A Cohort Study of Thyroid Cancer and Other Thyroid Diseases After the Chornobyl Accident: Thyroid Cancer in Ukraine Detected During First Screening

Mykola D. Tronko, Geoffrey R. Howe, Tetyana I. Bogdanova, Andre C. Bouville, Ovsiy V. Epstein, Aaron B. Brill, Illya A. Likhtarev, Daniel J. Fink, Valentyn V. Markov, Ellen Greenebaum, Valery A. Olijnyk, Ihor J. Masnyk, Victor M. Shpak, Robert J. McConnell, Valery P. Tereshchenko, Jacob Robbins, Oleksandr V. Zvinchuk, Lydia B. Zablotska, Maureen Hatch, Nickolas K. Luckyanov, Elaine Ron, Terry L. Thomas†, Paul G. Voillequé, Gilbert W. Beebe†

Background: The Chornobyl accident in 1986 exposed thousands of people to radioactive iodine isotopes, particularly ^{131}I; this exposure was followed by a large increase in thyroid cancer among those exposed as children and adolescents, particularly in Belarus, the Russian Federation, and Ukraine. Here we report the results of the first cohort study of thyroid cancer among those exposed as children and adolescents following the Chornobyl accident. ***Methods:*** A cohort of 32 385 individuals younger than 18 years of age and resident in the most heavily contaminated areas in Ukraine at the time of the accident was invited to be screened for any thyroid pathology by ultrasound and palpation between 1998 and 2000; 13 127 individuals (44%) were actually screened. Individual estimates of radiation dose to the thyroid were available for all screenees based on radioactivity measurements made shortly after the accident and on interview data. The excess relative risk per gray (Gy) was estimated using individual doses and a linear excess relative risk model. ***Results:*** Forty-five pathologically confirmed cases of thyroid cancer were found during the 1998–2000 screening. Thyroid cancer showed a strong, monotonic, and approximately linear relationship with individual thyroid dose estimate (*P*<.001), yielding an estimated excess relative risk of 5.25 per Gy (95% confidence interval [CI] = 1.70 to 27.5). Greater age at exposure was associated with decreased risk of radiation-related thyroid cancer, although this interaction effect was not statistically significant. ***Conclusion:*** Exposure to radioactive iodine was strongly associated with increased risk of thyroid cancer among those exposed as children and adolescents. In the absence of Chornobyl radiation, 11.2 thyroid cancer cases would have been expected compared with the 45 observed, i.e., a reduction of 75% (95% CI = 50% to 93%). The study also provides quantitative risk estimates minimally confounded by any screening effects. Caution should be exercised in generalizing these results to any future similar accidents because of the potential differences in the nature of the radioactive iodines involved, the duration and temporal patterns of exposures, and the susceptibility of the exposed population. [J Natl Cancer Inst 2006;98:897–903]

The 1986 accident at the Chornobyl nuclear power plant in northern Ukraine resulted in the exposure of substantial proportions of the population of Belarus, Ukraine, and the Russian Federation to radioactive fallout *(1)*. The principal components of that fallout were radioactive isotopes of iodine and cesium *(1)*. The most notable apparent health consequence of the accident has been the large increase in thyroid cancer among those exposed as children or teenagers starting 4–5 years after the accident *(2–6)*. This increase has been attributed, at least in part, to exposure of the thyroid gland to radioactive iodines, of which the major contributor for most individuals is ^{131}I *(1,7)*, although subjects may have been exposed to short-lived iodine isotopes as well. Other factors, such as enhanced surveillance and diets deficient in stable iodine (which would result in the increased uptake of radioactive iodine), almost certainly also have played a part in this increase *(8)*.

Quantifying the risk of thyroid cancer from exposure to radioactive iodines is a matter not only of scientific interest but also of public health importance. ^{131}I is used extensively in medical practice for therapeutic purposes. Moreover, ^{131}I and other radioactive iodines are likely to be major contaminants released in any future nuclear emergency.

A number of epidemiologic studies have shown that exposure of the thyroid gland to external x- and gamma-radiation substantially increases the risk of thyroid cancer in those exposed as children or adolescents. For example, a combined analysis by Ron et al. *(9)* of five cohort studies of subjects exposed to x- or gamma-radiation before age 15 yielded an estimate of the relative risk of

8.7 at 1 Gy (1 gray [Gy] is equivalent to 1 joule of radiation energy absorbed per kilogram of organ or tissue weight). In contrast, the risk of thyroid cancer from ^{131}I in children and adolescents is not clear, and results have been inconsistent. Based on non-Chornobyl studies, the ability of ^{131}I relative to external radiation to cause thyroid cancer is a matter of considerable uncertainty, with proposed values ranging from 0.01 to 1.0 *(1,10–14)*.

Only three analytic epidemiologic studies of thyroid cancer following the Chornobyl accident have been reported. These are all case–control studies that were done in Belarus *(8,15)* and/or in the Russian Federation *(8,16)*. Although all three studies provided evidence of a strong association between radiation dose and risk of thyroid cancer, they are limited by their retrospective design and the fact that radiation doses were estimated, in part, from ecologic models.

