

Risk of Thyroid Cancer After Exposure to ^{131}I in Childhood

Elisabeth Cardis, Ausrele Kesminiene, Victor Ivanov, Irina Malakhova, Yoshisada Shibata, Valeryi Khrouch, Vladimir Drozdovitch, Evaldas Maceika, Irina Zvonova, Oleg Vlassov, André Bouville, Guennadi Goulko, Masaharu Hoshi, Alexander Abrosimov, Jadvyga Anoshko, Larisa Astakhova, Sergey Chekin, Evgenyi Demidchik, Rosaria Galanti, Masahiro Ito, Elena Korobova, Evgenyi Lushnikov, Marat Maksioutov, Vladimir Masyakin, Alexander Nerovnia, Vladimir Parshin, Evgenyi Parshkov, Nikolay Piliptsevich, Aldo Pinchera, Semyon Polyakov, Nina Shabeka, Eero Suonio, Vanessa Tenet, Anatoli Tsyb, Shunichi Yamashita, Dillwyn Williams

Background: After the Chernobyl nuclear power plant accident in April 1986, a large increase in the incidence of childhood thyroid cancer was reported in contaminated areas. Most of the radiation exposure to the thyroid was from iodine isotopes, especially ^{131}I . We carried out a population-based case-control study of thyroid cancer in Belarus and the Russian Federation to evaluate the risk of thyroid cancer after exposure to radioactive iodine in childhood and to investigate environmental and host factors that may modify this risk. **Methods:** We studied 276 case patients with thyroid cancer through 1998 and 1300 matched control subjects, all aged younger than 15 years at the time of the accident. Individual doses were estimated for each subject based on their whereabouts and dietary habits at the time of the accident and in following days, weeks, and years; their likely stable iodine status at the time of the accident was also evaluated. Data were analyzed by conditional logistic regression using several different models. All statistical tests were two-sided. **Results:** A strong dose-response relationship was observed between radiation dose to the thyroid received in childhood and thyroid cancer risk ($P < .001$). For a dose of 1 Gy, the estimated odds ratio of thyroid cancer varied from 5.5 (95% confidence interval [CI] = 3.1 to 9.5) to 8.4 (95% CI = 4.1 to 17.3), depending on the risk model. A linear dose-response relationship was observed up to 1.5–2 Gy. The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas (relative risk [RR] = 3.2, 95% CI = 1.9 to 5.5) than elsewhere. Administration of potassium iodide as a dietary supplement reduced this risk of radiation-related thyroid cancer by a factor of 3 (RR = 0.34, 95% CI = 0.1 to 0.9, for consumption of potassium iodide versus no consumption). **Conclusion:** Exposure to ^{131}I in childhood is associated with an increased risk of thyroid cancer. Both iodine deficiency and iodine supplementation appear to modify this risk. These results have important public health implications: stable iodine supplementation in iodine-deficient populations may substantially reduce the risk of thyroid cancer related to radioactive iodines in case of exposure to radioactive iodines in childhood that may occur after radiation accidents or

during medical diagnostic and therapeutic procedures. [J Natl Cancer Inst 2005;97:724–32]

Until the Chernobyl accident, the carcinogenic effect of exposure to ^{131}I was considered to be small compared with that of external photon exposure (1,2). In fact, little information about the effects of exposure of the child's thyroid to radioactive iodine isotopes was then available, because most studies on the risk of cancer associated with exposure to ^{131}I had been conducted in adult populations with underlying thyroid disease. It was, however, well known that the child's thyroid was sensitive to external x-rays (3,4).

Affiliations of authors: International Agency for Research on Cancer, Lyon, France (EC, AK, VD, VT); Medical Radiological Research Center RAMS, Obninsk, the Russian Federation (VI, OV, AA, SC, EL, MM, VP, EP, AT); Belarusian Center for Medical Technologies, Computer Systems, Administration and Management of Health, Minsk, Belarus (IM, SP, NS); Nagasaki University, Nagasaki, Japan (YS, SY); State Research Center—Institute of Biophysics, Moscow, the Russian Federation (VK); Institute of Physics, Vilnius, Lithuania (EM); Research Institute of Radiation Hygiene, St. Petersburg, the Russian Federation (IZ); National Cancer Institute, Bethesda, MD (AB); Clinic and Polyclinic for Nuclear Medicine, Bayerische Julius-Maximilians University of Würzburg, Germany (GG); Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan (MH); Institute of Geological Sciences of the National Academy of Sciences of Belarus, Minsk, Belarus (JA); Center of Laser Medicine, Childhood Polyclinic No. 8, Minsk, Belarus (LA); Belarusian State Medical University, Minsk, Belarus (ED); Centre for Tobacco Prevention, Stockholm Centre of Public Health and Clinical Epidemiology Unit, Karolinska University Hospital, Sweden (RG); National Nagasaki Medical Center, Nagasaki, Japan (MI); Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, Moscow, the Russian Federation (EK); Republican Research Centre of Radiation Medicine and Human Ecology, Gomel, Belarus (VM); Belarusian State Medical University, Minsk, Belarus (AN, NP); Department of Endocrinology and Metabolism, University of Pisa, Italy (AP); Clinic of Oncology, Turku University Hospital, Turku, Finland (ES); Strangeways Research Laboratory, Cambridge, U.K. (DW).

Correspondence to: E. Cardis, PhD, International Agency for Research on Cancer, Lyon, France (e-mail: cardis@iarc.fr).

See "Notes" following "References."

DOI: 10.1093/jnci/dji129

Journal of the National Cancer Institute, Vol. 97, No. 10, © Oxford University Press 2005, all rights reserved.

