A Screening Study of Thyroid Cancer and Other Thyroid Diseases among Individuals Exposed *in Utero* to Iodine-131 from Chernobyl Fallout

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Background: Like stable iodine, radioiodines concentrate in the thyroid gland, increasing thyroid cancer risk in exposed children. Data on exposure to the embryonic/fetal thyroid are rare, raising questions about use of iodine 131 (I-131) in pregnant women. We present here estimated risks of thyroid disease from exposure *in utero* to I-131 fallout from the Chernobyl nuclear accident.

Methods: We conducted a cross-sectional thyroid screening study (palpation, ultrasound, thyroid hormones, and, if indicated, fine needle aspiration) from 2003 to 2006. Participants were 2582 mother-child pairs from Ukraine in which the mother had been pregnant at the time of the accident on April 26, 1986, or 2 months after the time during which I-131 fallout was still present (1494 from contaminated areas, 1088 in the comparison group). Individual cumulative *in utero* thyroid dose estimates were derived from estimated I-131 activity in the mother's thyroid (mean 72 mGy; range 0–3230 mGy).

Results: There were seven cases of thyroid carcinoma and one case of Hurthle cell neoplasm identified as a result of the screening. Whereas the estimated excess odds ratio per gray for thyroid carcinoma was elevated (excess odds ratio per gray 11.66), it was not statistically significant ($P = 0.12$). No radiation risks were identified for other thyroid diseases.

Conclusion: Our results suggest that *in utero* exposure to radioiodines may have increased the risk of thyroid carcinoma approximately 20 yr after the Chernobyl accident, supporting a conservative approach to medical uses of I-131 during pregnancy. (***J Clin Endocrinol Metab* 94: 899–906, 2009**)

Studies conducted on exposed populations after the accident at the Chernobyl nuclear power plant in April, 1986, leave little doubt that the risk of thyroid cancer has increased in relation to fallout of radioactive iodines (1), principally iodine-131 (I-131) (2, 3), with the largest increase among those exposed at younger ages when the consumption of I-131 contaminated milk is highest, the small size of the gland increases the absorbed dose, and rapid cell proliferation may raise the risk for carcinogenesis. There are scant data, however, on the post-Chernobyl thyroid cancer risk to those exposed *in utero*. An analysis of thyroid cancer throughout all of Ukraine in the period 1986–1997 reported four *in utero* cases among 348 children 0–4 yr old at the time of the accident (4). There is also a report from the Utah Fallout Study (5) on 400 subjects living downwind from a nuclear test site and exposed *in utero* to I-131. Thirty years later no cases of benign or malignant thyroid neoplasia were found; however, the sample is small, especially for investigating an uncommon outcome, and doses were low.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-2049 Received September 18, 2008. Accepted December 12, 2008.
First Published Online December 23, 2008

Abbreviations: ATG, Antibodies to thyroglobulin; ATPO, antibodies to thyroid peroxidase; CI, confidence interval; Cs-137, Cesium-137; CV, coefficient of variation; EOR, excess odds ratio; EOR/Gy, EOR per gray; ERR/sv, Excess Relative Risk per Sievert of radiation exposure; FNA, fine-needle aspiration; I-131, iodine-131; PTC, papillary thyroid cancer.

The fetal thyroid begins to develop in wk 3 of gestation, becoming active around wk 10–12 (6), when it starts to accumulate iodine from the maternal circulation via the placental iodine pump (7). By late gestation, fetal radioiodine concentrations may be many times higher relative to the maternal thyroid (8–10). Dose to the conceptus is thus influenced by the timing of exposure.

The study we report here supplements the findings of the Ukrainian-American Cohort Study involving clinical thyroid screenings of approximately 13,000 individuals under age 18 yr and exposed postnatally to I-131 from the Chernobyl accident (the main study) (11, 12). Using estimates of I-131 thyroid dose to the embryo/fetus, we evaluated the risks of thyroid cancer and other thyroid diseases in a separate cohort of 2582 subjects who were *in utero* at the time of the accident.

Subjects and Methods

The study population

By design, the sample was to consist of mother-child pairs in which the woman had been pregnant at some point during the period April 26, 1986, to June 30, 1986, because I-131 exposure would occur for 2 months after the event (3). Eligible women from contaminated areas [Cesium-137 (Cs-137) >37 kBq/m^2] in three northern oblasts (similar to a province or county) also had to have received a direct thyroid radioactivity measurement shortly after the accident and to have delivered a live child. Using these criteria, a total of 1411 mothers were identified from linkage of the records of the Institute of Pediatrics, Obstetrics, and Gynecology in Kyiv and the Center for Radiation Medicine. To increase statistical power, we later added a group that would include individuals born during the defined time period to mothers without direct thyroid radioactivity measurements who lived in the same contaminated settlements as a number of women with measured thyroid activity, which could be used to estimate doses to unmeasured mothers. A list of 1766 birth records was compiled, bringing the target population of mother-child pairs from contaminated regions to 3177.