In this article, we describe the results of the first cohort study of the effects of exposure to radioactive iodine from the Chornobyl accident on risk of thyroid cancer in those exposed as children or adolescents. This cohort was previously analyzed to evaluate iodine excretion patterns in regions of Ukraine affected by the Chornobyl accident *(17)*. The cohort is composed of people who were exposed to fallout when younger than 18 years of age in the three most heavily contaminated areas of Ukraine. Individual thyroid doses were estimated from radioactivity measurements made within weeks after the accident and from interviews collected during screening. Thyroid cancers are being diagnosed by screening the cohort using ultrasound, palpation, and laboratory tests every 2 years. This article presents excess relative risks (ERRs) per Gy estimated from the data obtained during the first round of screening, from 1998 to 2000. The present prospective study provides more accurate risk estimates than the previous case–control studies due to three major study strengths: the availability of individual dose estimates that were based on direct measurements of thyroid radioactivity made on each study subject shortly after the accident, the lack of potential recall or interviewer bias, and the screening of all subjects, irrespective of dose.

SUBJECTS AND METHODS

The Cohort

Full details of study methods, for both the Ukrainian study and a parallel study in Belarus, have been published previously *(7)*. In brief, a list of subjects born between April 26, 1968, and April 26, 1986 (the date of the accident), and who had thyroid activity measurements made in May or June 1986 in the Chernihiv, Zhytomyr, or Kyiv oblasts in Ukraine was compiled (an oblast is an administrative subdivision similar in size to a state or province). A sample of 32 385 subjects was selected from this list and included all subjects (*N* = 8752) in the highest dose group (≥1 Gy) and a randomly selected sample from two lower-dose groups (0–0.29 and 0.30–0.99 Gy, respectively, with 15 391 and 8242 subjects, respectively). A variety of methods were used to trace these subjects, who were invited in April 1998 through December 2000 to participate in the current study (i.e., to be interviewed and receive thyroid cancer screening) *(7)*. Among the subjects originally selected, 2466 (8%) were not eligible because they had moved out of the three study oblasts or were inaccessible for screening because of study at a university, military service, or incarceration, leaving 29 919 potential study subjects. Of these, 10 307 (34%) could not be traced and 6369 (21%) refused

to participate or failed to attend the screening, leaving 13 243 individuals (44%) who were screened between 1998 and 2000.

Of the screened individuals, 26 had inadequate dose estimates, 31 either were not born or were aged 18 years or older on April 26, 1986, 14 had had a previous thyroid cancer, and 19 had had their thyroid gland removed during surgery for benign pathology. In addition, 26 individuals lacked a final endocrine diagnosis because of incomplete examinations; however, none of these individuals was diagnosed with thyroid cancer by the end of the second screening cycle (data not shown). These individuals were excluded, leaving a cohort of 13 127 for analysis. This cohort consisted of 6990 subjects in dose group below 0.3 Gy, 3597 in dose group 0.3–1.0 Gy, and 2540 subjects in dose group ≥1 Gy. All subjects signed an informed consent form, and the study was reviewed and approved by the institutional review boards of the participating institutions in both Ukraine and the United States.

Cancer Screening and Data Collection Procedures

Each subject was screened for thyroid cancer either by a mobile team visiting the local area or at a screening center at the Research Institute of Endocrinology and Metabolism in Kyiv, Ukraine. The procedure consisted of ultrasonography and palpation by an ultrasonographer and independent clinical examination and palpation by an endocrinologist; in addition, a blood sample was collected for estimating thyroid and parathyroid hormones and antithyroid antibodies, a spot urine sample was collected for estimating iodine excretion, and a series of structured questionnaires was administered that asked about demographic and medical characteristics and items relevant to dose estimation such as residential history and milk consumption in May–June 1986.

An initial assessment of the presence or absence of any thyroid pathology was provided by the endocrinologist at the time of the screening. Subjects could be referred to the clinic in Kyiv for possible fine needle aspiration (FNA) for nodules 5 mm or more in size and/or possible surgery, recommended to attend for early recall (i.e., reexamination at a date earlier than the 2 years used for normal recall, typically in 3 or 6 months), or, for those with no thyroid abnormalities, recommended to follow the normal screening schedule.

Dosimetry

Details of the dosimetric methods have been published elsewhere *(7,18)*. The direct thyroid activity measurement entailed placing a gamma-radiation detector against the neck. Almost all of the direct thyroid measurements were made between 10 and 60 days after the accident, that is, after the short-lived ^{133}I (half-life: 21 hours) and ^{132}Te (half-life: 3.2 days) had substantially decayed and before ^{131}I (half-life: 8.0 days) had decayed to negligible levels. The radiation devices were calibrated every day. The detector reading was either in terms of exposure rate (μR h^{-1} or mR h^{-1}) or, for energy-selective devices using an NaI (Tl) scintillation detector, in count rate (counts per minute [cpm]) from an energy window centered on the 364-keV gamma-energy peak of ^{131}I. Measurements usually were made in unshielded rooms of public buildings, such as local medical clinics.