The accident that occurred in reactor 4 of the Chernobyl nuclear power plant in the Ukraine in April 1986 resulted in widespread radioactive contamination, particularly of the territories of Belarus, the Russian Federation, and the Ukraine. For most persons living in these territories, the main contribution to the radiation dose to the thyroid was from radioactive isotopes of iodine, mainly ^{131}I . It is estimated that, in Belarus, the thyroids of several thousand children received ^{131}I doses of at least 2 Gy (5).

A very large increase in the incidence of thyroid cancer in young people was observed as early as 5 years after the accident in Belarus (6,7) and slightly later in the Ukraine and the Russian Federation (8–10). Before the accident, incidence rates in children were, as in most countries in the world, less than one case per million per year; this rate increased to more than 90 per million in Gomel, the most contaminated region of Belarus, in the period from 1991 through 1994 (10). By the end of 2003, a total of 740 cases of childhood thyroid cancer had been observed in Belarus alone among those who were exposed as children (i.e., aged 0–14 years); about half of these were residents of Gomel region at the time of the accident (E. Demidchik, personal communication). An increased incidence of thyroid cancer continues to be observed in this population as it ages into adolescence and young adulthood. The evidence that this increase is related to the fallout of radioactive iodine from the Chernobyl accident is compelling (11–16). Questions remain, however, concerning the magnitude of the risk of thyroid cancer associated with these exposures (5) and the role of iodine deficiency, which was present in most of the affected areas at the time of the accident (17) and which has been postulated as a possible modifier of radiation-related thyroid cancer risk (18,19).

The Chernobyl experience provides the most important source of information for the quantification of risks to young people from exposure to ^{131}I and shorter-lived radioactive isotopes and for the study of factors—both environmental and host factors—that may play a role in the risk of radiation-related thyroid cancer in these areas (18,20,21). We carried out a case–control study of thyroid cancer in young people to evaluate the risk of thyroid cancer related to exposure to ^{131}I in childhood and to study environmental and host factors that may modify this risk, in particular iodine deficiency and stable (nonradioactive) iodine intake.

SUBJECTS AND METHODS

Study Design and Collection of Information

The study was designed as a population-based case–control study of thyroid cancer in young people. It was carried out in the regions of Belarus and the Russian Federation that were most contaminated by fallout from the Chernobyl accident.

We present risk estimates of thyroid cancer associated with exposure to ^{131}I that are based on 276 case patients and 1300 control subjects who resided in the Gomel and Mogilev administrative regions (i.e., oblasts) of Belarus or the Tula, Orel, Kaluga, and Bryansk administrative regions of the Russian Federation and were aged younger than 15 years at the time of the Chernobyl accident. The case patients were diagnosed with histologically verified thyroid carcinoma between January 1, 1992 [to avoid overlap with a previous case-control study in Belarus (13)], and December 31, 1998, and underwent surgery in Belarus or the Russian Federation. We included patients ascertained retrospectively as having been diagnosed with incident thyroid cancer

between January 1, 1992, and December 31, 1996, as well as patients with new incident thyroid cancers diagnosed from January 1, 1997, through December 31, 1998. In Bryansk region, the study was restricted to patients with new incident thyroid cancers diagnosed from January 1, 1998, through December 31, 1998, to avoid overlap with a separate study coordinated by the U.S. International Consortium for Research on the Health Effects of Radiation (16), because such overlap would have entailed too heavy a burden (reinterviewing and reexamining) on patients previously interviewed and examined in that study. In Gomel region, where the largest number of thyroid cancers has been diagnosed, it was not possible to include all cases diagnosed before 1997 for logistic and financial reasons. Therefore, a representative sample of these patients was included as follows: all patients who were younger than 2 years at the time of the Chernobyl accident and a 50% random sample, stratified by age at the time of the accident and by sex, of those who were 2 years old or older at the time of the accident. In Belarus, prospective case patients with thyroid cancer were identified directly from the Republican Scientific and Practical Center for Thyroid Tumors in Minsk, where most young people diagnosed with thyroid cancer in Belarus are referred to for surgery. The records of the oblast oncological dispensaries and of surgical departments of oblast hospitals were also consulted to ensure completeness of ascertainment of eligible cases. In the Russian Federation, prospective case patients with thyroid cancer were identified directly from the oblast oncologic dispensaries and surgical departments of the central hospitals of the regions under study. Collaboration was established with the hospitals in Belarus and the Russian Federation to ensure rapid identification of new cases of thyroid cancer in our study population. An international panel of pathologists from Belarus, the Russian Federation, Japan, and the United Kingdom reviewed histologic slides from the case patients included in the study and found that all but 11 of these tumors were papillary carcinomas.

To maximize statistical power, we interviewed at least four population-based control subjects for each case patient in the study. Control subjects were matched to case patients by age (within 1 year for those who were 18 months or older at the time of the accident, within 6 months for those aged 12–18 months, and within 1 month for those who were younger than 12 months at the time of the accident), sex, and administrative region of residence at the time of the accident. Control subjects were randomly drawn from records of the birth registry centralized at the region level in all regions except Kaluga and Orel, where access to the birth registry records was denied by local administrative authorities. In these regions, therefore, control subjects were selected from the records of the computerized medical insurance system, which covers virtually the entire population.

Information was collected on study subjects by use of a detailed questionnaire that was administered by a trained interviewer during an in-person interview. The interview included questions about selected lifestyle factors of the subject at the time of the accident and in the days and the first 2 months after the accident, as well as questions about the consumption of stable iodine immediately after the accident and during the following years. Questions were also included about other known or suspected risk factors for thyroid cancer. Subjects who were younger than 12 years at the time of the Chernobyl accident were mostly interviewed with their mothers. Because the scars from thyroidectomy are generally visible, it was not possible to blind the

interviewers to the case-control status of the interviewees. The interview was complemented by a clinical and ultrasound examination and analyses of blood and urine samples of subjects who consented to donate such samples. Response rates were very high among case patients in both Belarus (98%) and the Russian Federation (99%); the rate was lower among control subjects in Belarus (84.5%) and the Russian Federation (58%).