The comparison group consisted of children *in utero* during the same time period, whose mothers did not have thyroid radioactivity measurements and whose residence at birth was in an area with no or minimal contamination from Chernobyl fallout (Cs-137 ≤37kBq/m^2), principally in raions of the same three oblasts. A target list of 1865 birth records was generated from the medical institutions in these areas because the Institute of Pediatrics, Obstetrics, and Gynecology proved to have scant data for regions outside Kyiv.

Standardized procedures for tracing and inviting participation were applied, consisting of an invitation letter with a feedback form, short questionnaire, and prestamped envelope. If repeated letters produced no response, the mother received a personal invitation to participate from one of the local medical personnel.

Figure 1 is a flow chart showing the ultimate disposition of the target populations from contaminated and comparison areas, which produced a sample for analysis of 2582 mother-child pairs. Many potential subjects proved to be ineligible (42.8% from contaminated areas and 34.2% from comparison areas). The most common reason for ineligibility was a lack of a mailing address. Women from contaminated areas were more likely to have moved abroad or outside the study area. They were also more likely either not to have been pregnant during the target time or not to have delivered a live child.

The study was reviewed and approved by the institutional review boards in Ukraine and the United States, and all subjects signed an informed consent.

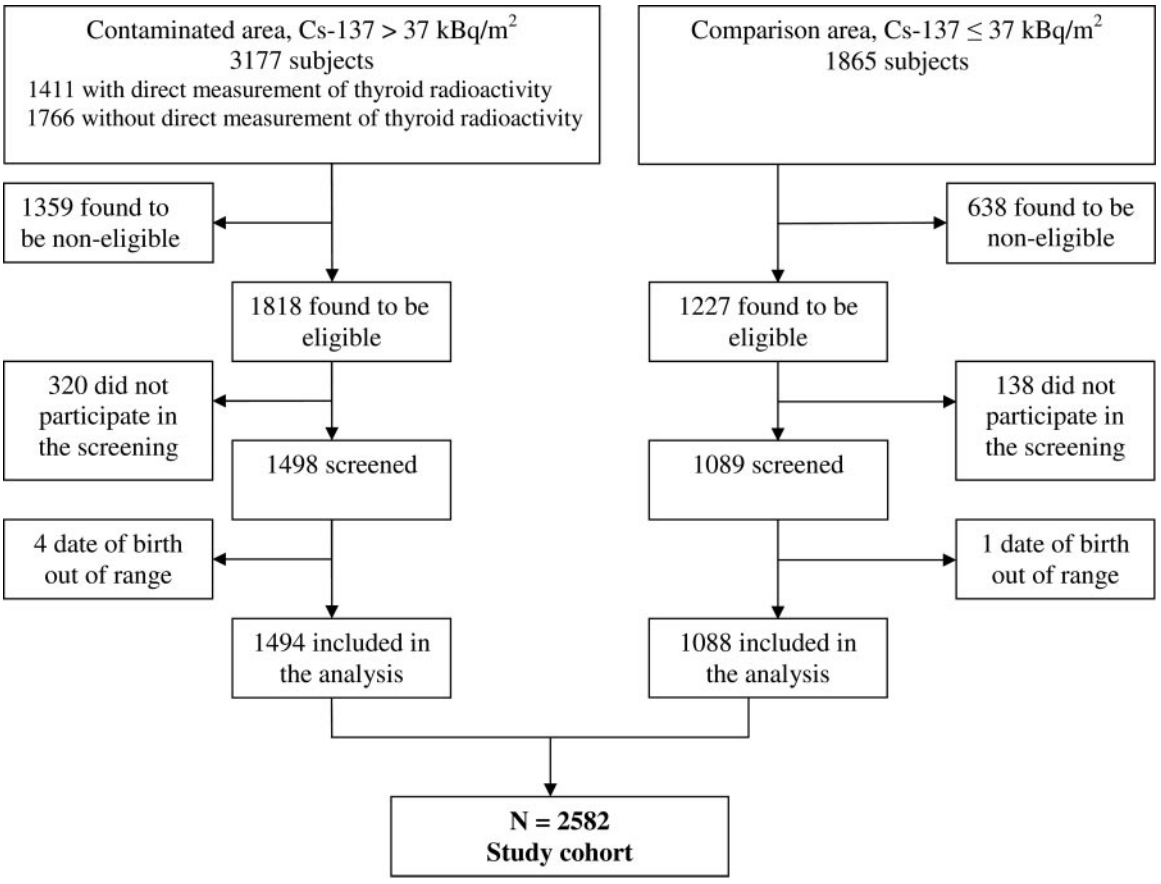

FIG. 1. Study profile.