Background count or exposure rate was subtracted from the direct measurement of the gross thyroid count or exposure rate to yield the net thyroid count or exposure rate. The background consists basically of three components: 1) surface contamination of the

skin, hair, and clothes; 2) internal contamination of the body by radionuclides other than ^{131}I; and 3) environmental contamination. To reduce the background to a minimum, the detectors were shielded and collimated with lead cylinders, and the necks of the persons to be monitored were thoroughly washed with alcohol solution before the measurements were taken. When exposure-rate meters were used, the background was observed to vary from 5 to 500 µR h^{-1} depending on location and time after the accident, the average value being approximately 40 µR h^{-1}. When spectrometers were used, the background values ranged from 20 to 4000 cpm.

The results of an investigation of the reliability and quality of the measurements as well as of the quantification of the uncertainties due to the variability of the age-dependent thyroid mass, the thickness of the overlying tissue, and the position of the detector relative to the thyroid are given elsewhere (19,20).

From the combination of the thyroid activity measurements, data from the individual's information on dietary and lifestyle habits, and environmental transfer models, individual doses resulting from intakes of ^{131}I and their uncertainties were estimated for all 13 127 subjects (18). It is estimated that, for most individuals, the major contributor to the thyroid dose came from ^{131}I with the remainder being due to other isotopes of iodine, and internal and external exposure to isotopes of cesium (7,18). However, evacuees from Pripyat, who represent a small fraction of the cohort, may have received thyroid doses from short-lived radioiodines that contributed about 30% of the internal thyroid doses for persons who did not use stable iodine prophylaxis and about 50% of the internal thyroid doses for persons who used stable iodine prophylaxis soon after the accident (21). For each subject, 1000 simulations of the ^{131}I thyroid dose were carried out by means of a Monte Carlo procedure, which provided an estimate of the uncertainty attached to the dose (18). Doses of ^{131}I for those younger than 2 years of age at the time of exposure may be more subject to measurement error than doses for those who were older (22).

Figure 1 shows the distribution of the thyroid doses for the cohort based on the arithmetic means of the 1000 dose simulations from ^{131}I and illustrates the stratified nature of the sampling referred to above. The 25th, 50th, and 75th percentiles of the thyroid doses from ^{131}I intake for all subjects were 0.01, 0.26, and 0.73 Gy. Individual arithmetic mean thyroid doses ranged up to 47.6 Gy, but only 91 subjects (0.7%), including one with thyroid cancer, had doses in excess of 10 Gy. Exclusion of those with doses 10 Gy or more from subsequent analyses (data not shown) gave results very similar to those presented.

Statistical Methods

The parameter of particular interest was the prevalence odds ratio for screening-detectable thyroid cancers. Given reasonable assumptions (7) about the progression of such cancers to a clinically detectable state, this parameter is a very good approximation of the relative risk of thyroid cancer as estimated from studies that do not involve screening (23). The odds ratios comparing thyroid cancer risk in the various categories of dose with those in the lowest dose category were estimated using logistic regression (24). The ERR per Gy was also estimated using individual doses and a linear excess relative risk model. By adding 1.0 to the ERR, one obtains the relative risk at 1 Gy of radiation. This risk model has the form:

$$\text{Risk of thyroid cancer} = \text{background risk} \times (1.0 + \text{ERR} \times \text{dose} \times \exp\{\Sigma_i y_i Z_i\}) \qquad [1]$$
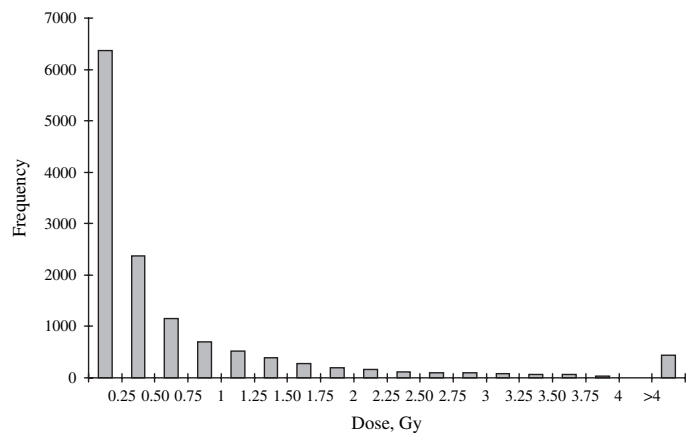

Fig. 1. The frequency distribution of thyroid doses to the 13 127 subjects in the cohort. Doses were based on the arithmetic means of 1000 thyroid dose simulations for each subject.

where background risk, i.e., risk in the absence of radiation, is parametrically adjusted for potential confounders, such as age at screening and sex, and variables in the exponential term Z_i are effect modifiers, such as age at exposure and sex, with their corresponding coefficients y_i (25). To test for curvature in the dose–response relationship, a second term in dose squared with its own coefficient was added to the linear term in dose. The presence of the cell sterilization term was tested by including a Z_i term in dose and/or dose squared term. (Cell sterilization refers to the phenomenon whereby cells receiving a substantial dose of radiation may not reproduce and thus not progress to cancer.)