Radiation Dose Estimation

For each study subject, individual radiation doses to the thyroid were reconstructed by taking into account knowledge of the whereabouts and dietary habits of the subjects, which was obtained by questionnaire, and information on environmental contamination and on dates when cattle were put out for pasture, which were available for each settlement where the subject resided during the period after the accident until interview. The following pathways of exposure were considered: 1) internal irradiation arising from the intake of ^{131}I via inhalation or ingestion of contaminated foodstuffs; 2) internal irradiation arising from the intake of short-lived radioactive iodine isotopes (^{132}I , ^{133}I , and ^{135}I) and radioactive tellurium isotopes ($^{131\text{m}}\text{Te}$ and ^{132}Te) via inhalation and ingestion; 3) external irradiation from radionuclides deposited on the ground and other materials; and 4) internal irradiation resulting from the intake of radionuclides other than iodine and tellurium (essentially, ^{134}Cs and ^{137}Cs). The total radiation dose to the thyroid was estimated as the sum of the doses from these different radiation types.

The approach taken to estimate the individual thyroid ^{131}I dose combined individual information on period and length of residence in each settlement, on dietary patterns, and on stable iodine prophylaxis immediately after the accident with the average age-specific doses for each settlement. Because ^{131}I decayed before sufficient contamination surveys could be performed, a semiempirical model for the estimation of settlement level dose (22,23), modified to take into account specificities of deposition in different territories (24), was used. Details of the model and of its implementation will be presented elsewhere (V. T. Khrouch, V. V. Drozdovitch, E. Maceika, I. A. Zvonova, O. K. Vlasov, A. Bouville, et al., unpublished results). The semiempirical model used was based on the relation between environmental contamination and thyroid dose estimated from 130 000 direct thyroid exposure rate measurements carried out in territories with different contamination levels and in populations of all ages (infants, children, adolescents, and adults).

The radiation dose reconstruction was validated through a series of intercomparison exercises. Group radiation doses were evaluated by calculating the average radiation doses to the thyroid in populations of specific age groups for several settlements where direct thyroid measurements were available. The calculated group radiation doses were compared with average radiation doses to the thyroid derived from direct thyroid measurements in these settlements, assuming the same lifestyle and dietary habits as used in the calculation of doses from direct thyroid measurements; agreement was very good (correlation coefficient = .98). Validation of individual thyroid radiation dose estimation was then carried out by comparing predicted individual doses with doses calculated from direct thyroid measurements for subjects for whom information on lifestyle and diet was obtained from the study questionnaire; again, the agreement was good. A detailed description of the intercomparison study results

will be presented elsewhere (V. T. Khrouch, V. V. Drozdovitch, E. Maceika, I. A. Zvonova, O. K. Vlasov, A. Bouville, et al., unpublished results).

Evaluation of Iodine-deficiency Status

For each subject in the study, the level of stable iodine in soil in the settlement of residence at the time of the Chernobyl accident was used as a surrogate of stable iodine status. This level was derived from the estimated average iodine content in the predominant soil types in the land used for agriculture in the area around the settlements and was based on a relation between soil type and iodine level established by Lozovsky (25). The majority of the subjects in the study resided in rural areas, and local vegetables, meat, and milk provided most of the daily iodine intake in the diet of such areas of the former Soviet Union (26,27). The determination of iodine status of a settlement also took into account whether the location was rural or urban. Because, at the time of the Chernobyl accident, the food supply in large cities was dependent mainly on foodstuffs imported from other regions of the former Soviet Union (notably non-iodine-deficient regions of the Ukraine and Kazakhstan, for example, for wheat), the populations of large cities were assumed to be iodine sufficient. For smaller towns, we assumed that half of the diet was composed of locally produced foodstuffs and half of imported foodstuffs.

Assurances

Written informed consent to participate in the study was obtained from each study subject or from his or her guardian, as appropriate. The study was approved by the IARC Ethical Review Committee, the Belarus Coordinating Council for Studies of the Medical Consequences of the Chernobyl Accident, and the Ethical Committee of the Medical Radiological Research Centre of the Russian Academy of Medical Sciences, Obninsk. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. Data analyses for this paper were carried out in Lyon, France, by E. Cardis, A. Kesminiene, and V. Tenet.

Statistical Analysis

Data were analyzed by conditional logistic regression. The primary risk model used was the excess relative risk model, a model commonly used in radiation risk estimation (5,28,29,30), where the estimate of the relative risk, the odds ratio (OR), at a dose d , is expressed as $\text{OR}(d) = 1 + \beta d + \gamma d^2 + \dots$, where β and γ denote, respectively, the slope coefficients of the linear and quadratic dose terms in the model. Analyses were also carried out with a model more commonly used in environmental epidemiology, the log-linear risk model, in which the odds ratio at a dose d is expressed as $\text{OR}(d) = \exp(\beta d + \gamma d^2 + \dots)$. As indicated below, both risk models yielded very similar risk estimates. However, convergence problems are sometimes encountered in fitting excess relative risk models, particularly when interaction terms are included in the model. Consequently, the log-linear risk model was used for the exploration of interactions.

