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Post-Chornobyl Thyroid Cancers in Ukraine. Report 2: Risk Analysis

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On April 26, 1986, the worst nuclear reactor accident to date occurred at the Chornobyl (Chernobyl) power plant in Ukraine. Millions of people in Ukraine, Belarus and Russia were exposed to radioactive nuclides, especially ^{131}I. Since then, research has been conducted on various subgroups of the exposed population, and it has been demonstrated that the large increase in thyroid cancer is related to the ^{131}I exposure. However, because of study limitations, quantified risk estimates are limited, and there remains a need for additional information. We conducted an ecological study to investigate the relationship between ^{131}I thyroid dose and the diagnosis of thyroid cancer in three highly contaminated oblasts in Northern Ukraine. The study population is comprised of 301,907 persons who were between the ages of 1 and 18 at the time of the Chornobyl accident and were living in 1,293 rural settlements in the three study oblasts. Twenty-four percent of the study population had individual thyroid dose estimates and the other 76% had "individualized" estimates of thyroid dose based on direct thyroid measurements taken from a person of the same age and gender living in the same or nearby settlement. Cases include 232 thyroid cancers diagnosed from January 1990 through December 2001, and all were confirmed histologically. Dose–response analyses took into account differences in the rate of ultrasound examinations conducted in the three study oblasts. The estimated excess relative risk per gray was 8.0 (95% CI = 4.6–15) and the excess absolute risk per 10,000 person-year gray was estimated to be 1.5 (95% CI = 1.2–1.9). In broad terms, these estimates are compatible with results of other studies from the contaminated areas, as well as studies of external radiation exposure.

INTRODUCTION

Due to the accident at the Chornobyl nuclear plant, very large quantities of radioactive materials were unintentionally released into the atmosphere from April 26 to May 10, 1986. Fallout from the accident affected almost the entire territory of Ukraine, and most of the population was exposed to radionuclides from inhalation and ingestion of local foodstuffs, resulting in substantial radioactive iodine exposure to the thyroid gland, especially in children. Fallout levels were extremely non-uniform, and the highest contamination occurred in northern Ukraine. Retrospective reconstruction of thyroid doses in Ukraine began in 1989 (*1–4*). Since then, methods have been developed for estimating doses for individuals with direct measurements of radioactive iodine in their thyroid glands as well as for those without such measurements (*5*).[2]

The first publication reporting unusually high thyroid cancer incidence rates among children and adolescents in northern Ukraine appeared 5 years after the Chornobyl accident (*6*). At about the same time, similar information was reported for Belarus (*7*) and some time later for the contaminated areas of Russia (*8*). A large number of other reports quickly followed (*9–18*). While there clearly is an association between thyroid cancer incidence and radiation exposure to the thyroid for persons born between 1968 and 1986, the relationship has not been quantified adequately (*19*). A dose–response relationship between radioiodines and thyroid cancer was demonstrated in three case-control studies conducted in Belarus and in Russia (*15, 20, 21*). Risk estimates have been reported from several ecological studies conducted in Ukraine, Belarus and Russia (*13, 22, 23–27*), but interpretation of the results from ecological studies is complicated by the potential influence of screening and the introduction of modern ultrasonography to detect thyroid nodules. By the year 2000, the number of ultrasound examinations in some areas in Ukraine was high enough to detect most nodules, whereas in other regions, ultrasonography was not introduced with the same intensity or at the same time. In the current study, we tried to address this issue by adjusting for screening intensity over time.

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[2] In ref. (*5*), these doses (which are based on the results of a thyroid activity measurement and on the reference values of dietary consumption and behavior) are called instrumentally individualized thyroid doses.