Estimation of the parameters in the Equation 1 was based on likelihood methods. Statistical significance of these terms was tested by the likelihood ratio tests comparing the likelihood of the model with the term to the model without such a term. The specific risk model used in our analyses was

Risk of thyroid cancer =
background risk$_{\text{sex, age at screening}}$
$\times$ (1.0 + ERR $\times$ dose
$\times$ exp $\{\Sigma_i y_{\text{sex, age at exposure}} Z_{\text{sex, age at exposure}}\}$)

It should be noted that, as stated, age at exposure and age at screening are highly correlated ($r = .99$) as would be expected. Thus, statistically speaking, the two variables are essentially interchangeable. Such measures of age can be used in two ways. First, they can be treated as a main effect, i.e., they can have an association with thyroid cancer that is independent of whether or not there has been any exposure to radiation. In this context, age at screening makes more biologic sense than age at exposure because age at screening is applicable whether or not an individual has been exposed to radiation. Second, the measure of age can be used as an effect modifier. That is, it modifies the risk of thyroid cancer from radiation dose. In statistical terms this is an interaction effect. Either measure of age could be used as an effect modifier, but conventionally, age at exposure has been treated as the biologically more meaningful measure. These then are the senses in which these two measures of age are used in the present article.

When variables were evaluated as possible background factors influencing the rates of thyroid cancer in this cohort, the dose parameter was retained in the model to control for the main effects of dose and for possible confounding between the dose effect and the background risk factor. The following variables were

considered as possible confounders: iodine excretion; age at screening; sex; place of screening, i.e., at the stationary center or by mobile teams; urban/ rural residence; marital status; oblast of current residence; personal history of leukemia and other tumors; personal history of thyroid diseases; and history of thyroid diseases in relatives. Variables were retained in the model if they statistically significantly improved the fit of the model as evaluated by the likelihood ratio test comparing the deviances from the two nested models or if they changed the risk estimate by more than 10%. All P values quoted, including the test for trend, are two-sided. We performed statistical analyses using the GMBO module of the EPICURE package *(25)*. The least squares method *(26)* was used to fit a straight line to the categorical point estimates.

RESULTS

Case Subjects

Thyroid cancer case subjects were defined as those who were referred for early recall or FNA from their screening examination and who had subsequent histologic confirmation of the diagnosis of malignant disease of the thyroid before undergoing a second, regular screening examination. Of the 347 subjects referred for FNA, the referral was deemed unnecessary for 55 subjects. By the end of the first 2-year screening cycle, FNA was performed for 92.8% of the remaining subjects. Forty-five subjects met our definition of having thyroid cancer, and all diagnoses were subsequently confirmed by a pathology review panel consisting of international and

Ukrainian expert thyroid pathologists by 2004 *(27)*. The average time between initial screening and final pathological confirmation by the study pathologist was 1.3 years. Thirty of the case subjects were female and 15 were male, with an average age at diagnosis of 23.7 years. Forty-three of the 45 case subjects had papillary carcinomas, and two had follicular carcinomas. Thus, the case subjects displayed the typical excess of female subjects seen for both spontaneous and radiation-related thyroid cancers. The high percentage of papillary carcinomas is also typical of young patients and persons with a history of radiation exposure *(28)*.

Nonradiation Risk Factors

To model the association of dose with thyroid cancer risk, it was first necessary to determine the appropriate variables to include in the background risk term of Equation 1, by assessing to what extent their inclusion affected the corresponding estimate for dose. Table 1 shows selected variables that were included in this analysis, together with the numbers of case and noncase subjects, and the corresponding odds ratios for thyroid cancer. All estimates shown in Table 1 were adjusted for age at screening, sex, and thyroid dose (expressed as a linear excess relative risk term). Estimates for age at screening were adjusted for sex and thyroid dose, and estimates for sex were adjusted for age at screening and thyroid dose.

Both sex and age at screening had statistically significant associations with thyroid cancer, as has previously been reported *(29)*. Females had more than twice the risk of thyroid cancer as males, and risks increased monotonically with age at screening in an approximately linear fashion over the 20 years of age represented in the data of Table 1. It should be noted that age at exposure and age

Table 1. Odds ratios (ORs) and 95% confidence intervals (CIs) of thyroid cancer among 13 127 subjects exposed to radiation from the Chornobyl accident in Ukraine