Screening examination

Subjects *in utero* at the time of the accident were screened for thyroid diseases using the methods developed for the main study (11). The screening procedures, carried out between 2003 and 2006 by a mobile team in most cases or at a clinic in the collaborating Institute of Endocrinology and Metabolism in Kyiv, included thyroid palpation and ultrasonographic examination by an ultrasonographer and independent clinical examination and palpation by an endocrinologist. In addition, we collected a serum sample for estimating thyroid hormones and antithyroid antibodies and a spot urine sample for estimating iodine concentration. Structured questionnaires were administered to the mother to gather information about demographics, medical history (child's gestational age at birth, maternal x-ray exposure during pregnancy, presence of thyroid disease), and items relevant to dose estimation (residential history, consumption of contaminated foods, and iodine prophylaxis during May-June 1986).

After an initial thyroid gland assessment, subjects were referred to the Institute of Endocrinology and Metabolism for fine-needle aspiration (FNA) biopsy for any nodules 10 mm or greater or smaller nodules 5–10 mm in their largest dimension, with ultrasound characteristics suggesting possible malignancy (11). Subjects with FNA findings diagnostic or suspicious for thyroid neoplasia were referred for surgery.

In those from contaminated areas, 74.3% of the 35 subjects were advised to go for FNA complied; among 22 referred from comparison areas, 86.4% complied. Of eight referred for surgery, including one from the comparison area, four were operated, one refused, and three have not yet undergone surgery.

Ultrasound examination

The thyroid was examined with the subject supine and neck extended. The majority of subjects (81%) were imaged using a 10-MHz linear probe (Terason Ultrasound, Burlington, MA); 10% were examined using a 7.5 MHz linear probe (Hitachi Medical System, Tokyo, Japan); and 9% were examined using Tosbee SSA 240s (Toshiba Medical Systems, Tokyo, Japan) with a 7.5-MHz SM-708A probe. Presence of nodules, echostructure, and pattern of echogenicity was recorded.

Serum assays

Antibodies to thyroid peroxidase (ATPO), antibodies to thyroglobulin (ATG), and TSH were measured in serum samples with LUMitest immunochemiluminescence assays (BRAHMS Diagnostica, GMBH, Heningsdorf, Germany) using a Berthold 953 luminometer (Pforzhein, Germany) according to the manufacturers' instructions. Values of ATPO above 60 U/ml were considered elevated, based on a reference sample from the main cohort and consistent with the package insert from BRAHMS. As recommended by BRAHMS, ATG levels above 60 U/ml were defined as elevated. Reference limits for TSH were set between 0.3 and 4.0 mIU/liter based on evaluation of a sample from the main cohort.

The analytical sensitivity of the TSH assay is 0.008 mIU/liter; the intraassay coefficients of variation (CVs) at 0.03 and 2.0 mIU/liter are 3 and 2.2%, respectively, and the interassay CVs are 10 and 2.8%, respectively. For ATPO antibodies, the analytical sensitivity of the assay is 16.7 U/ml; the intraassay CVs at 84 and 375 U/ml are 8.1 and 6.5%, respectively, and the interassay CVs are 11.4 and 7.7%, respectively. The analytical sensitivity of the assay for ATG antibodies was 8.2 U/ml with an intraassay CV at 62 and 523 U/ml of 10.8 and 3.9%, respectively; the interassay CVs were 9.0 and 6.0%, respectively.

Iodine determination

Details of the urinary iodine assay have been described previously (13). Iodine content was measured using the Sandell-Kolthoff reaction and expressed in micrograms per liter (14).

Outcome definitions

Thyroid disease end points considered in the analysis and their definitions are presented in Table 1.

Dosimetry

The estimates of *in utero* thyroid doses of I-131 were established by first estimating the variation with time of the I-131 activity in the thyroid of the mother and then estimating dose to the embryo/fetus.

The methodology used to estimate the variation of I-131 activity in the thyroid of the mother after the Chernobyl accident is based on the dosimetry experience acquired in Ukraine (15). It makes use of: 1) direct thyroid measurements of the γ-radiation emitted during the decay of I-131 activity in the thyroid by means of a radiation detector placed against the neck of the mother; 2) personal interviews, which were conducted with the mothers of all subjects to obtain information on their pregnancy as well as their residence history and dietary habits during the 2 months after the Chernobyl accident; and 3) published information on the behavior of I-131 in the environment and in the body.

