness, such as lymphatic invasion and intrathyroidal tissue invasion. Individuals who were exposed at the highest dose level were 5 times more likely to have cancer multifocality. Compared with patients who had screening-detected cancers, 52 patients who had prescreening cancers were significantly younger at the time of the accident and had more advanced cancer at the time of diagnosis. Patients with prescreening cancers were significantly more likely than those with screening-detected cancers to have thyroid capsule invasion and extrathyroidal spread, although they were less likely to have concurrent noncancer thyroid pathology such as hyperplastic thyroid nodules, follicular adenomas, or adenomatous goiter.

To our knowledge, this is the first study to systematically evaluate the association between thyroid cancer pathology detected using similar screening methods and individual I-131 thyroid doses. Although larger series of patients with post-Chernobyl thyroid cancers have been published recently,[12,26] those series lacked individual thyroid doses, and the diagnoses were made during routine medical care, not by means of standardized detection procedures.

The Belarusian cohort analyzed here is 1 of 2 screening cohorts that were established in the mid-1990s to follow children and adolescents who lived on territories contaminated by Chernobyl fallout in Ukraine and Belarus and had thyroid radioactivity measurements taken within 2 months after the accident.[18] The Belarusian cohort is comparable to the Ukrainian cohort in size (11,664 and 13,243 individuals, respectively), age at exposure, and sex distribution.[19,20] Thyroid I-131 radiation doses in the BelAm cohort were significantly lower than in the Ukrainian American cohort (mean ± SD: 560 ± 1180 mGy[19] and 643 ± 1663 mGy,[29] respectively; $P < .0001$). However, thyroid radiation doses were comparable for patients with prevalent thyroid cancers in both cohorts (mean ± SD, 1083 ± 1660 mGy[19] and 1721 ± 2455 mGy,[29] Belarus and Ukraine, respectively; $P = .09$). The number of self-reported thyroid cancers diagnosed before initial screening was much higher in Belarus (56 vs 14 self-reported cancers in Ukraine) and included more tumors measuring ≤10 mm in greatest dimension (59.6% vs 0% in Ukraine). The number of thyroid cancers identified during the first round of screening also was much higher in Belarus (87 vs 45 in Ukraine). Patients with screening-detected prevalent cancers in Ukraine[21] tended to have larger tumors at pathology (76.7% had tumors >10 mm vs 48.3% in Belarus) and tended to be diagnosed at a later tumor stage (44.2% had T4 tumors vs 0% in the current study). Although the patients who had thyroid cancers detected during initial screening in Ukraine and Belarus had similar proportions of cancers with solid structure (34.9% vs 27.9%, respectively) and intrathyroidal infiltration (72.1% vs 70.1%, respectively), extrathyroidal spread was significantly greater among the patients diagnosed in

TABLE 3. Histopathologic Features of Screen-Detected Thyroid Cancers (N = 158) by Categories of Thyroid Radiation Dose

Feature	OR[a] (95% CI)			P[b]
	<200 mGy	200-949 mGy	950-17,472 mGy	
Tumor size at pathology: ≤10 mm vs 11-47 mm	1.00	0.90 (0.38-2.15)	1.06 (0.41-2.72)	.77
Presence of tumor capsule: No vs Yes	1.00	0.50 (0.19-1.28)	0.70 (0.24-2.10)	.96
Lymphatic invasion: Yes vs No	1.00	1.04 (0.44-2.43)	2.65 (0.96-7.36)	.03
Blood vessel invasion: Yes vs No	1.00	1.76 (0.43-7.20)	1.53 (0.32-7.24)	.88
Intrathyroidal infiltration: Yes vs No	1.00	1.23 (0.53-2.86)	2.96 (1.09-8.03)	.02
Thyroid capsule invasion: Yes vs No	1.00	1.63 (0.39-6.79)	2.10 (0.46-9.50)	.43
Extrathyroidal spread: Yes vs No	1.00	0.44 (0.06-3.56)	0.35 (0.04-3.17)	.52
Multifocality: Yes vs No[c]	1.00	2.24 (0.64-7.79)	4.86 (1.30-18.1)	.02
TC with other nodular pathology: Yes vs No[d]	1.00	1.28 (0.48-3.39)	1.57 (0.56-4.41)	.44
Histopathologic variant of PTC: Solid and diffuse sclerosing vs Other	1.00	0.64 (0.23-1.75)	2.75 (0.99-7.65)	<.01