The main analyses were carried out by assuming that β is constant and by using dose as a continuous variable. Departures from linearity of risk were explored by fitting polynomial equations in dose. Departures from a constant relative risk model were

explored by carrying out analyses that address the possible modifying effects of other variables (including soil iodine content and iodine supplementation) by the introduction of interaction terms. The statistical significance of model parameters was tested with the likelihood ratio test. For descriptive purposes, analyses of risk in 11 distinct radiation dose categories (the lower bounds of the intervals were respectively 0, 0.016, 0.20, 0.40, 0.60, 0.80, 1.0, 1.25, 1.5, 2.0, and 3.0 Sv) were carried out; the lowest, reference category represents the lowest decile of the dose distribution. Estimated odds ratios and 95% confidence intervals (CIs) were calculated for the mean of each dose class. For analyses of the impact of soil iodine level, this variable was categorized into tertiles. All risk models were fit by use of the EPICURE software package (31). All statistical tests were two-sided.

RESULTS

The majority of case patients were from the Gomel region in Belarus (Table 1). Case patients from the regions of Kaluga, Orel, and Tula, which had the lowest contamination levels in the study, tended to be older (mean age = 7.4 years; standard deviation [SD] = 4.2 years) at the time of the accident than case patients from other regions (mean = 4.4 years; SD = 3.9 years); consequently, a higher proportion of these cases may have been spontaneous thyroid cancers, because the baseline incidence of thyroid cancer is extremely low in very young children and increases with age (32). As shown in Table 1, the number of boys and girls with thyroid cancer were similar in Bryansk and Kaluga regions; in all other regions, the number of girls was much greater than the number of boys.

The distribution of thyroid radiation doses was highly skewed for all subjects (Fig. 1). The median radiation dose from all radiation types was estimated to be 365 mGy (95% intercentile ranges = 7 to 3109 mGy) in Belarus and 40 mGy (95% intercentile ranges = 3 to 1691 mGy) in the Russian Federation. The highest doses were about 10.2 Gy in Belarus and 5.3 Gy in the Russian Federation. Most of the dose was from ¹³¹I. The median dose from ¹³¹I in Belarus was 356 mGy and in the Russian Federation was 39 mGy (maximum dose from ¹³¹I was 9.5 and 5.3 Gy, respectively). The median estimated dose from short-lived iodine and tellurium isotopes was 1.2 mGy (1.6 in Belarus and 0.1 mGy in the Russian Federation) and the highest dose was 534 mGy (95% intercentile range in Belarus = 0.1 to 32 mGy, and 95% intercentile range in Russia = 0 to 9 mGy). Individual estimated thyroid doses from external exposure ranged from

close to 0 to 98 mGy (median = 2.2 mGy, 95% intercentile range = 0.2 to 24 mGy) and from internal exposure from cesium ingestion up to 42 mGy (median = 1 mGy, 95% intercentile range = 0.1 to 7 mGy). The total dose to the thyroid decreased with increasing age at exposure: the median doses were 400, 365, 124, and 43 mGy, respectively, in the age groups of younger than 2, 2–4, 5–9, and 10–14 years.

Figure 2 shows the variation in odds ratios as a function of dose level. A strong dose–response relationship was observed ($P < .001$); the odds ratio appeared to increase linearly with dose up to 1.5–2 Gy and then to plateau at higher doses. Statistically significant increases in risk were associated with all radiation dose categories greater than 0.2 Gy.

The statistical models that best describe these data are the linear excess relative risk model up to 1 Gy, the linear excess relative risk model up to 2 Gy, and the linear-quadratic excess relative risk model over the entire dose range. As shown in Fig. 2, however, the latter model tended to underestimate risks up to 2 Gy. The estimated odds ratios of thyroid cancer at 1 Gy calculated with the best fitting log-linear and excess relative risk models in different dose ranges were similar, however (Table 2). Estimates derived from analyses restricted to doses of less than 1 Gy were slightly higher than, but statistically compatible with, those derived from analyses carried out on a wider dose range. Because of the absence of a consistent pattern in risk at greater doses, further analyses were restricted to subjects who received doses of less than 2 Gy.

The odds ratios at 1 Gy estimated for total thyroid dose, as well as dose from ¹³¹I alone and in combination with short-lived isotopes of iodine and tellurium, are shown in Table 3. These odds ratios are very similar, indicating that the risk is related mainly to ¹³¹I exposure. Adjusting for doses from longer-lived radionuclides and external radiation had little effect on the risk estimate.

We investigated the possible modifying effect of the stable iodine deficiency on the radiation-related thyroid cancer risk based on estimated average level of soil iodine in the areas in which study participants resided at the time of the accident. We found a statistically significant interaction between radiation dose to the thyroid and iodine level in soil on the risk of thyroid cancer (χ^2 for interaction = 25.0, 2 degrees of freedom; $P < .001$). There was no statistically significant difference in radiation risk estimates between settlements in the highest and middle tertiles of soil iodine. However, for subjects living in settlements in the lowest tertile of soil iodine, the odds of developing thyroid cancer after a 1-Gy exposure was 3.2 (95% CI = 1.9 to 5.5) times higher than that for subjects living in areas of greater soil iodine.

Table 1. Characteristics and distribution of study subjects

Characteristic	Belarus		Russian Federation				Total
	Gomel	Mogilev	Bryansk	Kaluga	Orel	Tula	
Case patients, No.	188	32	11	10	18	17	276
Region control subjects, No.	877	167	49	39	87	81	1300
Age at exposure*, No.							
<2 y	69	10	4	1	1	2	87
2–4 y	59	8	3	2	3	5	80
5–9 y	45	3	2	4	6	6	66
10–14 y	15	11	2	3	8	4	43
Sex*, No.							
Boys	74	7	6	4	6	5	102
Girls	114	25	5	6	12	12	174

*Distribution shown is for case patients only. Because control subjects were matched to case patients by age at exposure and sex, the proportion of control subjects and case patients in the different age and sex categories are identical.