| Variable | Case subjects (*n* = 45) | | Noncase subjects (*n* = 13 082) | | OR* (95% CI) | *P* value† |
	n	%	*n*	%		
Sex						.01
Male	15	33.3	6456	49.4	1.00 (referent)	
Female	30	66.7	6626	50.6	2.21 (1.18 to 4.13)	
Age at screening, y						.003
12–14	3	6.7	1406	10.7	1.00 (referent)	
15–19	11	24.4	3931	30.0	2.05 (0.57 to 7.39)	
20–24	15	33.3	4015	30.7	4.84 (1.36 to 17.1)	
25–33	16	35.6	3730	28.5	6.08 (1.71 to 21.5)	
Marital status						.06
Single	20	44.4	8296	63.4	1.00 (referent)	
Married	25	55.6	4579	35.0	2.15 (0.94 to 4.92)	
Current residence						.59
City	9	20.0	3779	28.9	1.00 (referent)	
Town	7	15.6	2157	16.5	1.10 (0.40 to 2.98)	
Rural	29	64.4	7141	54.6	1.43 (0.67 to 3.04)	
Personal history of goiter						.09
No	35	77.8	11 603	88.5	1.00 (referent)	
Yes	7	15.6	816	6.4	2.19 (0.96 to 5.03)	
History of goiter in relatives						.75
No	31	68.9	8745	66.8	1.00 (referent)	
Yes	5	11.1	1086	8.3	1.20 (0.46 to 3.11)	
Iodine excretion (µg/L)						.98
0–24	8	20.5	2449	18.7	1.00 (referent)	
25–39	9	23.1	2553	19.5	1.19 (0.46 to 3.11)	
40–54	7	17.9	2466	18.9	0.99 (0.36 to 2.75)	
55–79	7	17.9	2107	16.1	1.24 (0.46 to 3.44)	
80–1820	8	20.5	2252	17.2	1.22 (0.46 to 3.29)	

*ORs were adjusted for sex, age at screening, and thyroid dose, except for ORs for sex and age at screening, which were adjusted for age at screening and thyroid dose and for sex and thyroid dose, respectively.

†Two-sided tests of statistical significance of adding variable(s) to model.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CI) of thyroid cancer by thyroid dose category among 13 127 subjects exposed to radiation from the Chornobyl accident in Ukraine*

Dose category (Gy)	Mean dose (Gy)	Case subjects ($n = 45$)		Noncase subjects ($n = 13\,082$)		OR (95% CI)
		n	%	n	%	
0.00–0.24	0.11	9	20	6357	48.6	1.00 (referent)
0.25–0.74	0.44	9	20	3521	26.9	2.31 (0.91 to 5.88)
0.75–1.49	1.07	10	22.2	1591	12.2	6.25 (2.50 to 15.6)
1.50–2.99	2.06	8	17.8	944	7.2	8.97 (3.39 to 23.7)
3.00–47.63	6.48	9	20	669	5.1	15.3 (5.88 to 40.0)

*Adjusted for sex and age at screening. Two-sided $P_{trend}<.001$ based on the trend for dose categories.

at screening are highly correlated in the data, so any main effect of age at exposure is accounted for by use of age at screening.

None of the other variables shown in Table 1 had a statistically significant association with thyroid cancer risk. However, several observations are of interest. For example, married subjects had approximately twice the risk as single subjects, although the increase was not statistically significant. A personal history of thyroid goiter was also associated with a nonstatistically significant doubling in risk, although a history of goiter in relatives did not show a meaningful association with risk. Current iodine excretion was not associated with thyroid cancer risk. Goiter is known to be associated with iodine deficiency, and the latter, as discussed earlier, can lead to increased risk of thyroid cancer *(8)*. No self-reported history of thyroid pathologies other than diffuse or nodular goiter was noted for any of the 45 case subjects.

Association With Dose

The arithmetic mean of the dose was 2.00 (SD = 2.52) Gy for case subjects and 0.78 (SD = 1.85) Gy for noncase subjects. This difference was highly statistically significant ($P<.001$).

Of the variables modeled as covariates, only sex and age at screening altered the coefficient for dose (Table 1). Therefore, to investigate the shape of the dose–response curve, we analyzed risks in five categories of dose adjusted for sex and age at screening (Table 2). Dose categories were chosen to give approximately equal numbers of case subjects in each of the categories. The odds ratios increased monotonically with dose, with those in the highest dose category (≥3 Gy) having an odds ratio 15 times that of those in the lowest dose category. The odds ratios for each of the upper three categories (i.e., doses ≥0.75 Gy) were all highly statistically significant ($P<.001$). A plot (Fig. 2) of the data from Table 2 shows that risks increased approximately linearly with dose.

To further explore the shape of the dose–response curve, we fitted the excess relative risk model for dose (Equation 1), again adjusting for sex and age at screening (Table 3). The ERR was 5.25 (95% confidence interval [CI] = 1.70 to 27.5) per Gy, corresponding to a relative risk of 6.25 (95% CI = 2.70 to 28.5) at 1 Gy. This association was highly statistically significant ($\chi^2_1 = 40.5$, $P<.001$). The addition of a dose^2 (i.e., quadratic) term to the model did not demonstrate upward curvature in the dose–response curve, with a two-sided P value $>.99$ and a slightly negative estimate for this term (not shown). Fitting a cell-sterilization term in the Z_i term of Equation 1 using linear and quadratic terms in dose to test for downward curvature gave a P value of .08, with a negative estimate for this term (not shown). The estimated ERR for those with doses of less than 10 Gy was 6.2 per Gy. Thus, there was no indication of any substantial departure from a linear

dose–response relationship in these data, particularly for doses up to 10 Gy.