Abbreviations: CI, confidence interval; mGy, milligrays; OR, odds ratio; PTC, papillary thyroid cancer; TC, thyroid cancer.
[a] Logistic regression models were adjusted for age at the time of surgery and sex.
[b] P values were calculated using the test of linear trend.
[c] These were patients who had more than 1 carcinoma at pathology.
[d] These were patients who had 1 or more thyroid follicular adenoma, nodular goiter, or adenomatous goiter.

the Ukrainian cohort (46.5% vs 3.5%). The larger number of prescreening cancers in Belarus and the smaller size and earlier stage of the prevalent cancers may reflect the widespread screenings that took place before the initiation of our screening study, but the earlier screenings do not seem to explain the larger number of prevalent cancers in Belarus. This suggests that some factors other than screening may have played a role in the observed differences in thyroid cancer pathology between the 2 cohorts.

In terms of tumor classification at presentation and the number of regional and distant metastases, our results are similar to those from a large consecutive series of 738 thyroid cancers among children aged <15 years from Belarus[30] (T1, 72.6%; N0, 30.4%; M0, 97.6%). Although the majority of patients in that series had a history of residing in areas contaminated by the Chernobyl accident, individual doses to the thyroid gland were not available, and some patients were diagnosed shortly before the accident or were born after the accident.

Similar to our findings, a large series of 2658 thyroid cancers from Ukraine[12] reported a high percentage of PTCs (>90%) and increasing proportions (approximately 20%) of small cancers over time. In contrast to our findings, Bogdanova et al[12] did not observe any association between radiation exposure status based on patient age and place of residence at the time of the accident and tumor characteristics of PTCs in age-matched groups of patients who were born before and after the Chernobyl accident. In our analyses, which were adjusted for age and sex, we observed significant associations between several characteristics of tumor aggressiveness and individual I-131 radiation doses.

Our findings related to radiation doses also stand in contrast to other recent analyses of morphologic characteristics and aggressiveness of post-Chernobyl childhood thyroid cancers.[17,31] Williams et al reported differences in differentiation and invasiveness of thyroid cancers diagnosed in children from Belarus, Ukraine, and the Russian Federation compared with childhood thyroid cancers diagnosed in England, Wales, and Japan, suggesting that they could be caused not by radiation exposure but by differing levels of iodine deficiency, which can increase incidence, reduce latency, and influence tumor morphology and aggressiveness.[17] However, their study did not measure either individual thyroid doses or iodine concentrations. Although we did not have urinary iodine measurements at the time of the accident, urinary iodine levels during baseline screening revealed no association with morphologic characteristics of incident thyroid cancers.

In other large series of thyroid cancers among individuals without known exposure to radiation from Greece,[32] the Mallinckrodt Institute of Radiology in the United States (St. Louis, Mo),[33] and pooled US[34] and Japanese[35] data, a higher proportion of follicular thyroid cancers (9%,[32] 5%,[33] and 10%[34] vs 1%), multifocality (48%[32] and 57%[33] vs 19%), and family history of thyroid cancer (10%[34] and 9%[35] vs 2%) have been reported compared with our study.

The histologic pattern of thyroid cancers in our cohort appeared to change over time, with a gradual reduction observed in the solid variant of PTC, similar to other studies of Chernobyl-associated thyroid cancers[26,31] and reflective of shorter latency for this variant compared

with the typical follicular or papillary variants. In our current study, this reduction in the proportion of solid variant from prescreening to screening cancers was accompanied by a reduction in aggressive biologic behavior, as expected. In particular, there were significantly lower rates of thyroid capsule invasion and extrathyroidal spread in the patients who had screening-detected cancers compared with those who had prescreening cancers. It is possible that the apparent change in histopathologic variant observed over time may have been caused by differences in nodule conspicuity, in which a relatively more aggressive solid variant of papillary type carcinoma is more conspicuous than other variants and is more likely to be diagnosed earlier.[36]

Our study has some notable strengths. These include systematic screening according to a strict protocol; referral to FNAB and surgery according to well defined, standardized criteria; a high rate of compliance for FNAB (94.8%) and surgery (78.4%); a short interval between FNAB and surgery (average, 4 months); and independent review and confirmation of all histopathologic specimens by international panels of experts.