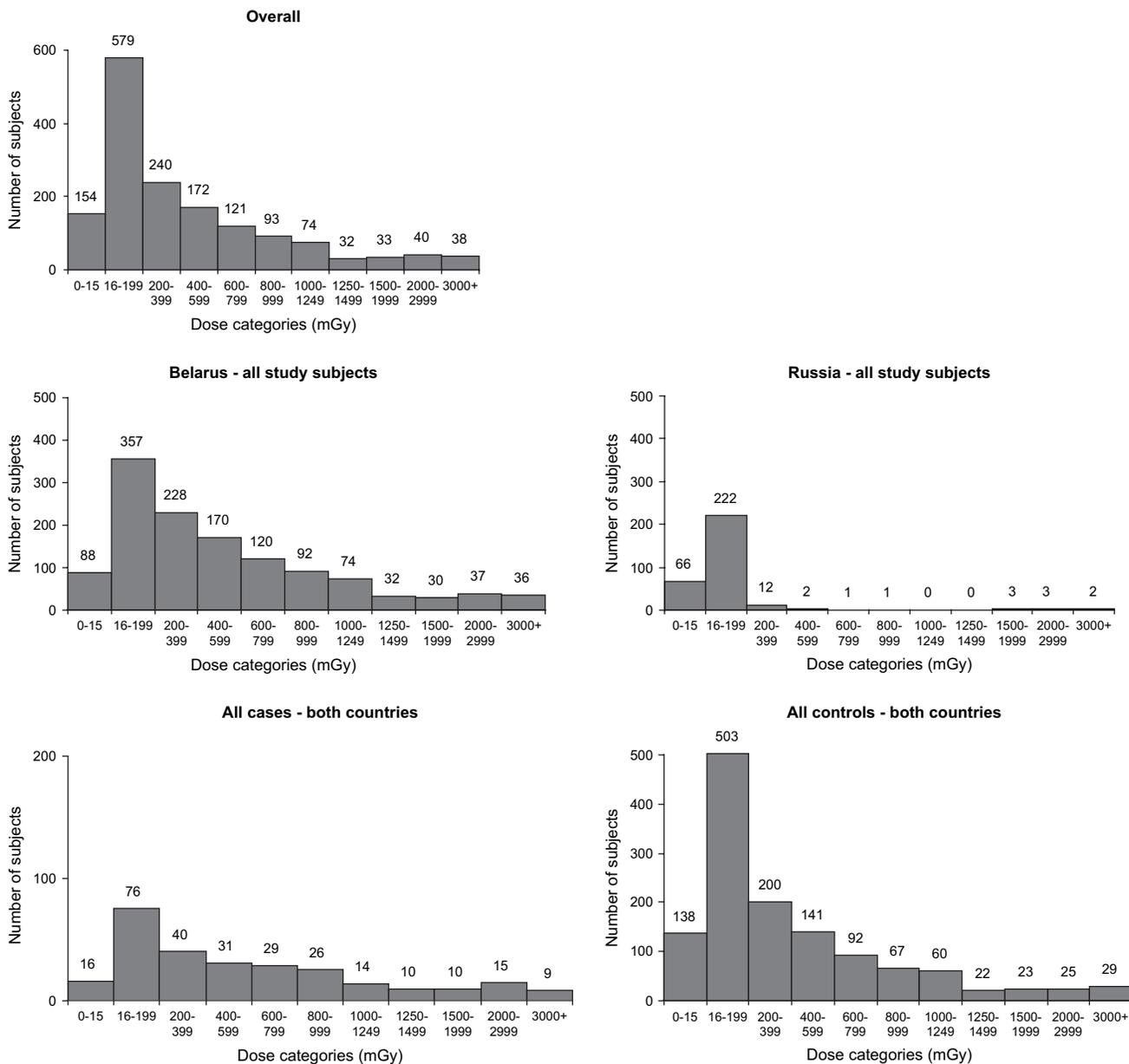


Fig. 1. Total thyroid dose among study subjects (overall, by country, and by case-control status). The lowest, reference category represents the lowest decile of the dose distribution; other dose cutpoints were chosen to be equally spaced in different dose ranges (every 200 mSv up to 1 Sv, every 250 mSv up to 1.5 Sv, and every 1000 mSv above). Intervals are larger in the higher dose categories because of the small number of subjects.

We also investigated the possible modifying effect of the stable iodine consumption on radiation-related thyroid cancer risk based on information collected on the consumption of potassium iodide as antistrumin, a preparation that was used in the former Soviet Union for goiter prophylaxis and that was distributed, mainly in Belarus, to children evacuated after the Chernobyl accident. The usual doses for goiter prophylaxis were as follows: 0.5 mg every 15 days for children aged 1–3 years, 0.5 mg weekly for children aged 3–7 years, and 1 mg weekly for children older than 7 years (33). Consumption of potassium iodide appeared to be associated with a statistically significantly reduced risk of radiation related thyroid cancer (χ^2 for interaction = 5.16, 1 degree of freedom; $P = .02$). The odds of developing thyroid cancer after a 1-Gy exposure in subjects who consumed potassium iodide was about 3 times less (0.34, 95% CI = 0.1 to 0.9) than in those who did not.

The effects of these variables were similar when both were included in the model: Consumption of potassium iodide was again associated with a threefold reduction (OR = 0.31, 95% CI = 0.1 to 0.9) in risk of thyroid cancer at 1 Gy, compared with no consumption. Residence in the areas of lowest tertile of soil iodine content was associated with a threefold increase (OR = 3.1, 95% CI = 1.7 to 5.4) in thyroid cancer risk at 1 Gy, compared with residence in areas of higher soil iodine content (highest and middle tertiles). Both variables appeared to act independently (P for interaction = .99). Table 4 shows the resulting estimated odds ratios at 1 Gy, cross-classified by potassium iodide consumption status and soil iodine. As shown, consumption of potassium iodide reduced the odds ratio at 1 Gy from 3.5 to 1.1 in areas of higher iodine soil content and from 10.8 to 3.3 in areas of low iodine soil content.