TABLE 1. Outcome definitions: cohort study of *in utero* exposure to Chernobyl fallout, Ukraine, 2003–2006

Outcome	Definition	
Thyroid cancer	Based on cytological (FNA) or pathomorphological (surgery) conclusion of cancer	
Follicular neoplasm	Based on cytological (FNA) or pathomorphological (surgery) conclusion of follicular neoplasm	
Diffuse goiter	Based on palpation by the screening endocrinologist. Grading is according to the WHO classification. Grades 1 and 2 are combined and compared in the analysis to grade 0	
Ultrasound-detected nodule	Any nodule or lesion (irrespective of size) recorded by the study ultrasonographer. Separate analyses according to nodule's border, outline, structure, ecogenicity, and echostructure	
Hypothyroidism	TSH >4 mIU/liter with or without free T_4 <10 pmol/liter (overt and sub-clinical hypothyroidism, respectively)	
Hyperthyroidism	TSH <0.3 mIU/liter with or without free T_4 >25 pmol/liter (overt and subclinical hyperthyroidism, respectively)	
Elevated ATPO	ATPO >60 U/ml	
Elevated ATG	ATG >60 U/ml	
Elevated ATPO or ATG	ATPO >60 U/ml or ATG >60 U/ml	
Autoimmune thyroiditis	Main criteria	Minor criteria
Type I: at least two main criteria	ATPO ≥250 U/ml	60 <ATPO <250 U/ml
Type II: one main and one+ minor criteria, or two+ minor criteria)	ATG ≥500 U/ml	60 <ATPO <500 U/ml
	TSH ≥10 mIU/liter; heterogeneous echostructure with hypoechoic pattern on ultrasound	4 >TSH <10 mIU/liter; firm or moderately firm thyroid on palpation

WHO, World Health Organziation.

For mothers with direct thyroid measurements (n = 720), the I-131 activity in the thyroid at the time of measurement was derived from the measurement itself. The relative variation of thyroidal I-131 activity before and after the direct measurement was obtained by means of an ecological model that accounts for the intakes of I-131 by inhalation, ingestion of milk, and leafy vegetables, drawing on the mother's residential history and dietary habits acquired during the personal interviews. For mothers from contaminated areas who did not have direct thyroid measurements but who resided in villages in which a number of adult women had direct thyroid measurements (n = 774), the average value of the available direct thyroid measurements was used to infer the activity of I-131 in the thyroid of the subject's mother at a reference date. The relative variation with time of the I-131 activity in the thyroid before and after the reference date was obtained by means of the ecological model and the personal interview, as indicated above.

For the mothers from uncontaminated regions, who had not been measured and who resided in villages in which no adult women were measured (n = 1088), the activity of I-131 in the thyroid of the subject's mother at a reference date was inferred from the relationship observed between the Cs-137 activity deposited on the ground and the I-131 activity in the thyroid in villages with available direct thyroid measurements. The relative variation with time of the I-131 activity in the thyroid before and after the reference date was obtained by means of the ecological model and the personal interview.

The second step of the dose assessment consists in the calculation of the *in utero* thyroid dose of the subject, given the variation with time of the I-131 activity in the thyroid of the mother. For all subjects, this was done by means of Berkovski's model (16–20), which predicts a continuous increase in dose with increasing gestational age.

The estimated I-131 doses were cumulative doses including for some subjects a postnatal as well as an *in utero* component, depending on the date of birth.

Statistical analysis

We estimated the odds ratios and computed 95% confidence intervals (CIs) using logistic regression as implemented in the GMBO module of EPICURE (21). The primary models fitted to evaluate the relationship with individual I-131 thyroid dose estimates were linear in dose OR (dose) = 1 + βdose, where β is an excess odds ratio (EOR) per gray (EOR/Gy). We based our analyses on individual dose estimates because all subjects were exposed to some level of fallout.

In dose-response analyses, the adjustment factors (shown in table footnotes) were outcome specific and included gender, age at examination, number of cigarettes smoked per day, family history of thyroid disease, urban/rural residence, and province of residence. Maternal risk factors from the questionnaire (history of x-ray exposure during pregnancy, *etc.*) were also evaluated. Adjustments were applied if differences between the contaminated and comparison groups were observed and if their inclusion into the model changed the dose-response estimate by more than 15%.

When the numbers permitted, the dose-response analyses were repeated based only on the *in utero* subjects exposed during the second or third trimesters. The influence of postnatal dose was assessed by sensitivity analysis (including and excluding any individual with a postnatal I-131 dose estimate of 30 mGy or more). We also examined the data on cancer cases among a subcohort of 3700 1- to 5-yr-olds without prenatal exposure who were drawn from the related main study. When comparing in a pooled analysis the dose-response of those exposed *in utero* and those from the main cohort, we allowed EOR/Gy to vary according to the study.