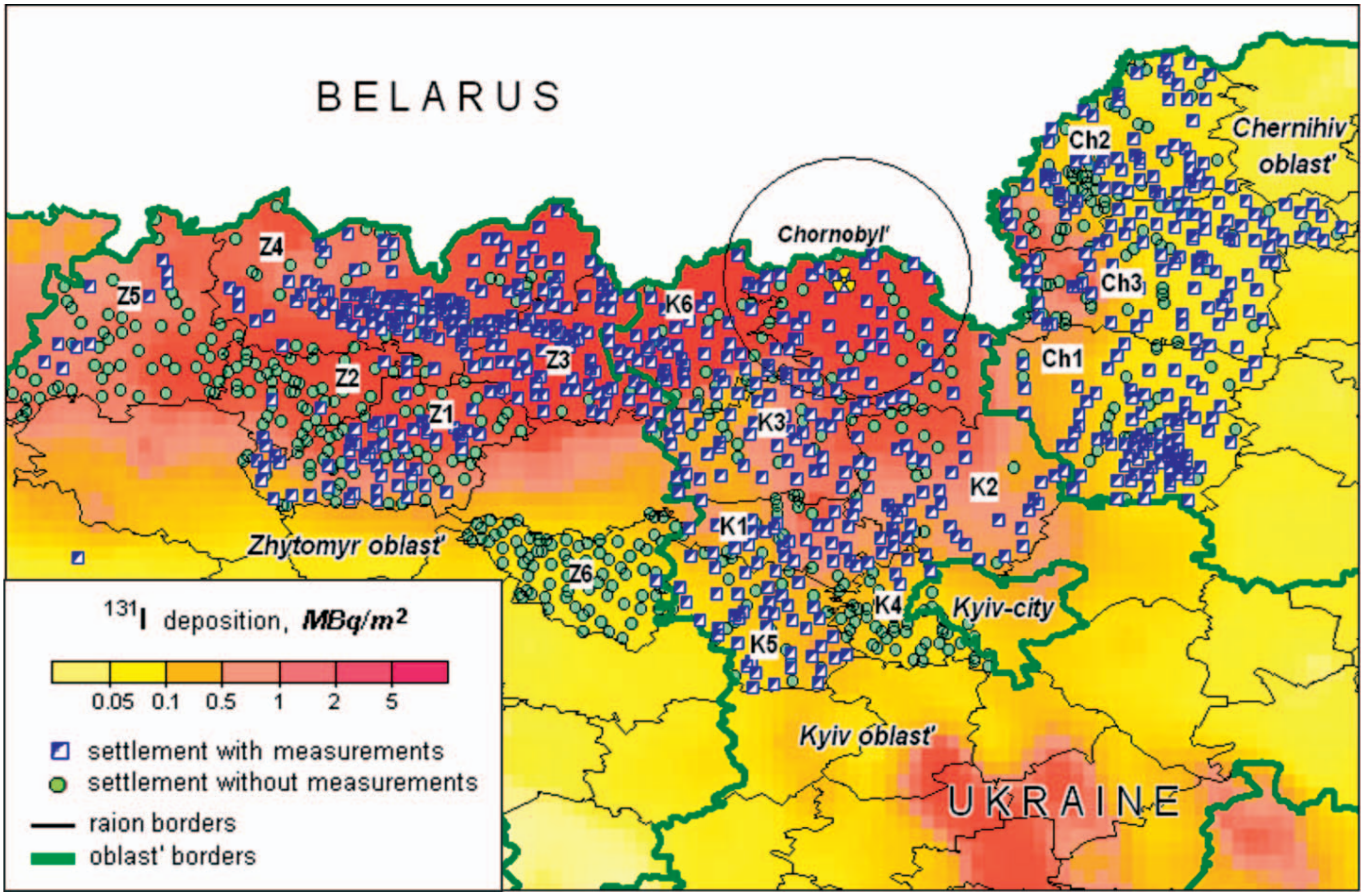

FIG. 1. Radioactive ^{131}I contamination of the northern part of Ukraine and distribution of the study population by settlements with (Group 1) and without (Group 2) direct thyroid measurements.

This study is also unique in that we have estimated individual doses for study subjects who had direct thyroid measurements taken shortly after the accident. We developed group-averaged ''individualized'' doses for study subjects who did not have direct measurements, based on direct measurements of people of the same age and sex who were living in the same or nearby settlements.

MATERIALS AND METHODS

Study Population

The study is comprised of the population of 1,293 rural settlements in Kyiv, Zhytomyr and Chernihiv regions (oblasts[3]), three heavily contaminated oblasts in northern Ukraine (Fig. 1). In May and June of 1986, direct measurements of ^{131}I activity in the thyroid were performed on part of the population living in the northern districts (raions) of Kyiv and Zhytomyr and western raions of Chernihiv oblasts. At the time of the accident, 320,040 persons between the ages of 0 and 18 were living in the study settlements. The gender and age distributions for each settlement were available. Because the doses for children less than 1 year old at the time of the accident are very uncertain due to potential *in utero* exposure, the 18,133 infants in this age group were excluded. With this exclusion, 301,907 individuals (152,474 males and 149,433 females) with thyroid dose estimates of different levels of reliability comprise the study population. Table 1 presents the distribution of the study subjects by gender and dose group.

[3] Raion is an administrative unit within an oblast. Usually, there are 10 to 20 raions in an oblast. The raion is comparable to a county in the U.S., while the oblast is comparable to a state.

Thyroid Doses

As described in a companion paper (*5*), a three-level system of ^{131}I thyroid dose reconstruction was developed for the entire population of Ukrainian children. For subjects with direct measurements of ^{131}I activity in the thyroid, individual absorbed thyroid doses were reconstructed on the basis of the results of these measurements, as well as an ecological model that describes the transport of ^{131}I through the environment and in people. The model takes into account inhalation of contaminated air, the process of ^{131}I deposition on ground and vegetation, the transfer of ^{131}I into milk and leafy vegetables, the reference daily consumption of these contaminated foodstuffs, and the uptake and retention of ^{131}I in the thyroid. The ecological model was used to estimate the time-integrated ^{131}I activities in the thyroids of the subjects with a direct thyroid measurement. These activities were then adjusted to the results of the direct thyroid measurements. The individual thyroid doses are directly proportional to the time-integrated ^{131}I activities in the thyroids. All together, 24% of the study population (73,216 persons) had direct thyroid measurements.

For the 228,691 persons without direct measurements, the set of reconstructed individual doses was used to estimate age- and gender-specific group-average ''individualized'' thyroid doses with two levels of reliability. About 62% (140,951) of these people resided in 745 rural settlements (called group 1 settlements) where reliable high-quality direct thyroid measurements were made in May and June 1986 for at least part

TABLE 1
Thyroid Cancer in Ukraine (1990–2001) after the Chornobyl Accident: Distribution of Study Population by Gender and Thyroid Dose Interval[a]

Thyroid dose interval, mGy	Males		Females		Total	
	No.	Percentage	No.	Percentage	No.	Percentage
<20	10,130	6.6	13,725	9.2	23,855	7.9
20–50	33,514	22.0	34,823	23.3	68,337	22.6
50–100	33,187	21.8	32,249	21.6	65,436	21.7
100–200	31,367	20.6	28,982	19.4	60,349	20.0
200–300	16,423	10.8	15,208	10.2	31,631	10.5
300–500	12,931	8.5	11,226	7.5	24,157	8.0
500–800	7,078	4.6	6,261	4.3	13,339	4.4
800–1,200	3,900	2.6	3,255	2.2	7,155	2.4
1,200–2,000	2,166	1.4	2,222	1.5	4,388	1.5
2,000–4,000	1,161	0.8	979	0.7	2,140	0.7
4,000+	617	0.4	503	0.3	1,120	0.4
Total	152,474	100.0	149,433	100.0	301,907	100

[a] Includes people who were ages 1–18 years old at the time of the accident.

of the inhabitants who were between the ages of 1 and 18 at that time. The group-average doses for these subjects were reconstructed based on the results of direct measurements and thyroid dose estimates taken for subjects of the same age and gender living in the same settlement. In 45% of these settlements, more than half of the residents had direct thyroid measurements, whereas in 18% of the settlements, fewer than 10% of the residents had direct measurements. Overall, about 35% of the population from these settlements had direct thyroid measurements made within the first few weeks after the accident. The remaining 87,740 (38%) people resided in 548 rural settlements (called group 2 settlements) where direct thyroid measurements were not made but are located in raions where direct thyroid measurements were made in nearby settlements. The group-average doses for these persons were reconstructed as described for people living in group 1 settlements, but instead of being based on direct thyroid measurements from the same settlements, direct measurements from the closest settlements in the same raion with an adequate number of direct measurements were used. Figure 1 shows the location of group 1 and group 2 settlements.