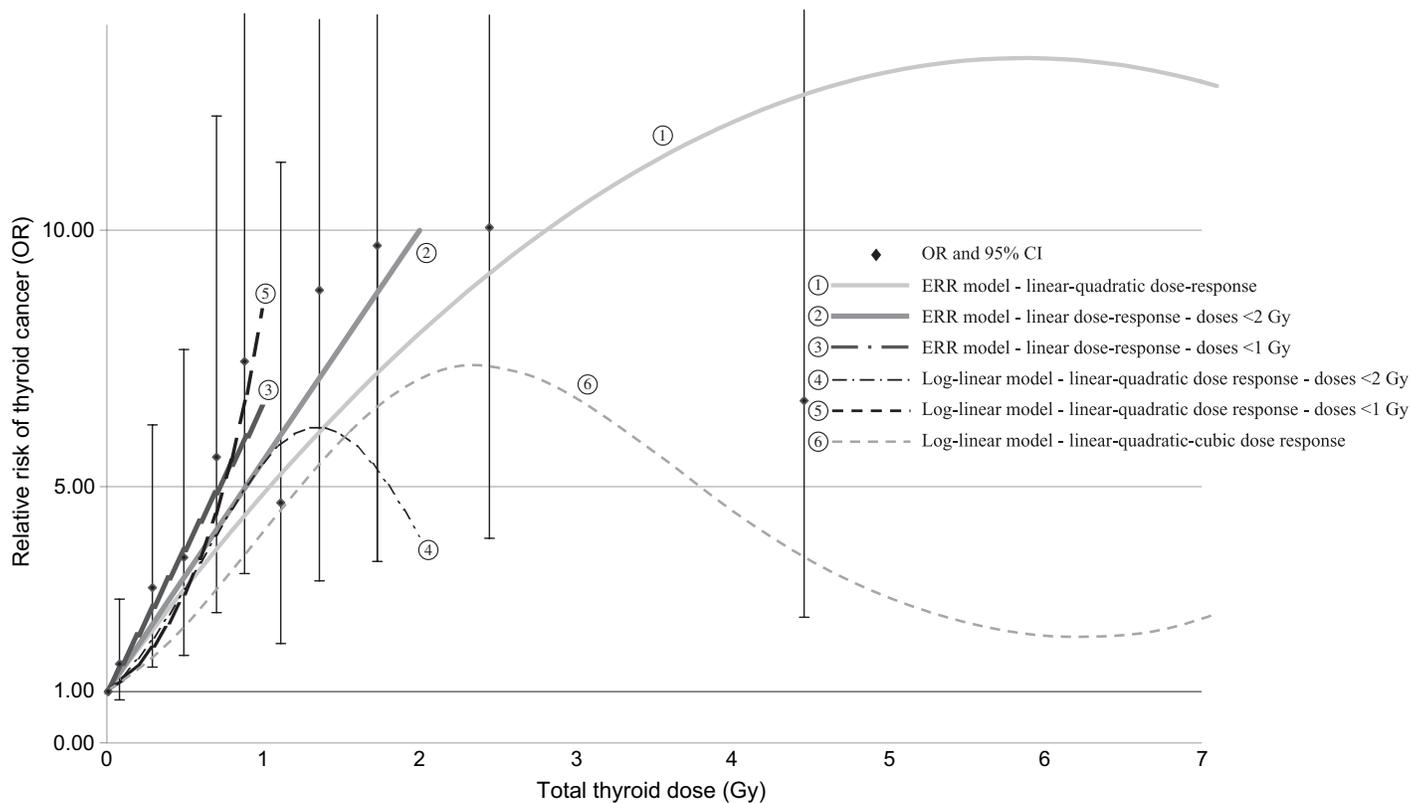


Fig. 2. Comparison of odds ratios (ORs) predicted by the best-fitting risk models with categorical odds ratios estimated in 11 dose categories. Results from the following models are presented: the excess relative risk (ERR) model—linear-quadratic (L-Q) dose-response model over the entire dose range (**curve 1**); the ERR model—linear dose-response model for doses of <2 Gy (**curve 2**); the ERR

model—linear dose-response model for doses of <1 Gy (**curve 3**); the log-linear model—linear-quadratic dose-response model for doses of <2 Gy (**curve 4**); the log-linear model—linear-quadratic dose-response model for doses of <1 Gy (**curve 5**); the log-linear model—linear-quadratic-cubic dose-response model over the entire dose range (**curve 6**). **Error bars** = 95% confidence intervals.

Similar modifying effects of soil iodine level and potassium iodide consumption were seen (data not shown) when analyses included all subjects, regardless of their radiation dose level, and when analyses were restricted to subjects who received doses of less than 1 Gy. Among subjects who received less than 1 Gy, however, the interactions between radiation dose and potassium iodide and between radiation dose and soil iodine levels were no longer statistically significant. The modifying effects of soil iodine level and of potassium iodide consumption on the risk of radiation-related thyroid cancer were also similar when an excess relative risk model was used. The radiation-related risk of thyroid cancer was not statistically significantly different between males and females (OR at 1 Gy, compared with no exposure, in

girls = 5.3, 95% CI = 2.8 to 10.1; OR at 1 Gy, compared with no exposure, in boys = 5.7, 95% CI = 2.8 to 11.8; $P = .86$), by country (OR at 1 Gy in Belarus = 5.1, 95% CI = 2.9 to 8.9; and OR at 1 Gy in the Russian Federation = 31.5, 95% CI = 1.3 to 761; $P = .11$), by region (P for heterogeneity = .20), or by time since the accident ($P = .75$).