The statistical significance of model parameters, test of linear trend, and variation in dose-response slope was evaluated with likelihood ratio χ^2 tests with degrees of freedom equal to the difference in number of parameters in nested models. All statistical tests were two sided and considered significant for $P < 0.05$.

Results

The 2582 participants in the *in utero* study were screened between February 2003 and October 2006. Response rates by group can be derived from Fig. 1. Among those found to be eligible, participation rates were at least 70% and did not differ by group.

The 1494 subjects from the contaminated group and 1088 subjects from the comparison group (Table 2) appear to be similar in most respects. The groups differed slightly on age at examination and calendar year, reflecting the later decision to revise the protocol to add unmonitored mothers from contaminated areas. Based on limited information, individuals from contaminated areas were more likely to report a family history of thyroid disease but not a personal history of thyroid disease. Mothers of individuals from the comparison group tended to be less educated ($P = 0.02$) and reported more x-ray examinations during pregnancy ($P = 0.001$), mainly due to dental examinations (not shown).

Thyroid dose estimates by trimester

Our data show the model-based increase in estimated I-131 thyroid doses by trimester of exposure, from an overall mean of 2.1 mGy in the first trimester to 131.1 mGy in the third trimester. For each trimester, the estimated mean doses for those in the contaminated group are more than 10 times higher than for those in the comparison group (4.7, 104.2, and 232.2 mGy, respectively, for the first, second, and third trimester in the contaminated group compared with 0.3, 7.0, and 19.2 mGy from the first to third trimester in the comparison group). The I-131 thyroid dose estimates for individuals in the comparison group, although small, are above zero because everybody in the area received some I-131 exposure as a result of the Chernobyl accident.

Thyroid cancer and Hurthle cell neoplasm in the *in utero* cohort

Due to the screening, we identified seven cases of thyroid carcinoma (no. 1–7, Table 3) and one case of a Hurthle cell neoplasm (no. 8). Six of the seven (85%) were definite or suspect papillary thyroid cancers (PTCs) [three (no. 1, 3, 4) based on pathomorphological conclusion and three (no. 2, 5, 6) based on FNA]; the remaining cancer case (no. 7) was a follicular thyroid carcinoma (pathomorphological diagnosis). A single Hurthle cell neoplasm (no. 8) was diagnosed based on an FNA conclusion. Six of the seven definite or suspect cancers occurred in the contaminated group (n = 1494), with estimated thyroid doses ranging from 3.1 to 453.6 mGy. All but one case of thyroid cancer arose in individuals whose estimated gestation at the time of the accident was in the second or third trimester. All seven cancer cases were in females, and the case of Hurthle cell neoplasm was in a male. The age at diagnosis ranged from 16.5 to 20.9 yr.

One case of follicular carcinoma and one follicular adenoma identified before screening are also shown in Table 3 because they were pathomorpologically confirmed. Both occurred in the contaminated group.

TABLE 2. Descriptive characteristics of the participants in the study of *in utero* exposure to Chernobyl fallout, Ukraine, 2003–2006

	Comparison	Contaminated			
Characteristic	n (%)	n (%)	OR	95% CI	*P* value[a]
Sex					
Male	530 (48.7)	699 (46.8)	1.00		
Female	558 (51.3)	795 (53.2)	1.08	0.92–1.26	0.33
Age at examination, yr					
16–	652 (59.9)	634 (42.4)	1.00		
18–	428 (39.3)	195 (13.0)	0.47	0.38–0.57	
19–20.4	8 (0.7)	665 (44.5)	85.5	42.2–173.1	<0.001
Year of examination					
2003–2004	800 (73.5)	704 (47.1)	1.00		
2005–2006	288 (26.5)	790 (52.9)	3.12	2.63–3.69	<0.001
Smoking status at the examination					
Nonsmoker	788 (72.4)	1081 (72.4)	1.00		
Smoker	289 (26.6)	408 (27.3)	1.03	0.83–1.23	
Unknown	11 (1.0)	5 (0.3)	0.33	0.11–0.96	0.75
Mean number of cigarettes smoked per day	2.0	2.3			0.12
History of thyroid disease in relatives					
No	518 (47.6)	588 (39.4)	1.00		
Yes	131 (12.0)	271 (18.1)	1.82	1.43–2.32	
Unknown	439 (40.4)	635 (42.5)	1.27	1.08–1.51	<0.001
Personal history of thyroid disease prior to the screening examination					
No	918 (84.4)	1255 (84.0)	1.00		
Yes	143 (13.1)	164 (11.0)	0.84	0.66–1.07	
Unknown	27 (2.5)	75 (5.0)	2.03	1.30–3.18	0.15
Urinary iodine concentration, g/liter					
Less than 20	68 (6.2)	81 (5.4)	1.00		
20-	227 (20.9)	314 (21.0)	1.16	0.81–1.67	
50-	361 (33.2)	496 (33.2)	1.15	0.81–1.64	
100-	329 (30.2)	401 (26.8)	1.02	0.72–1.46	
Unknown	103 (9.5)	202 (13.5)	1.65	1.10–2.46	0.54
Median urinary iodine concentration, g/liter	65.6	65.07			0.64
Total	1088	1494			

OR, Odds ratio.