Modifiers of the Dose–Response Relationship

Table 3 also shows several models that include interaction terms between dose and sex and/or age at exposure, corresponding to effect modification by sex and/or age at exposure. Females had larger ERRs than males, and those exposed at older ages had lower ERRs than those exposed at younger ages; however, neither of these ERRs was statistically significant, nor were interactions between dose and the other variables shown in Table 1 (data not shown). In particular, there was no detectable interaction of dose with risk of diffuse goiter ($P = .22$), a marker of past iodine deficiency. Caution should be applied with regard to such interpretations because they are not statistically significant.

Discussion

This study is, to our knowledge, the first reported cohort study to examine, at the individual level, the relationship between thyroid dose and risk of thyroid cancer in a Chornobyl population exposed at younger than 18 years of age. The study has clearly demonstrated a strong, positive, and approximately linear relationship between thyroid dose from radioactive iodines and subsequent thyroid cancer risk, with an excess relative risk of 5.25 per Gy (95% CI = 1.70 to 27.5). There was some indication that the effect of dose was modified by sex and age at exposure, with
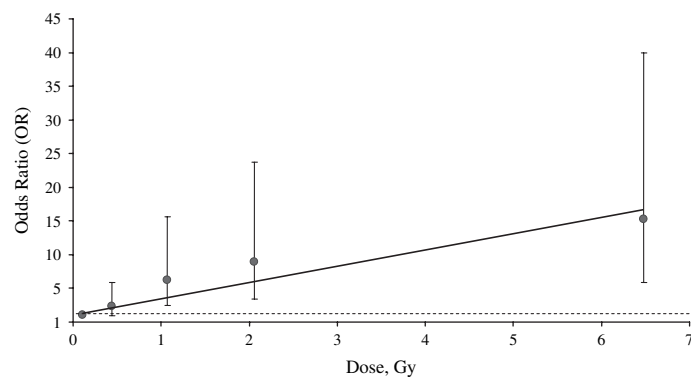

Fig. 2. Odds ratios (ORs) with 95% confidence intervals of thyroid cancer by mean dose for each of five dose categories. The data from Table 2 were plotted, and a fitted dose–response line was constructed using the least squares method fitted to the categorical point estimates. **Dots** = odds ratios; **vertical lines** = 95% confidence intervals; **heavy solid line** = fitted dose–response line; **dashed line** indicates OR = 1.0.

Table 3. Models of excess relative risk (ERR) per Gy and interactions of dose, sex, and age at exposure among 13 127 subjects exposed to radiation from the Chornobyl accident in Ukraine*

Model	Variable	ERR per Gy	95% CI	Test statistic†
1	Dose	5.25	1.70 to 27.5	$\chi^2_1 = 40.5, P<.0001$
2	Dose			$\chi^2_1 = 2.17, P = .14$
	Sex			
	Male	2.21	0.40 to 13.80	
	Female	16.57	1.08 to 1651	
3	Dose			$\chi^2_2 = 1.08, P = .58$
	Age at exposure, y			
	0–4	9.08	1.33 to 84.8	
	5–9	7.00	1.76 to 33.04	
	10–18	3.39	0.68 to 19.68	

*All models were adjusted for the main effects of sex and age at screening. CI = confidence interval.

†Tests of the statistical significance of the interaction terms. All *P* values are two-sided.

females having a larger ERR than males and those exposed at young ages having larger ERRs than those exposed at later ages. However, neither interaction was statistically significant.

The strengths of this study include its prospective cohort design and the availability of radioactivity measurements of the thyroid gland for all subjects made shortly after the accident. Another strength is the fact that, because all subjects were screened for thyroid disease, the possible confounding effect of screening has been eliminated. The contribution of radioactive iodines to the large increase in thyroid cancer seen in Belarus, the Russian Federation, and Ukraine after the Chornobyl accident has been a matter of some controversy *(1)*. One of the considerations in that controversy is the impact on this increase of screening, particularly that using ultrasonography. The present study, in which all subjects were screened, provides an estimate of the risk arising from thyroid radiation without confounding by screening.

The study also has some limitations, in particular, the fact that only 44% of the targeted cohort participated in the first screening. The greatest cause for nonparticipation (34%) was the inability to trace potential subjects. Tracing efforts were hampered by the long interval between the accident and the start of screening. However, a response rate of this magnitude or lower is seen in the great majority of cohort studies, which depend on voluntary participation. Nonparticipation can introduce a bias, but to bias relative risk measures, it must be correlated both with exposure (i.e., thyroid dose) and, independently, with thyroid cancer risk *(30)*. However, we previously reported that the distribution of dose was similar among participants and nonparticipants in this study *(7)*. In addition, potential confounders or effect modifiers such as age and sex were adjusted for in the analysis, which therefore avoids any potential bias from differential distribution of such variables. It seems unlikely, therefore, that any meaningful or serious bias will have been introduced by failure to participate in the study, although the possibility of some residual bias associated with nonparticipation cannot be completely discounted.

A second possible limitation of this study is our use of the prevalence odds ratio to estimate relative risks. However, the prevalence odds ratio should be a good approximation of the relative risk under reasonable assumptions about the progression of screening-detected cancers to a clinically detectable state *(7)*. The results from subsequent screenings will provide direct estimates of incidence relative risks.