Hence the study population consists of subjects with instrumentally individualized thyroid doses and subjects with group-average ''individualized'' doses based on direct measurements from group 1 settlements or group 2 settlements. The distribution of the study population with individual direct measurements and those with group-average doses and corresponding cancer cases is presented for Zhytomir, Kyiv and Chernihiv oblasts in Table 2.

As seen in Table 1, the study subjects have a wide distribution of doses. The average thyroid dose for the study population was 353 mGy. Slightly over 70% of subjects had thyroid doses below 200 mGy and about 1% had doses above 2000 mGy. Doses were similar for males and females.

Cancer Ascertainment

Between April 26, 1986 and December 31, 2001, 232 thyroid cancers were diagnosed among all people who were born between 1968 and 1986 and who lived in the study regions at the time of the accident. Cases were identified from the databases of the two medical institutions that had collected information on thyroid cancers: the Institute of Endocrinology and Metabolism and the National Cancer Registry of Ukraine. The medical records of cases fitting the diagnostic, age and residence criteria were abstracted. The National Cancer Registry, which began active follow-up in 1995, obtains information on all malignancies from oblast oncology centers, state medical research institutes, and public hospitals. The diagnoses for the thyroid cancer cases included in the study were validated through medical records (*28, 29*). For each case, data were available on the settlement of residence at the time of the accident, gender, age in 1986, date of thyroid surgery, and age at diagnosis. The distribution of the cancer cases by raion is given in Table 2.

Thyroid Screening

To take into account both the geographic and temporal differences in the intensity of thyroid screening, the use of ultrasound as a diagnostic tool, and a general heightened awareness of the relationship between radiation exposure from Chornobyl and development of thyroid neoplasia, we developed a variable called ''screening rate.'' This variable was defined as the number of ultrasound examinations performed per 100,000 population (including both children and adults) in the three study oblasts in 1990, 1995 and 2002 (data from the Ukraine Ministry of Health). As seen in Fig. 2, the number of ultrasound examinations increased dramatically in all oblasts between 1990 and 2002, over 20-fold in Chernihiv and Zhytomyr Oblasts.

Statistical Analysis

Person-years at risk were computed using the population data. It was not possible to take into account in- or out-migration or loss due to death because these data were unavailable. Loss to follow-up would be expected to be relatively small in view of the young age of the cohort. Person-years and the four thyroid cancers diagnosed in the period of 1986–1989 were excluded from the analyses due to the less intense case detection in the first few years after the accident and because these years presumably represent the latent period for radiation-induced thyroid cancers. Thus each person contributed a total of 12 years at risk between January 1, 1990 and December 31, 2001.

Case counts and person-years at risk were cross-classified by oblast (Kyiv, Chernihiv and Zhytomyr), gender (male and female), age in 1986 (1–, 5–, 10– and 15–18 years), age at risk (1–, 5–, . . . and 30–34), and dose (0–, 50–, 100–, 150–, 200–, 250–, 300–, 400–, 500–, 600–, 800–, 1000–, 1500–, 2000– and 4000– mGy). The dose categories were selected to give an approximately equal distribution of thyroid cancer cases in each category. The cross-classification also included screening rate (<0.7, 0.7–1.2, 1.3–1.8 and ≥1.8 per 100 population) or calendar year (1990–, 1993–, 1996– and 1999–2001).

Poisson regression methods were used to model the background rate of thyroid cancer in terms of gender, age at risk (attained age), oblast and screening rate, with an interaction term for gender and attained age and an indicator variable for individual thyroid measurements. The variables were simultaneously adjusted for each other and also for the effect of dose using a linear excess relative risk model. Adjusting for gender and age was necessary because both factors substantially influence rates of

TABLE 2
Thyroid Cancer in Ukraine (1990–2001) after the Chornobyl Accident: Study Settlements, Population and Number of Cancer Cases for Persons with and without Direct Thyroid Measurements

Oblast	Raion code[b]	Raion name	No. of settlements	Study population with measurements[a]		Study population without measurements[a]	
				No.	Cancers	No.	Cancers
Zhytomyr	Z1	Korosten'	113	6,926	3	24,665	11
	Z2	Luhyny	49	12	0	7,040	3
	Z3	Narodychi	76	5,189	14	1,465	11
	Z4	Ovruch	154	11,850	7	9,756	10
	Z5	Olevs'k	60	611	0	17,249	8
	Z6	Radomishel'	82	16	0	12,385	2
		Novograd-Volins'k	1	241	0	14,215	3
Kyiv	K1	Borodianka	45	4,795	1	10,052	4
	K2	Vyshhorod	58	5,913	5	11,366	12
	K3	Ivankiv	67	3,441	1	3,226	6
	K4	Kievo-Sviatoshyn	56	2,200	1	66,510	28
	K5	Makariv	63	4,123	0	5,658	8
	K6	Polis'ke	61	3,380	5	4,339	8
	K7	Chernobyl'	62	4,173	3	5,824	7
		Pripjat-town[c,d]	2	3,775	6	9,987	29
Chernihiv	Ch1	Kozelet's	107	4,801	2	10,282	3
	Ch2	Ripky	112	3,878	2	5,445	4
	Ch3	Chernihiv	125	7,892	8	9,227	17
Total			1,293	73,216	58	228,691	174

[a] Includes people who were 1 to 18 years old at the time of the accident.
[b] The codes are used in Fig. 1 to indicate the location of the raions within the Zhytomyr, Kyiv and Chernihiv oblasts.
[c] Includes Jarniv railway station.
[d] Population evacuated to other raions.