DISCUSSION

A very strong dose-response relationship was observed in this study between radiation dose to the thyroid received in childhood and the risk of a subsequent thyroid cancer. This relation appears to be mainly related to exposure to ^{131}I . The estimated odds ratio of thyroid cancer in children who received a thyroid dose of 1 Gy compared with unexposed children varied from 5.5 to 8.4, depending on the model used (Table 2). This estimate is slightly lower than, but similar to, that (i.e., OR at 1 Gy = 8.7, 95% CI = 3.1 to 29.7) observed in studies of children exposed to external radiation (3).

We provide evidence of nonlinearity in the relationship between radiation dose and the risk of thyroid cancer for doses greater than 1.5–2 Gy. Although flattening of the dose-response relationship has been observed in other populations (e.g., atomic bomb survivors and patients treated with radiotherapy) and attributed mainly to cell killing, doses in the range of 1–3 Gy are not thought to be sufficiently high to kill a substantial number of cells. Other explanations of the nonlinearity are therefore needed. Errors in the dose estimates or possible recall bias among case

Table 2. Risk of thyroid cancer at a 1-Gy radiation dose, from different models*

Model	OR at 1 Gy (95% CI)
Logistic regression—excess relative model	
L-Q* model over the entire dose range	4.9 (2.2 to 7.5)
Linear model up to 2 Gy	5.5 (2.2 to 8.8)
Linear model up to 1.5 Gy	5.8 (2.1 to 9.4)
Linear model up to 1 Gy	6.6 (2.0 to 11.1)
Logistic regression—log-linear risk model	
L-Q model up to 2 Gy	5.5 (3.1 to 9.5)
L-Q model up to 1.5 Gy	5.9 (3.3 to 10.5)
Linear model up to 1 Gy	8.4 (4.1 to 17.3)

*L-Q = linear-quadratic; OR = odds ratio at 1 Gy compared with no exposure; CI = confidence interval.

Table 3. Risk of thyroid cancer at a 1-Gy radiation dose by radiation type (analyses restricted to subjects with radiation doses to the thyroid of <2 Gy)

Radiation type	OR at 1 Gy (95% CI)*
Total dose	5.5 (2.2 to 8.8)
¹³¹ I	5.2 (2.2 to 8.2)
All iodine isotopes	5.2 (2.2 to 8.3)
All iodine isotopes, adjusting for external and long-lived nuclides	5.9 (1.6 to 10.2)

*OR = odds ratio at 1 Gy compared with no exposure; CI = confidence interval.

patients who may have overestimated their milk consumption (and for whom dose would, therefore, be overestimated) could account for this result. The relatively small number of subjects in the highest dose categories may also affect the apparent dose-response relationship in this range (24 case patients received doses of >2 Gy, but only nine of them received doses of >3 Gy). The possibility of differential levels of iodine supplementation (through the use of iodized salt and/or distribution of iodine supplements) between territories with different contamination levels also may have contributed to this result.

Our results also indicate that iodine deficiency increases the risk of ¹³¹I-related thyroid cancer. Because no reliable population indicators of iodine-deficiency status at the time of the Chernobyl accident were available for all of the areas under study, soil iodine concentration in settlements of residence at the time of the Chernobyl accident was used as a surrogate marker for iodine status of study subjects. It is noted that measurements of thyroid volume and urinary iodine levels also provide an indication of the stable iodine status of a population. Measurements of thyroid volume were in fact carried out in control subjects, and measurements of urinary iodine in all study subjects, at the time of interview in this study. However, although these measurements provide information on recent iodine status of the subjects, they do not necessarily reflect iodine status at the time of the accident because changes in dietary habits, in the availability of iodized food, and in commercial food distribution circuits that have occurred since the accident are likely to have modified the iodine status of study subjects. Population studies of iodine deficiency have been carried out in the years after the Chernobyl accident by several national and international organizations (19,34). Although they provide important information, they do not cover all of the territories included in this study. Data from these studies are being sought to validate the classification of iodine status based on soil iodine content used in this study. Nevertheless, any error in iodine status classification is likely to be random and, therefore, would tend to bias estimates toward the null. Thus, it is unlikely that the observed effect of iodine deficiency is artificial. We note, moreover, that our findings support the results of a recent ecologic study carried out in Bryansk region of the Russian Federation (19), in which the excess relative risk per Gy from ¹³¹I in areas of severe iodine deficiency was found to be approximately twice that in areas with normal iodine intake.

Our findings also indicate that use of a dietary iodine supplement containing potassium iodide can reduce the risk of ¹³¹I-related thyroid cancer. Unlike Poland, where the rapid, countrywide distribution of potassium iodide was organized to reduce the dose from iodine isotopes to the thyroid (35), no widespread systematic prophylaxis occurred in the most contaminated areas of Belarus and the Russian Federation immediately after the

Table 4. Estimated risk of developing thyroid cancer after a radiation dose of 1 Gy, by level of soil iodine in the settlement of residence at the time of the accident and by potassium iodide (i.e., antistrumin) consumption status (analyses restricted to subjects with radiation doses to the thyroid of less than 2 Gy)*

Consumption of potassium iodide	OR at 1 Gy (95% CI)	
	Highest two tertiles of soil iodine	Lowest tertile of soil iodine
No	3.5 (1.8 to 7.0)	10.8 (5.6 to 20.8)
Yes	1.1 (0.3 to 3.6)	3.3 (1.0 to 10.6)

*Levels of iodine in soil in settlement of residence at time of accident were divided into tertiles. OR = odds ratio at 1 Gy compared with no exposure; CI = confidence interval.

accident (5). Several different measures were, however, taken months and years after the Chernobyl accident to provide stable iodine to children in exposed regions, including the distribution of potassium iodide as antistrumin, multivitamins containing iodine, and iodized salt. More detailed analyses are also under way to evaluate the effect of these measures, in particular those of the timing, dose, and length of administration of iodine-containing supplements on the risk of ¹³¹I-related thyroid cancer. Potassium iodide (which was administered to evacuated children in the days after the accident and continued to be given to some school children in the following years) alone, however, appears to reduce the risk of ¹³¹I-related thyroid cancer by a factor of approximately 3.