A third limitation is that the impact on risk estimates of uncertainty in dose estimates was not taken into account. In general, classic nondifferential random error in dose estimates (i.e., error that does not vary by case status) will bias risk estimates toward the null. On the other hand, Berkson's measurement error bias will not generally bias risk estimates *(31)*. Both types of error are almost certainly present in the current dose estimation procedures. The estimation of these two types of errors is a complex process, and their potential impact on risk estimates will be considered in detail in a later publication.

It is also of interest to note that current iodine excretion is not associated with thyroid cancer risk in the present data (Table 1). The power of this study to detect weak or moderate associations is limited by the number of cases and the distribution ranges for iodine excretion are narrow, which may limit the ability to detect any effect, and measuring iodine excretion today does not necessarily reflect iodine status years ago. However, as noted, the presence of diffuse goiter, which is probably a better marker of past inadequate iodine nutrition, is positively associated with thyroid cancer, although we found no evidence of a modifying effect of diffuse goiter on the risk of radiation-induced thyroid cancer.

The results of the present study can be used to compare risks from gamma- and x-rays as reported by Ron et al. *(9)* (ERR = 7.7 per Gy, 95% CI = 2.1 to 28.7) to that of radioactive iodine isotopes from the present study (ERR = 5.3, 95% CI = 1.7 to 27.5). The estimates are similar in magnitude, although the estimate from exposure to radioactive iodine isotopes is somewhat smaller than that for exposure to external x- and gamma-rays. There remains, however, a good deal of uncertainty in this comparison, both because of the fairly wide confidence intervals for the two estimates and because these estimates were not adjusted for age at exposure.

Age at exposure was a notable modifier of the effect of dose on risk of thyroid cancer in the analysis reported by Ron et al *(9)* for external radiation; there also was a suggestion of a modifying effect of sex, although it was not seen in a recent case–control study of thyroid cancer and Chornobyl exposure *(8)*.

It is also of interest to compare the present results with those reported from other studies of exposure to radioactive iodine and thyroid cancer following Chornobyl *(8,15,16)*. Three case–control studies have been reported, two in Belarus and one in the Russian Federation. All showed evidence of a strong positive relationship, but only one study *(8)* has provided estimates of the ERR per Gy. The estimates for iodine-deficient areas in that case–control study *(8)* are similar to the estimate of 5.25 in this study. Historically, northern Ukraine, where the present study is based, is a region of moderate iodine insufficiency *(32)*. Recent reports suggest that iodine intake has been increasing in the whole of Ukraine, primarily through changes in diet and iodine supplementation *(33,34)*.

Caution should be applied in extrapolating the results of the present study to non-Chornobyl situations involving exposure to radioactive iodines. The main considerations in such extrapolations are the nature of the radioactive iodines involved (i.e., the contribution to dose of the various iodine isotopes, for example, the Hanford study *(14)* was of pure ^{131}I exposure); the duration and temporal pattern of exposure (e.g., exposure in the Hanford study was over a number of years); and the susceptibility of the underlying population (e.g., the Hanford population was at essentially adequate iodine intake at the time of exposure). Also, it is worth noting that, in the event of future similar nuclear accidents, thyroid radiation dose could be reduced by curtailing intake of milk.

Based on model 1 in Table 3, in the absence of Chornobyl radiation, 11.2 thyroid cancer cases would have been expected compared with the 45 observed, i.e., a reduction of 75% (95% CI = 50%–93%).

In summary, the results of the present study show a strong positive and approximately linear relationship between thyroid dose and subsequent risk of thyroid cancer, a result that essentially could not be due to chance or to screening because all subjects were screened. This finding strongly suggests that radioactive iodines caused an increase in thyroid cancer risk among those exposed to Chornobyl fallout as children and adolescents. Our results also indicate that the carcinogenic effects of childhood exposure to radioactive iodines do not differ substantially from those of external irradiation. In the present cohort, we estimate that 75% of the thyroid cancer cases would have been avoided in the absence of radiation. With appropriate adjustment for dose, this estimate demonstrates a substantial contribution of radioactive iodines to the excess of thyroid cancer that followed the Chornobyl accident.

REFERENCES

(1) United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). 2000 report to the General Assembly, with scientific annexes. Vol II: Effects. New York (NY): United Nations; 2000.

(2) Heidenreich WF, Kenigsberg J, Jacob P, Buglova E, Goulko G, Paretzke HG, et al. Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. Radiat Res 1999;151:617–25.

(3) Jacob P, Kenigsberg Y, Zvonova I, Goulko G, Buglova E, Heidenreich WF, et al. Childhood exposure due to the Chernobyl accident and thyroid cancer risk in contaminated areas of Belarus and Russia. Br J Cancer 1999;80:1461–9.

(4) Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl [Letter]. Nature 1992;359:21.

(5) Likhtarev IA, Sobolev BG, Kairo IA, Tronko ND, Bogdanova TI, Oleinic VA, et al. Thyroid cancer in the Ukraine [Letter]. Nature 1995;375:365.

(6) Goldman M. The Russian radiation legacy: its integrated impact and lessons. Environ Health Perspect 1997;105 Suppl 6:1385–91.