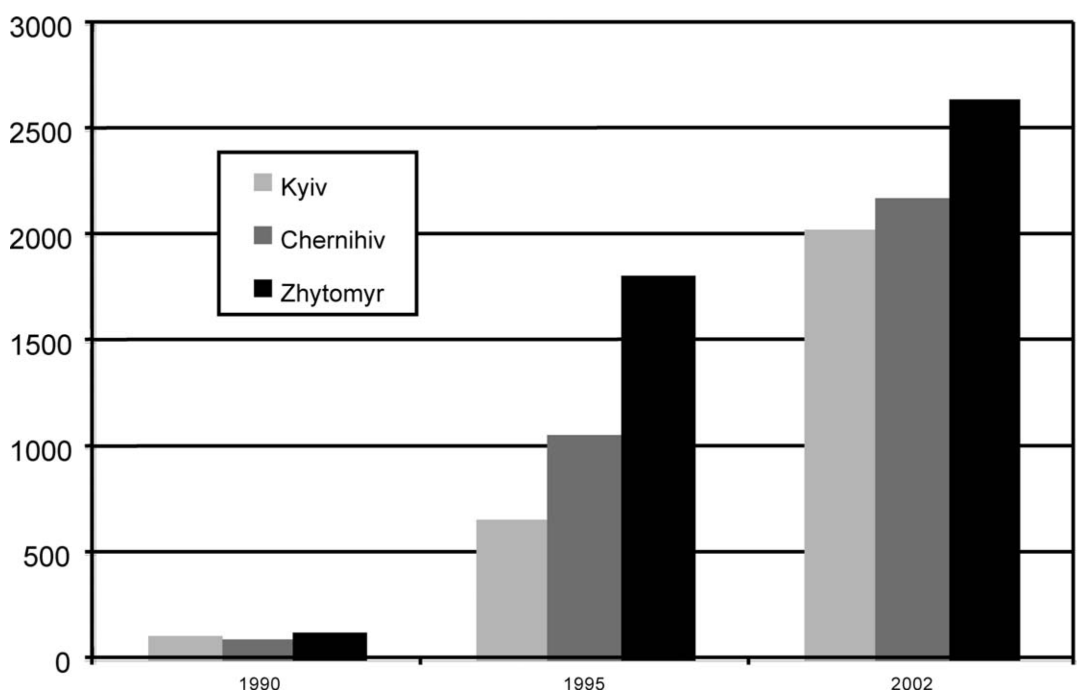

FIG. 2. Number of ultrasound examinations per 100, 000 population by time and oblast.

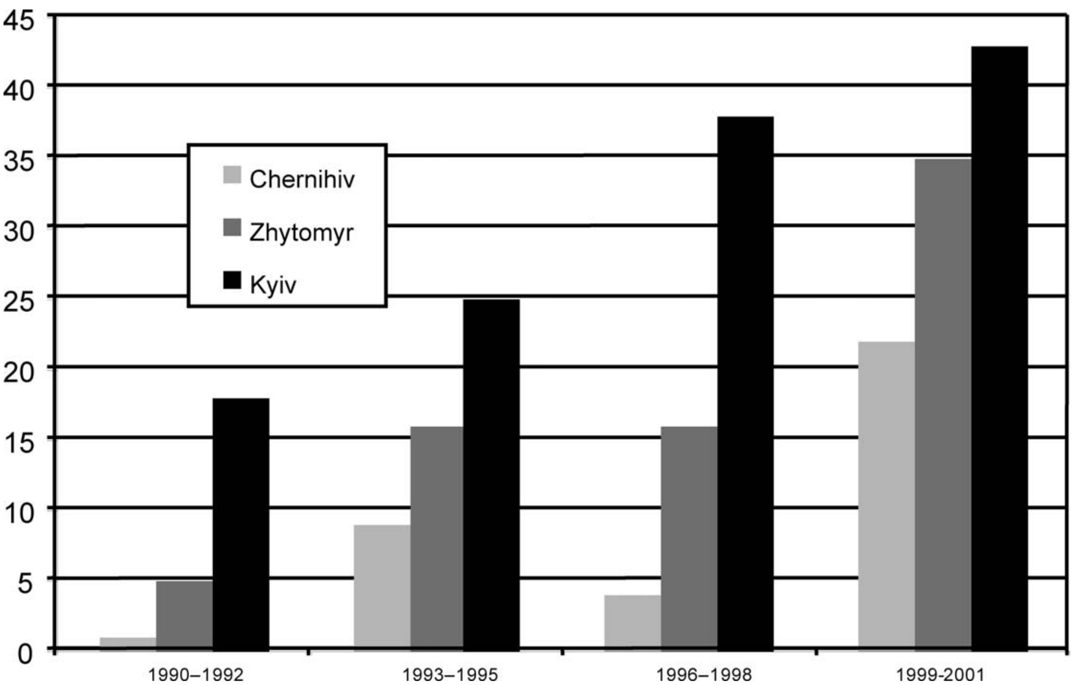

FIG. 3. Number of thyroid cancer cases diagnosed in Ukraine by time period and oblast.

thyroid cancer (*19*). Oblast and screening rate were included in the model to allow for the possible effects of time and geographic variation in early detection thyroid screening and the introduction and use of technical advances in diagnosis of thyroid diseases. In an alternative model, calendar time replaced screening rate. These two variables could not be included together in the same model because they were too highly correlated. Using the described model assumes that the intensity of the screening rate was constant for a given oblast in a given year, which we think is a reasonable assumption.

Poisson regression also was used to fit both excess relative risk models (ERR) and excess absolute risk (EAR) models to the observed and person-year data. These models may be expressed, respectively, as

$$R_0 \times (1 + \beta D \times e^{(\Sigma\gamma_i Z_i)}), \quad (1)$$

$$R_0 + \beta D \times e^{(\Sigma\gamma_i Z_i)}, \quad (2)$$

where the background term (R_0) represents the effect of such non-radiation variables as gender and age, β is the ERR per gray (Eq. 1) or the EAR per 10,000 person-year (PY) Gy (Eq. 2), which may be modified by factors represented by variables Z_i.

Point and interval estimates and tests of significance were based on standard likelihood techniques. The AMFIT program of the computer package EPICURE (*30*) was used to fit the data. Confidence intervals are likelihood-based unless indicated otherwise.

RESULTS

Background Rates

In the 12-year period from January 1990 through December 2001, 232 thyroid cancers fitting the study criteria were diagnosed, of which 156 were in females and 76 in males. The number of thyroid cancers increased sharply during this period in all three oblasts (Fig. 3). Table 3 shows the number and crude rates of thyroid cancers by gender, oblast and calendar time. The overall crude incidence rate was 6.2 per 100,000 PY. The largest population and highest incidence rate are in Kyiv Oblast. As expected, the crude background rates of thyroid cancer for females were higher than the rates for males (8.4 and 4.0 per 100,000 PY, respectively; female/male ratio = 2.1). Among women, rates jumped from 3.7 per 100,000 PY in 1990–1992 to 14.1 in 1999–2001, and among men, the rates rose from 1.5 to 7.4 during the same period.