[a] *P* value of homogeneity of ORs or *t* test for continuous variables.

Dose response for thyroid cancer

The EOR for thyroid cancer and Hurthle cell neoplasm based on eight cases is 5.35/Gy with a wide confidence interval (Table 4) and changes little after exclusion of the one case with a postnatal I-131 dose of at least 30 mGy (EOR/Gy = 4.93). Including the prescreening cases has little influence on the risk estimate (not shown). The estimated EOR/Gy for the seven definite or suspect carcinomas is 11.66 with an extremely wide confidence interval. As indicated by the confidence intervals including 0, none of these estimates was statistically significant.

TABLE 3. Description of cases with thyroid cancer or follicular neoplasm in the cohort study of *in utero* exposure to Chernobyl fallout, Ukraine, 2003–2006

Case no.	Trimester ATA	Gestation ATA, d	Study group	Total thyroid dose, mGy[a]	Postnatal thyroid dose, mGy	Sex	Age at diagnosis, yr	Source of diagnosis	Diagnosis
Diagnosed during screening									
1	3	252	Contaminated	18.6	4.2	F	19.9	PMC	PTC
2	3	251	Contaminated	421.2	395.2	F	19.8	FNA	PTC
3	3	227	Contaminated	453.6	3.6	F	19.8	PMC	PTC
4	3	179	Comparison	16.2	0	F	17.7	PMC	PTC
5	2	173	Contaminated	139.3	0	F	16.5	FNA	PTC
6	2	159	Contaminated	86.4	0	F	20.9	FNA	PTC
7	1	68	Contaminated	3.1	0	F	19.4	PMC	FTC
8	2	167	Contaminated	33.0	0	M	20.8	FNA	HCN
Diagnosed prior to screening									
9	3	264	Contaminated	36.1	35.7	F	15.4	PMC	FTA
10	3	200	Contaminated	159.7	0	F	5.7	PMC	FTC

ATA, At the time of the Chernobyl accident; PMC, pathomorphological conclusion after surgery; FTC, follicular thyroid carcinoma; HCN, Hurthle cell neoplasm; FTA, follicular thyroid adenoma.

[a] Cumulative ^{131}I dose including pre- and postnatal dose components.

TABLE 4. Dose-response relationship between I-131 and thyroid cancer or Hurthle cell neoplasm excluding and including individuals with postnatal I-131 dose of 30 mGy or higher relative to postnatally exposed only 1- to 5-yr-olds from the main study: cohort study of *in utero* exposure to Chernobyl fallout, Ukraine, 2003–2006

Outcome (n)	EOR/Gy	95% CI	*P* value for linear trend
In utero			
Screening cases with thyroid cancer or Hurthle cell neoplasm (n = 8)	5.35	NE-77.29	0.24
Individuals with postnatal I-131 dose 30 mGy or greater are excluded (n = 7)	4.93	NE-97.27	0.36
Screening cases with thyroid cancer (n = 7)	11.66	NE-1982	0.12
1–5 yr old			
Screening cases with thyroid cancer (n = 13)	3.24	NE-539	0.01

NE, Not estimable.

The EOR for the group of 1- to 5-yr-olds from the main cohort who have definite or suspect thyroid cancer is 3.24/Gy. This estimate is based on 13 cases, has a wide confidence interval, and is compatible with the estimates for those exposed *in utero*.

Dose response for other outcomes

The EORs/Gy for other thyroid disease outcomes provide no evidence of a radiation-related increase in risk (Table 5). Indeed, most of the point estimates are negative. The results did not change meaningfully for any outcome when analyses were limited to those exposed during the second or third trimester (not shown).

Discussion

In the largest study to date of *in utero* exposure to environmental radioiodines, involving a unique cohort of individuals exposed to fallout from the Chernobyl accident with estimated individual or individualized I-131 doses, we found an elevated, but not statistically significant, risk of thyroid cancer. The number of cases was small, limiting statistical power and precluding accurate quantitative risk estimates, but we did obtain unique descriptive information. Cases 1–7 were definite or suspect carcinomas; all but one arose in individuals from the contaminated group exposed after the first trimester, when the thyroid gland is able to accumulate iodine and doses are highest. The gender distribution of cancer cases in our series is unusual for 20-yr-olds (22, 23), whereas the proportion of papillary thyroid cancers is slightly lower than is generally reported for radiation-associated thyroid cancers at young ages (88 *vs.* 95%) (24, 25). Moreover, the latency period is quite long, although this may be explained by the timing of the screening. We found no evidence of an I-131-related increase in risk of other thyroid diseases among those exposed *in utero*.