(7) Chornobyl Thyroid Diseases Study Group of Belarus, Ukraine, and the USA. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: objectives, design and methods. Radiat Res 2004;161:481–92.

(8) Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, et al. Risk of thyroid cancer after exposure to 131I in childhood. J Natl Cancer Inst 2005;97:724–32.

(9) Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259–77.

(10) Committee on the Biological Effects of Ionizing Radiations (BEIR V). Health effects of exposure to low levels of ionizing radiation. Washington (DC): National Academy Press; 1990.

(11) National Council on Radiation Protection and Measurements. Induction of thyroid cancer by ionizing radiation. Bethesda (MD): NCRP Report No. 80; 1985.

(12) Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. Radiat Res 1992;131:98–111.

(13) Institute of Medicine and National Research Council. Exposure of the American people to iodine-131 from Nevada nuclear-bomb tests: review of the National Cancer Institute report and public health implications. Washington (DC): National Academy Press; 1999.

(14) Davis S, Kopecky KJ, Hamilton TE, Onstad L. Thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism in persons exposed to iodine 131 from the Hanford nuclear site. JAMA 2004;292:2600–13.

(15) Astakhova LN, Anspaugh LR, Beebe GW, Bouville A, Drozdovitch VV, Garber V, et al. Chernobyl-related thyroid cancer in children of Belarus: a case-control study. Radiat Res 1998;150:349–56.

(16) Davis S, Stepanenko V, Rivkind N, Kopecky KJ, Voilleque P, Shakhtarin V, et al. Risk of thyroid cancer in the Bryansk oblast of the Russian Federation after the Chernobyl power station accident. Radiat Res 2004;162:241–8.

(17) Tronko M, Kravchenko V, Fink D, Hatch M, Turchin V, McConnell R, et al. Iodine excretion in regions of Ukraine affected by the Chornobyl accident: experience of the Ukrainian-American cohort study of thyroid cancer and other thyroid diseases. Thyroid 2005;15:1291–7.

(18) Likhtarev I, Minenko V, Khrouch V, Bouville A. Uncertainties in thyroid dose reconstruction after Chernobyl. Radiat Prot Dosimetry 2003;105:601–8.

(19) Likhtarev IA, Gulko GM, Sobolev BG, Kairo IA, Prohl G, Roth P, et al. Evaluation of the 131I thyroid-monitoring measurements performed in Ukraine during May and June of 1986. Health Phys 1995;69:6–15.

(20) Likhtarev IA, Gulko GM, Kairo IA, Sobolev BG, Chepurnoy NI, Cheban AK, et al. Reliability and accuracy of the 131I thyroid activity measurements performed in the Ukraine after the Chernobyl accident in 1986. Munich (Germany): Institut fur Strahlenschutz, GSF-Bericht; 1993.

(21) Balonov M, Kaidanovsky G, Zvonova I, Kovtun A, Bouville A, Luckyanov N, et al. Contributions of short-lived radioiodines to thyroid doses received by evacuees from the Chernobyl area estimated using early in vivo activity measurements. Radiat Prot Dosimetry 2003;105:593–9.

(22) Likhtarov I, Kovgan L, Vavilov S, Chepurny M, Bouville A, Luckyanov N, et al. Post-Chornobyl thyroid cancers in Ukraine. Report 1: estimation of thyroid doses. Radiat Res 2005;163:125–36.

(23) Hosmer D, Lemeshow S. Applied logistic regression. 2nd ed. New York (NY): Wiley; 2000.

(24) Breslow NE, Day NE, editors. Statistical methods in cancer research. Vol 1: The analysis of case-control studies. Lyon (France): International Agency for Research on Cancer; 1980.

(25) Preston DL, Lubin JH, Pierce DA, McConney ME. EPICURE user's guide. Seattle (WA): Hirosoft International; 1993.

(26) Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia (PA): Lippincott-Raven; 1998.

(27) Thomas GA, Williams ED. Thyroid tumor banks [Letter]. Science 2000; 289:2283.

(28) World Health Organization. World cancer report. Lyon (France): International Agency for Research on Cancer; 2003.

(29) Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents. Vol VIII, No. 155. Lyon (France): IARC Scientific Publications; 2003.

(30) MacMahon B, Pugh TF. Epidemiology: principles and methods. 1st ed. Boston (MA): Little, Brown; 1970.

(31) Armstrong BG. The effects of measurement errors on relative risk regressions. Am J Epidemiol 1990;132:1176–84.

(32) Bolshova EV, Tronko ND, VanMiddlesworth L. Iodine deficiency in Ukraine. Acta Endocrinol (Copenh) 1993;129:594.

(33) Robbins J, Dunn JT, Bouville A, Kravchenko VI, Lubin J, Petrenko S, et al. Iodine nutrition and the risk from radioactive iodine: a workshop report in the Chernobyl long-term follow-up study. Thyroid 2001;11:487–91.

(34) Tronko ND, Kravchenko VI, Fink DJ, Hatch M, Turchin V, McConnell RJ, et al. Iodine excretion in regions of Ukraine affected by the Chornobyl accident: Experience of the Ukrainian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases. Thyroid 2005;15:1291–7.