The relationship between gender and age was complicated. Taking gender, attained age, oblast, screening rate and dose into account, with an interaction term for gender and age, the relative risks for background variables are shown in Table 4. With males aged 5–9 years at risk as the referent group, female thyroid cancer incidence was lowest between age 15–19 years and then increased rapidly with age. For males, the risk decreased from early childhood through age 20–24 and then remained stable. A statistically significant modifying effect was seen for oblast of residence in 1986, with Zhytomyr Oblast having the lowest incidence rate. The rate in Zhytomyr was less than half the rate in Kyiv Oblast ($P < 0.0001$). Females were more than twice as likely to develop thyroid cancer as males in all but the 15–19 age-at-risk category.

The thyroid cancer incidence rate increased substantially with increasing screening rate, an observation that is highly statistically significant ($P < 0.0001$). The RR for the highest screening rate category (≥1.8 per 100) was more than three times greater than for the lowest category (<0.7 per 100). There also was a steadily increasing incidence of thyroid cancer when calendar year period was substituted in the model for screening rate ($P < 0.0001$). In the final 3-year period (1999–2001), the relative risk was 4.5 times higher than in the period from 1990 to 1992. Analyzing the

TABLE 3
Thyroid Cancer in Ukraine (1990–2001) after the Chornobyl Accident: Thyroid Cancer Cases and Crude Incidence Rates[a] by Oblast and Calendar Year

Oblast		1990–1992 Male	1990–1992 Female	1993–1995 Male	1993–1995 Female	1996–1998 Male	1996–1998 Female	1999–2001 Male	1999–2001 Female	Total Male	Total Female	Total All
Kyiv	No.	5	13	9	16	8	30	12	31	34	90	124
	PY[b]	222,148	222,138	224,148	222,138	224,148	222,138	224,148	222,138	896,592	888,552	1,785,144
	Rate[a]	2.2	5.9	4.0	7.2	3.6	13.5	5.4	14.0	3.8	10.1	6.9
Chernihiv	No.	1	0	2	7	2	2	10	12	15	21	36
	PY	76,534	75,724	76,534	75,724	76,534	75,724	76,534	75,724	306,136	302,896	609,032
	Rate	1.3	0.0	2.6	9.2	2.6	2.6	13.1	15.8	4.9	6.9	5.9
Zhytomyr	No.	1	4	5	11	8	8	13	22	27	45	72
	PY	170,655	164,205	170,655	164,205	170,655	164,205	170,655	164,205	682,620	656,820	1,339,440
	Rate	0.6	2.4	2.9	6.7	4.7	4.9	7.6	13.4	4.0	6.9	5.4
Total	No.	7	17	16	34	18	40	35	65	76	156	232
	PY[b]	471,337	462,067	471,337	462,067	471,337	462,067	471,337	462,067	1,885,348	1,848,268	3,733,616
	Rate	1.5	3.7	3.4	7.4	3.8	8.7	7.4	14.1	4.0	8.4	6.2

[a] Crude rate per 100,000 person years.
[b] PY = person years.

data using alternative ways of adjusting for the effects of screening on thyroid cancer incidence, e.g., adjusting for the possible combination of oblast, calendar year and settlement size, essentially made no difference in the results.

Radiation Risks

Estimates of adjusted relative risks by dose categories are shown in Table 5. Monotonically increasing relative risks with dose were seen (Fig. 4), and these relative risks were statistically significant starting with the dose category of 0.2–0.5 Gy. The relative risk associated with a dose of 1 Gy or more was estimated to be close to 12. The *P* values for trend and homogeneity were <0.0001.

Table 6 shows the results of fitting four linear ERR models to the data and examines the effects of various effect modifiers. The linear model (Model 1), in which only the main effect of dose was examined, estimates an ERR per gray of 8.0 (CI = 4.6–15).

Males were estimated to have an ERR per gray about five times higher than females (Model 2). However, the difference was only of borderline statistical significance ($P = 0.069$), and changes in the adjustment variables resulted in a fair amount of variation in the results. With 76 male thyroid cancer cases, data were limited for the evaluation of dose–response differences by gender.

Model 3 shows statistically significant variation in the ERR per gray by age at the time of the accident in 1986 ($P = 0.02$), with the ERR per gray decreasing with increasing age at exposure and estimates that persons exposed to radiation from Chornobyl before age 5 years would have approximately 4.4 times the effect from dose as those exposed at 15 to 18 years of age. There was evidence of an increasing dose effect with calendar year period ($P < 0.001$), especially in the more recent period (Model 4).

Table 7 shows the results when the EAR model is used. The estimate for the EAR per 10,000 PY Gy was 1.5 (95% CI = 1.2–1.9). There was some suggestion of a gender interaction effect ($P = 0.15$), with females having a higher risk than males. The interaction effects with age at exposure and time since exposure are similar in pattern to those seen for the corresponding relative risk model with the effect of dose decreasing with age at exposure and increasing with time since exposure. Thus, with the exception of gender, the patterns observed from the excess relative risk analysis (Table 6) and the excess absolute risk analysis (Table 7) are qualitatively similar and complement each other.

Finally, we estimated the ERR per gray and EAR per 10,000 PY Gy for the group of individuals with direct thyroid measurements and for those without measurements. The ERR and EAR estimates differed significantly in the two groups, with the risks being lower in the group with direct measurements. The ERR and EAR estimates were 3.89 (95% CI = 0.94–6.84) and 0.82 (95% CI = 0.45–1.19), respectively, for those with direct measurements and 13.03 (95% CI = 5.32–20.7) and 2.06 (95% CI = 1.57–2.55), respectively, for those without direct measurements.

DISCUSSION

The massive explosion at the Chornobyl nuclear power plant resulted in the worst industrial radiation accident ever to occur. Large quantities of radioiodines, mainly ^{131}I, were spewed into the atmosphere in northern Ukraine and were carried by the winds to Belarus and the Bryansk, Orel and Tula regions of Russia. Since the thyroid gland concentrates iodines, it is the organ of greatest concern when considering the public health consequences from the radiation exposure.