Our analyses combined thyroid cancers diagnosed histologically and cytologically because cytological diagnosis of malignancy, particularly for papillary thyroid cancers, is known to have a high positive predictive value (>95%) (26, 27). The Hurthle cell neoplasm has been excluded from our cancer series. However, a report on more than 5000 cases suggested that a cytologic diagnosis of Hurthle cell neoplasm should be considered an indicator of high risk for malignancy (27). Interestingly, exclusion of this single case from the analyses resulted in a large increase in the estimated EOR as well as the width of the 95% CI. However, whether this is attributable to the unique histology, male gender, or statistical instability due to the small numbers remains unclear.

TABLE 5. Summary of the dose-response analyses for selected thyroid disease outcomes in the cohort study of *in utero* exposure to Chernobyl fallout, Ukraine, 2003–2006

	Comparison	Contaminated			
Outcome[a]	n	n	EOR/Gy[b]	95% CI	*P* value for linear trend
Diffuse goiter	174	263	0.24[c]	−0.32 to 1.16	0.48
US-detected nodule[d]	63	100	−0.31[e]	NE to 0.88	0.49
Hypothyroidism	38	48	−0.40[f]	NE to 0.93	0.35
Hyperthyroidism	6	9	NE		
Elevated ATPO	66	61	0.25[f]	−0.51 to 1.74	0.62
Elevated ATG	50	41	−0.17[g]	NE to 1.45	0.76
Elevated ATPO or ATG	87	87	−0.08[g]	−0.59 to 1.06	0.86
Autoimmune thyroiditis	14	9	−0.73[h]	NE to 1.41	0.26

US, Ultrasound; NE, not estimable.

[a] Individuals with history of prior thyroid neoplasia or thyroid surgery are excluded from the analysis of diffuse goiter and US-detected nodules; in addition, individuals who reported intake of thyroid hormones are excluded from the analysis of all other outcomes.

[b] EOR/Gy using cumulative I-131 dose estimates that include pre- and postnatal components.

[c] Adjusted for sex, age at examination, number of cigarettes smoked per day, family history of thyroid disease, urban/rural residency, and oblast of residence.

[d] All nodules that satisfied referral criteria described in *Subjects and Methods* were referred to FNA; among biopsied nodules, only cases with benign cytology are included.

[e] Adjusted for sex, age at examination, and presence of diffuse goiter.

[f] Adjusted for sex and age at examination.

[g] Adjusted for sex, age at examination, presence of diffuse goiter, and oblast of residence.

[h] Adjusted for sex and oblast.

Our findings for thyroid diseases in relation to *in utero* I-131 exposure can be compared with the findings in 319 atomic bomb survivors exposed *in utero* and clinically examined (28), a sample representing approximately a third of the *in utero* cohort who were alive and eligible at the time of follow-up. The exposure in Japan was instantaneous and involved whole-body external radiation at high dose rates rather than the protracted internal I-131 irradiation experienced by our subjects. In addition, the *in utero* cohort from Japan was evaluated in their mid-50s. Nonetheless, these findings are of interest. Among the 319 subjects, five papillary thyroid cancers were reported, ranging in age at diagnosis from 34 to 56, all occurring in females. The gender pattern and long latency are comparable to the profile of our cases. Dose-response analyses for thyroid cancer were not carried out due to the small numbers. The major finding from the Japanese study was a nonsignificant dose-response relationship for prevalent solid thyroid nodules (EOR/Gy = 1.78), which was similar in magnitude to the estimate for those exposed in childhood.

A report of 94 incident solid cancers among 2452 atomic bomb survivors exposed *in utero* (29), of which eight cases were thyroid, estimated an Excess Relative Risk per Sievert of radiation exposure (ERR/Sv) at age 50 yr of 1.0 (95% CI 0.2-2.3), which was not significantly different from the ERR/Sv at age 50 yr of 1.7 found for those exposed in early childhood. The ERRs/Sv decreased with attained age for both groups but during their early 20s, the exposed *in utero* subjects had higher ERRs/Sv than those exposed in early childhood, whereas at later ages, the ERRs/Sv were somewhat higher among those exposed postnatally.