This study also has some limitations. Approximately 20% of those who were referred to surgery after an FNAB did not comply. However, study participants were not aware of their I-131 thyroid doses, and follow-up and referrals were done without regard to thyroid dose. Among the patients with prescreening cancers, dose-dependent participation cannot be excluded. However, those with prescreening cancers were diagnosed at more advanced tumor stages and had a somewhat higher proportion of regional—but not distant—metastases, arguing against dose-related self-selection. Furthermore, all statistical analyses were adjusted for other potential risk factors, such as age at the time of surgery and sex, to eliminate possible effects of differential selection.

In summary, the systematic screening of a cohort of 11,664 individuals who were exposed to I-131 after the Chernobyl accident in Belarus identified a large number of thyroid cancers. We observed that higher radiation doses to the thyroid gland were associated with solid and diffuse sclerosing variants of PTCs, with more biologically aggressive cancers, and with a higher probability of multifocal cancers and multiple nodular pathology. The biologic explanation for these radiation dose-dependent findings should be pursued in genetic/molecular studies. Study findings provide important evidence about the clinical follow-up of patients who have been exposed to environmental radiation doses of I-131.

FUNDING SUPPORT

Funding for this study was provided by the National Cancer Institute (grant CA132918 to L.B.Z.; contract NO1-CP-21178 to L.B.Z., Z.G., R.J.M. and P.O; and the Intramural Research Program, Division of Cancer Epidemiology and Genetics to A.V.B., M.P.L., E.O., A.B., V.D., K.M., and M.H.).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). 2008 Report to the General Assembly with Scientific Annexes. Volume II. Annex D: Health Effects Due to Radiation From the Chernobyl Accident. New York: United Nations; 2011.
2. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of 7 studies. *Radiat Res*. 1995; 141:259-277.
3. Holm LE, Hall P, Wiklund K, et al. Cancer risk after iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst*. 1991;83:1072-1077.
4. Holm LE, Wiklund KE, Lundell GE, et al. Cancer risk in population examined with diagnostic doses of 131I. *J Natl Cancer Inst*. 1989;81:302-306.
5. Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl [letter]. *Nature*. 1992;359:21.
6. Abelin T, Egger M, Ruchti C. Fallout from Chernobyl. Belarus increase was probably caused by Chernobyl [letter]. *BMJ* 309:1298, 1994; author reply 1300.
7. Ito M, Yamashita S, Ashizawa K, et al. Pediatric thyroid diseases around Chernobyl: morphological aspects of the Chernobyl Sasakawa Health and Medical Cooperation Project. In: Yamashita S, Shibata Y, eds. Chernobyl: A Decade. Amsterdam, the Netherlands: Elsevier Science BV; 1997.
8. Astakhova LN, Anspaugh LR, Beebe GW, et al. Chernobyl-related thyroid cancer in children of Belarus: a case-control study. *Radiat Res*. 1998;150:349-356.
9. Cardis E, Kesminiene A, Ivanov V, et al. Risk of thyroid cancer after exposure to 131I in childhood. *J Natl Cancer Inst*. 2005;97:724-732.
10. Williams D. Cancer after nuclear fallout: lessons from the Chernobyl accident. *Nat Rev Cancer*. 2002;2:543-549.
11. Nikiforov Y, Gnepp DR. Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991-1992) from the Republic of Belarus. *Cancer*. 1994;74:748-766.
12. Bogdanova T, Zurnadzhy LY, LiVolsi V, et al. Thyroid cancer pathology in Ukraine after Chernobyl. In: Tronko M, Bogdanova T, Saenko VA, Thomas GA, Likhtarev I, Yamashita S, eds. Thyroid Cancer In Ukraine after Chernobyl: Dosimetry, Epidemiology, Pathology, Molecular Biology. Nagasaki, Japan: Nagasaki Association for Hibakushas' Medical Care (NASHIM); 2014.
13. Harach HR, Williams ED. Childhood thyroid cancer in England and Wales. *Br J Cancer*. 1995;72:777-783.
14. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. *J Surg Res*. 2009;156:167-172.
15. Williams D. Twenty years' experience with post-Chernobyl thyroid cancer. *Best Pract Res Clin Endocrinol Metab*. 2008;22:1061-1073.
16. Rybakov SJ, Komissarenko IV, Tronko ND, et al. Thyroid cancer in children of Ukraine after the Chernobyl accident. *World J Surg*. 2000;24:1446-1449.
17. Williams ED, Abrosimov A, Bogdanova T, et al. Morphologic characteristics of Chernobyl-related childhood papillary thyroid carcinomas are independent of radiation exposure but vary with iodine intake. *Thyroid*. 2008;18:847-852.
18. Stezhko VA, Buglova EE, Danilova LI, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: objectives, design and methods. *Radiat Res*. 2004;161:481-492.