Studies of external radiation such as those of the atomic bomb survivors and patients treated with radiotherapy for a variety of head and neck conditions have clearly shown

TABLE 4
Thyroid Cancer in Ukraine (1990–2001) after the Chornobyl Accident: Relative Risks and 95% Confidence Intervals for Background Variables

Variable	Estimate[a]	Lower 95% bound	Upper 95% bound	χ^2	*df*	*P* value[b]
Oblast						
Kyiv	1			27.43	2	<0.0001
Chernihiv	0.58	0.38	0.90			
Zhytomyr	0.45	0.33	0.61			
Age at risk, years						
males				22.05	11	0.005
5–9	1					
10–14	0.84	0.68	4.37			
15–19	0.68	0.35	2.05			
20–24	0.52	0.28	1.68			
25–29	0.54	0.19	1.38			
30+	0.62	0.18	1.55			
females						
5–9	1.72	0.15	2.60			
10–14	1.86	0.82	4.23			
15–19	0.80	0.35	1.83			
20–24	1.50	0.60	3.75			
25–29	2.18	0.80	5.98			
30+	2.22	0.55	8.96			
Screening rate per 100						
<0.7	1			25.50	3	<0.0001
0.7–1.2	2.11	1.40	3.18			
1.3–1.7	2.53	1.60	3.98			
≥1.8	3.30	1.99	5.46			
Calendar time				14.37	3	0.002
1990–1992	1					
1993–1995	2.05	1.17	3.58			
1996–1998	2.06	0.93	4.56			
1999–2001	4.54	1.70	12.10			

[a] Adjusted for gender, oblast, age, screening intensity and interaction effects of age and sex.
[b] Tests addition of corresponding variables.

that relatively low doses to children can significantly increase the risk of thyroid tumors (*19, 31–33*). On the other hand, the role of internal doses of radioiodines and especially ^{131}I is not as clear, and a recent study of children living near the U.S. Hanford nuclear facility at the time it was releasing ^{131}I into the atmosphere found no elevated risk of thyroid cancer or any other thyroid disorders (*34*). The Chornobyl accident offers an unprecedented opportunity to evaluate the thyroid cancer risks associated with exposure to internally deposited radioactive iodines. In the 18 years since the accident, a huge jump in the number of pediatric thyroid cancers occurred due to fallout of radioactive iodines from the Chornobyl plant.

Risk estimates for radiation-related thyroid cancer have been published from ecological studies (*22, 24, 25, 27, 35, 36*), but they have limited use for radiation protection due to inherent methodological problems with ecological studies (*37–39*). In a series of well-designed investigations, Jacob *et al.* (*24, 25, 27, 36*) established that a linear dose–response relationship adequately described the data for Belarus and the contaminated regions of Ukraine and Russia and that the EAR was of the order of about 2 per 10, 000 PY Gy and the ERR close to 20 per gray. In the most recent study (*27*), Jacob and colleagues reported an EAR of 2.66 (95% CI = 2.19–3.13) and an ERR of 18.9 (95% CI = 11.1–27) for 426 settlements in Belarus and 608 settlements in Ukraine.

In the current study, we estimated the ERR per Gy to be 8.0 (95% CI = 4.6–15) and the EAR per 10,000 PY gray to be 1.5 with a 95% CI of 1.2–1.9. Since Jacob *et al.* (*27*) noted that the excess relative and excess absolute risks in Belarus were approximately 1.6 and 1.4 times higher, respectively, than in Ukraine, our results for the three contaminated oblasts in Ukraine are very similar to, albeit slightly lower than, those estimated by Jacob *et al.* (*27*).

Two relatively small, population-based case-control studies (*15, 21*) have confirmed the association between ^{131}I and childhood thyroid cancer, but these studies did not quantify risk estimates that could be used for radiation protection purposes. A recent larger study (*20*) included 276 cases and 1300 matched controls from the contaminated areas of Belarus and Russia. Based on a linear dose–response model, an odds ratio of 5.5 (95% CI = 3.1–9.5) was observed after childhood exposure to radioiodines. In iodine-deficient areas, the risk was three times larger than in iodine-sufficient areas, and potassium iodide intake was shown to reduce risk to about one-third. While this study has added signif-

TABLE 5
Thyroid Cancer in Ukraine (1990–2001) after the Chornobyl Accident: Relative Risks and 95% Confidence Bounds by Dose Categories

	Dose category, mGy				
Mean dose, mGy	0–0.03	0.05–0.12	0.20–0.32	0.50–0.70	1.00–2.79
Cases	37	52	50	43	50
Person-years	1,097,180	1,519,090	668,976	205,152	132,480
Relative risk[a]	1	1.2	2.63	7.25	11.59
Lower 95% bound		0.78	1.67	4.47	7.13
Upper 95% bound		1.87	4.14	11.76	18.84
χ^2 (trend)	138.6, *df* = 1, *P* <0.0001				
χ^2 (homogeneity)	146.1, *df* = 4, *P* <0.0001				

[a] Adjusted for gender, oblast, age, screening intensity and interaction effects of age and sex.