Radiosensitivity of the fetal thyroid relative to the postnatal thyroid was also evaluated in the Utah Fallout Study mentioned above (4), which, like our study, involved *in utero* exposure to radioiodines. In the absence of observed cases of thyroid neoplasia, an analysis relying on calculations using Biological Effects of Ionizing Radiation (BEIR) III (1980) (30) data and assumptions by the investigators estimated that the sensitivity of the fetal *vs.* postnatal thyroid could be no more than one to two greater. Our study found that the central risk estimates for thyroid cancer among those exposed to I-131 *in utero*, although larger, are comparable with those exposed in early childhood; however, both have large uncertainties due to the small number of cases and uncertain dose estimates. Thus, whereas internal as well as external radiation exposures seem to be particularly carcinogenic to the young thyroid, the epidemiological evidence to date is not sufficient to accurately quantify a difference in risk between prenatal and early postnatal exposure (31).

The evidence from *in vitro* and *in vivo* studies on whether the fetal thyroid is more sensitive to tumor induction than the postnatal thyroid is inconsistent. Using thyroids obtained at autopsy from subjects of varying ages, Saad *et al.* (32) applied immunohistochemical analysis to measure proliferative activity of thyroid cells and found that the proliferative rate was higher in the fetal period than in early childhood, providing some support for the concept of increased fetal radiosensitivity. In irradiated fetal lymphocytes from 40-yr-old survivors of *in utero* A-bomb exposure, Ohtaki *et al.* (33) observed no evidence of a higher prevalence of chromosome translocations, except perhaps at very low doses. There have been a few animal studies, the most noteworthy a study of beagles irradiated both *in utero* and postnatally (34), with increased risk for thyroid disease found only among those who received radiation postnatally.

Ours is one of the very few, and certainly the largest, studies to look at effects on the thyroid gland from *in utero* exposure to I-131. Unlike any previous study, it has the added advantage of carefully developed estimates of fetal thyroid dose. All subjects received standardized thyroid examinations, which generated data on subclinical as well as clinical outcomes. Response rates for the *in utero* subjects from both contaminated and comparison areas were quite reasonable. However, the relatively small study size defined by a special experience, the low prevalence of thyroid disease end points in early adulthood, and the low mean thyroid dose (72 mGy) limited our power to detect moderate-sized effects as significant. Whereas fetal I-131 thyroid doses were estimated for all subjects, these have larger uncertainties than the doses estimated for members of the main cohort because they involve dose extrapolation from maternal to fetal thyroid. Using the geometric SD as an indicator of uncertainty, these are three and two for dose estimates in the second and third trimester, respectively. We have no reason to believe that uncertainties are related to the thyroid diseases that were studied and the usual effect of random error is attenuation of the dose-response relationships.

In summary, our cross-sectional study conducted approximately 20 yr after the accident suggests that *in utero* exposure to radioiodines at the dose levels associated with fallout from the Chernobyl accident may have increased the risk for thyroid cancer, reinforcing concern about exposure of pregnant women to I-131 through medical applications or nuclear incidents. We found no evidence for an adverse effect on other thyroid diseases. However, larger studies are needed to provide more accurate risk estimates, and prospective data are necessary to evaluate the pattern of radiation-related risk over time.

Acknowledgments

We are grateful to Professor V. E. Dashkevitch (Research Institute of Pediatrics, Obstetrics, and Gynecology, Academy of Medical Sciences of Ukraine) and her staff for providing access to their files of pregnant women. Thanks are also owed to the local medical institutions that allowed us to review their birth records. We acknowledge the clinical team from the Institute of Endocrinology and Metabolism that carried out the screening examinations as well as the contributions to the development of the *in utero* dosimetry by Mykola Chepurny (Center of Radiation Medicine). We also gratefully acknowledge the confirmation of diagnosis provided by the International Pathology Panel of the Chernobyl Tissue Bank: Dr. A. Abrosimov, Professor T. Bogdanova, Professor M. Ito, Professor V. LiVolsi, Professor J. Rosai, and Professor E. D. Williams.

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This work was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The Nuclear Regulatory Commission provided the initial funds for purchase of equipment. The study team is grateful to the Louise Hamilton Kyiv Data Management Center of the

University of Illinois at Chicago, supported in part by the National Institutes of Health Fogarty International Center, and to its head, Oleksandr Zvinchuk, and his assistant, Tatiana Odnolko, for database support and management.

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The late Dr. Jacob Robbins contributed valuable comments on earlier versions of this manuscript, as did Dr. Robert McConnell. Special acknowledgments are due to the late Drs. Gilbert Beebe and Robert Miller (National Cancer Institute), who first pointed up the importance of following up the thyroid disease experience of those exposed to fallout from the Chernobyl accident *in utero*, and to Dr. Ihor Masnyk for his encouragement and support.

Disclosure Statement: The authors have nothing to disclose.

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