19. Zablotska LB, Ron E, Rozhko AV, et al. Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. *Br J Cancer*. 2011;104:181-187.
20. Tronko MD, Howe GR, Bogdanova TI, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: thyroid cancer in Ukraine detected during first screening. *J Natl Cancer Inst*. 2006;98:897-903.
21. Bogdanova TI, Zurnadzhy LY, Greenebaum E, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: pathology analysis of thyroid cancer cases in Ukraine detected during the first screening (1998-2000). *Cancer*. 2006;107:2559-2566.
22. Drozdovitch V, Minenko V, Khrouch V, et al. Thyroid dose estimates for a cohort of Belarusian children exposed to radiation from the Chernobyl accident. *Radiat Res*. 2013;179:597-609.
23. Thomas GA. The Chernobyl Tissue Bank: integrating research on radiation-induced thyroid cancer. *J Radiol Prot*. 2012;32:N77-N80.
24. Sobin LH, Wittekind C, eds. TNM Classification of Malignant Tumors. 6th ed. New York: John Wiley & Sons; 2002.
25. Hedinger C, Williams ED, Sobin LH, eds. World Health Organization Histological Typing of Thyroid Tumours. Berlin, Germany: Springer Inc.; 1988.
26. LiVolsi VA, Abrosimov AA, Bogdanova T, et al. The Chernobyl thyroid cancer experience: pathology. *Clin Oncol (R Coll Radiol)*. 2011;23:261-267.
27. SAS Institute Inc. SAS Version 9.3 for Windows. Cary, NC: SAS Institute Inc.; 2012.
28. World Health Organization (WHO). Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination: A Guide for Programme Managers. Lyon, France: International Agency for Research on Cancer; 2007.
29. Likhtarov I, Kovgan L, Masiuk S, Talerko M, Chepurny M, Ivanova O, et al. Thyroid cancer study among Ukrainian children exposed to radiation after the Chornobyl accident: Improved estimates of the thyroid doses to the cohort members. *Health Phys*. 2014;106:370-396.
30. Demidchik YE, Demidchik EP, Reiners C, et al. Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus. *Ann Surg*. 2006;243:525-532.
31. Williams ED, Abrosimov A, Bogdanova T, et al. Thyroid carcinoma after Chernobyl latent period, morphology and aggressiveness. *Br J Cancer*. 2004;90:2219-2224.
32. Pazaitou-Panayiotou K, Kaprara A, Boudina M, et al. Thyroid carcinoma in children and adolescents: presentation, clinical course, and outcome of therapy in 23 children and adolescents in Northern Greece. *Hormones (Athens)*. 2005;4:213-220.
33. Grigsby PW, Gal-or A, Michalski JM, Doherty GM. Childhood and adolescent thyroid carcinoma. *Cancer*. 2002;95:724-729.
34. Newman KD, Black T, Heller G, et al. Differentiated thyroid cancer: determinants of disease progression in patients <21 years of age at diagnosis: a report from the Surgical Discipline Committee of the Children's Cancer Group. *Ann Surg*. 1998;227:533-541.
35. Enomoto Y, Enomoto K, Uchino S, Shibuya H, Watanabe S, Noguchi S. Clinical features, treatment, and long-term outcome of papillary thyroid cancer in children and adolescents without radiation exposure. *World J Surg*. 2012;36:1241-1246.
36. O'Kane P, Shelkovoy E, McConnell RJ, et al. Differences in sonographic conspicuity according to papillary thyroid cancer subtype: results of the Ukrainian-American cohort study after the Chornobyl accident. *Am J Roentgenol*. 2008;191:W293-W298.