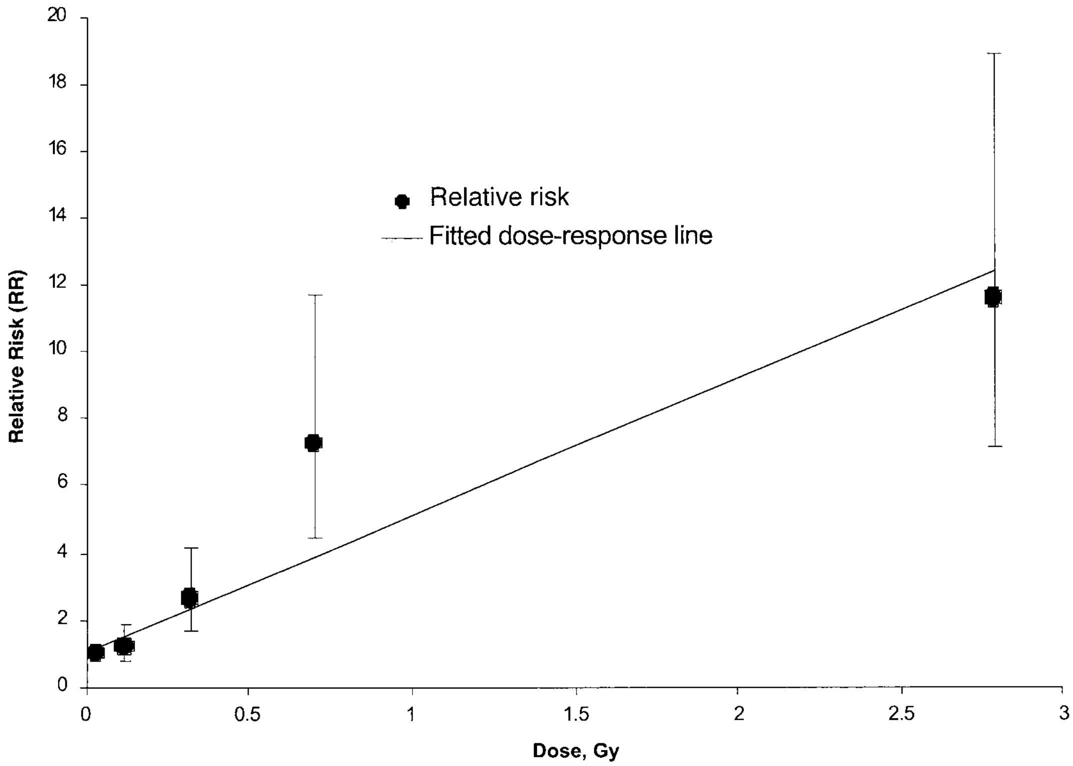

FIG. 4. Plot of the odds ratio estimates and the corresponding 95% confidence limits from the categorical analysis and a fitted dose–response line.

icantly to what is known about ^{131}I, more information is needed about the role of iodine deficiency, the effects of age at exposure and gender, and whether the risk from ^{131}I is equal to, lower than or higher than that from external radiation. In other words, the effectiveness of internal doses of ^{131}I in inducing thyroid cancer relative to doses from external radiation is still not quantified adequately.

The variation in background rates of thyroid cancer by oblast is curious. Since the oblast analysis is adjusted for radiation dose, the oblast effect should not be due to vary-

TABLE 6
Thyroid Cancer in Ukraine (1990–2001) after the Chernobyl Accident: Excess Relative Risk (ERR) Models for Dose Main and Interaction Effects

Model[a]	Variable	ERR per Gy[b]	Lower 95% bound	Upper 95% bound	χ^2	*df*	*P* value[c]
1	Dose[d]	8.00	4.57	14.7			
2	Gender						
	Male	17.93	1.6	117.3	3.31	1	0.069
	Female	5.73	2.05	9.41			
3	Age in 1986, years						
	1–4	15.52	3.55	27.48	5.78[e]	1	0.016
	5–9	11.15	3.15	19.16			
	10–14	5.39	0.89	9.91			
	15–18	3.52	1.01	8.04			
4	Calendar year period						
	1990–1992	1.77	0.66	4.18	10.5[e]	1	0.001
	1993–1995	5.15	1.34	8.95			
	1996–1998	7.15	2.2	12.1			
	1999–2001	17.01	5.37	28.64			

[a] Adjusted for gender, oblast, age, screening intensity and interaction effects of age and sex.
[b] Excess relative risk per gray.
[c] Tests difference of model relative to model 1, i.e., tests interaction effects.
[d] Deviance of the baseline model = 2052.69, *df* = 67,337.
[e] Test based on continuous variable with 1 *df*.

TABLE 7
Thyroid Cancer in Ukraine (1990–2001) after the Chornobyl Accident: Excess Absolute Risk (EAR) Models for Dose Main and Interaction Effects

Model[a]	Variable	EAR per 10^4 per Gy[b]	Lower bound	Upper bound	χ^2	*df*	*P* value[c]
1	Dose[d]	1.53	1.19	1.88			
2	Gender						
	Male	1.37	0.97	1.77	2.10	1	0.148
	Female	1.93	1.33	2.53			
3	Age in 1986, years						
	0–4	1.96	1.44	2.49	9.02[e]	1	0.003
	5–9	1.46	0.88	2.05			
	10–14	0.82	0.21	1.42			
	15–18	0.68	0.15	1.52			
4	Calendar year period						
	1990–1992	[f]			34.03[e]	1	<0.001
	1993–1995						
	1996–1998						
	1999–2001						

[a] Adjusted for gender, oblast, age, screening intensity and interaction effects of age and sex.
[b] Excess absolute risk per 10,000 person years per gray.
[c] Tests difference of model relative to model 1, i.e., tests interaction effects.
[d] Deviance of the baseline model = 2069.90, *df* = 67,337.
[e] Test based on continuous variable with 1 *df*.
[f] MLE may be infinite or may not exist.

ing levels of radiation contamination. While most of the areas in the study are iodine deficient, it is not known whether the degree of deficiency is similar everywhere, but all three oblasts are in the zone of moderate iodine deficiency based on iodine concentration in ground water (3–5 μg per liter). Differences in iodine nutrition can affect dose, thyroid cancer incidence, and radiation-related risk (*20, 21, 40*), but because our whole study population lived in moderately deficient areas, we were not able to compare thyroid cancer risks associated with varying levels of iodine deficiency.

The EAR per 10,000 PY Gy was 4.4 (95% CI = 1.9–10) and the ERR per gray was 7.7 (95% CI = 2.1–29) in a pooled analysis of childhood external radiation exposure and the risk of developing thyroid cancer (*32*). In the current study, the EAR was about one-third of that found in the pooled analysis, but the ERR was just about the same. The reasons for the lower EAR are not evident, but it could be related to special characteristics of the Chernobyl study population, e.g. moderate iodine deficiency, short latent period, and young age at diagnosis. However, since differences in background rates generally have a larger impact on the ERR than the EAR, it is difficult to understand why the ERRs should be so similar while the EARs differ. The substantially older age at risk in the pooled analysis of external radiation would result in considerably higher thyroid cancer background rates, and thus a lower ERR and higher EAR might be expected. As mentioned above, Ukraine is a moderately iodine-deficient area, whereas none of the study populations in the pooled analysis came from regions with iodine deficiency. Indeed, the Japanese atomic bomb survivors have a very high iodine intake from seaweed and fish consumption, and the other studies were conducted in the U.S. and Israel, which are largely iodine sufficient. Some studies suggest that iodine deficiency is associated with follicular thyroid carcinoma, whereas iodine-rich diets are more often associated with papillary carcinoma (*41*). In fact, Japan, Israel and the U.S. do have a high incidence of papillary carcinoma. Thus the higher background rate of papillary thyroid cancer in the pooled analysis populations might also contribute to the higher EAR and lower ERR in the Chornobyl studies. Finally, although a formal test was not done, the EAR estimate in the current study falls within the confidence interval of the pooled study, so the difference in the estimates may not have any real importance.

Another possible reason for variation in risk estimates among studies is that there are methodological limitations to ecological studies. Of primary concern is the fact that dose estimates pertain to groups of people, not to individual study subjects, that individual doses cannot be linked to individual cancers, and that there is little or no information on potential confounders. In the present investigation, we were able to minimize some, but certainly not all, of the problems of ecological studies. We estimated individual doses based on direct thyroid measurements for about 25% of the study population. For the rest of the study population, measurements for people of the same sex and age and living in the same or nearby villages were used to estimate group-average doses. This approach is an improvement over many ecological studies in which only mean regional doses are available, but uncertainty in the dose estimates remain, and the level of uncertainty differs for the different quality of dose estimates. The main sources of dose uncertainties are related to the ecological dose model, which describes the time variation of ^{131}I in milk and leafy vegetables, the results of the individual direct thyroid measurements, and the function of relative age-gender time-integrated thyroid activity. Doses for subjects who live in ''measured settlements'' are subject to Berkson error, with the degree of uncertainty a function of the number of measurements carried out. Doses for subjects who live in ''unmeasured settlements'' that use mean doses from nearby measured settlements would also be subject to Berkson error, but the level of uncertainty would be larger. We did find a significant difference in risk estimates for the group of people with direct measurements compared with those with ''individualized'' dose estimates. This finding requires further exploration to try to understand where these differences come from.

We also tried to compensate for lack of information on early detection thyroid screening by using Ukrainian Ministry of Health data on the number of ultrasound examinations performed by oblast and calendar time. The available data, however, are not ideal, because the information on ultrasound examinations is specific for an oblast, while the thyroid cases and estimated doses are for raions. This difference can introduce correlated errors. Nonetheless, we think the uncertainties in thyroid cancer surveillance rates are relatively small due to the general standardization of medical delivery and procedural protocols, as well as the limits of residential mobility. If we over-adjusted for screening by using this proxy measure, we may have artificially decreased the EAR estimate.

Spontaneous thyroid cancer is two to three times more common among women than men, although the sex ratio changes with age. At young ages, there typically is very little difference in thyroid cancer incidence by gender, but from young adulthood until about menopause, women have substantially higher rates than men. In our study in northern Ukraine, the background rates of thyroid cancer were higher for young girls than boys, but the rates for girls began to rise rapidly during the late teenage years, so that by age 30 the incidence rate for females was about five times that for males. An elevated thyroid cancer incidence after radiation exposure has been demonstrated for both sexes, but in several investigations of external (*32*) and ^{131}I radiation (*21, 26*), the risk was higher in females than males. Cardis *et al.* (*20*) found no gender difference in radiation effects. In this study, we observed a lower excess relative risk for females than males, and the difference was of borderline statistical significance ($P = 0.069$). Our finding is in line with similar results in Belarus and Ukraine (*27, 35*). In the Michael Reese cohort of people irradiated with X rays for enlarged tonsils and other benign head and neck conditions when they were children, the excess relative risk also was larger for males than females, but the difference was not statistically significant (*42*).

After external irradiation, age at exposure is an important modifying factor for the development of thyroid cancer, with risk increasing as age at exposure decreases (*19, 30, 31*). After radioiodine exposure from the Chornobyl accident, a similar trend has been observed in most (*11, 13, 26, 27, 36, 43–46*) but not all (*47*) studies. We found a steady reduction in risk with increasing age at exposure using either ERR or EAR model; however, the trend was not statistically significant using the EAR model.

An excess risk of thyroid cancer is still observed in the regions near Chornobyl among persons exposed as children. The long-term time trends are not yet known, i.e., whether this elevated risk will continue throughout life and if it does whether the risk will remain at the same level seen until now or whether it will stabilize or decrease.

Chornobyl differs from other situations in which populations were unintentionally exposed to radiation because the size and location of the contaminated areas resulted in enormous exposed populations, some of which received appreciable thyroid doses. The combination of the large population and relatively high doses meant that risks could be detected among children who have very low naturally occurring thyroid cancer incidence. While we generally can make comparisons of radiation-related effects with those observed among the atomic bomb survivors, in this case there is virtually no information on childhood cancers among the survivors because routine cancer incidence follow-up only began 13 years after the bombings (*48*). Thus many of the findings linked to exposure from Chornobyl actually may be due to the early latent period or to very young age at diagnosis for the majority of the cancers, especially since pediatric thyroid cancers differ in many respects from thyroid cancers diagnosed later in life.

From the data currently available, it is difficult to compare the carcinogenic effectiveness of ^{131}I to that of external X or γ radiation since the results differ depending on whether an ERR or EAR model is used and the potential confounding effects of iodine deficiency are not yet adequately quantified. A very short latent period has been demonstrated after the accident in Chornobyl, but this finding may be the result of the enhanced statistical power to observe such findings because of the extremely large number of exposed individuals, the relatively high doses, and the early detection screening rather than to a true biological difference. In the pooled analysis of external radiation, excess risks continued throughout the 40-year follow-up period, although the excess risk began to decline after 30 years. Thus further follow-up of the Chornobyl-exposed populations is needed to learn whether risks will persist throughout life. With a longer follow-up and larger number of cases, a better understanding of the tumorigenic effects of ^{131}I relative to external radiation should be gained.

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