There are two mechanisms through which dietary iodine supplementation could be related to the incidence of thyroid cancer after exposure to radioiodines. First, stable iodine given shortly before, during, or immediately after exposure reduces the uptake of radioactive iodine by the thyroid and, therefore, reduces the radiation dose to the thyroid (35,36). However, as indicated above, no widespread systematic iodine administration occurred in the regions under study. Second, long-term dietary iodine supplementation reduces the size of the thyroid in iodine-deficient areas, and a reduction in thyroid growth, particularly in children, would be expected to be associated with reduced incidence of cancer.

We found that iodine deficiency and consumption of potassium iodide appeared to act independently as modifiers of radiation-related thyroid cancer risk. This result is somewhat surprising because we expected that iodine supplementation in iodine-sufficient areas would have little or no additional benefit. Most of the areas studied are mildly to moderately deficient in soil iodine, and so the comparison group (highest two tertiles of soil iodine) is not really iodine sufficient. Furthermore, the number of subjects who lived in the most iodine-deficient areas and consumed potassium iodide is small ($n = 12$ subjects). Consequently, this study did not have the statistical power to detect a difference associated with potassium iodide consumption among residents of areas with different iodine soil contents.

Uncertainties in thyroid dose estimates and possible biases resulting from selection, recall, confounding, or effect modifiers need to be considered carefully when interpreting the results of this study. The main sources of dosimetric uncertainty are as follows: 1) variability of model parameters related to the transfer of ¹³¹I from deposition on the ground to the human thyroid; 2) uncertainties in information on individual lifestyle and dietary habits obtained by questionnaire; and 3) uncertainties in the original direct thyroid measurements made some days or weeks after the

accident and in the dose estimates derived from these measurements. These uncertainties are currently being estimated, and their impact on the risk estimates will be reported elsewhere.

The low participation rate among control subjects, particularly in the Russian Federation, is of concern because it may have introduced a selection bias. Although it is not possible to estimate individual doses for nonrespondents because information on their dietary intake is not available, an estimation of the average age-specific “settlement doses” is possible, using age and place of residence at the time of the accident and standard assumptions about food consumption in different age groups. We compared the distribution of these settlement doses among participating control subjects and nonrespondent controls; the distribution was similar, with the median dose among nonrespondents slightly lower (198 mGy) than among participating control subjects (245 mGy). Thus, although a small selection bias is possible, its most likely effect would have been to artificially increase the dose among control subjects, and so bias the risk estimates downward.

Interviews were carried out with case patients and control subjects (or their mothers) years after the Chernobyl accident, and the possibility that recall bias may have played a role in the magnitude of the observed risk estimate cannot be excluded. Although a few study subjects have had direct thyroid measurements and were interviewed about their dietary habits shortly after the accident, it has not been logistically possible in this study to obtain the questionnaire data for intercomparison. A comparison was made, however, of the estimated doses for these subjects. For case patients, the dose derived from model estimates tended to be somewhat lower than the dose derived from direct thyroid measurements, and hence a recall bias related to case patients systematically overestimating their dietary habits appears unlikely.

This study, to our knowledge, is the largest population-based case-control study of thyroid cancer in young people. The very large increase in the risk of thyroid cancer after the Chernobyl accident has provided a unique opportunity to 1) estimate the magnitude of the thyroid cancer risk associated with exposure to ^{131}I in childhood and 2) evaluate the modifying effect of stable iodine on the risk of radiation-related thyroid cancer. The risk from ^{131}I appears to be similar to that observed after external radiation exposures and to that reported by Davis et al. (16) in a case-control study (including 26 case patients) in the Bryansk region of the Russian Federation.

Both iodine deficiency and iodine supplementation appear to be important and independent modifiers of the risk of thyroid cancer after exposure to ^{131}I in childhood. This result has important public health implications in the case of exposure to radioactive iodines in childhood that may occur after radiation accidents or during medical diagnostic and therapeutic procedures. Indeed, stable iodine supplementation in iodine-deficient populations may reduce the subsequent risk of radiation-related thyroid cancer in these situations.

REFERENCES

- (1) United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Sources and effects of ionizing radiation. New York (NY): United Nations; 1994.
- (2) Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiat Res* 1992;131:98–111.
- (3) 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.
- (4) Ron E. Cancer risks from medical radiation. *Health Phys* 2003;85:47–59.
- (5) United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Sources and effects of ionizing radiation—Vol. II Effects. New York (NY): United Nations; 2000.
- (6) Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl. *Nature* 1992;359:21.
- (7) Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D. Thyroid cancer after Chernobyl. *Nature* 1992;359:21–2.
- (8) Tronko ND, Epstein Y, Oleinik V, et al. Thyroid gland in children after the Chernobyl accident (yesterday and today). In: Nagataki S, ed. Nagasaki Symposium on Chernobyl: Update and Future. Elsevier Science, B.V. Amsterdam (The Netherlands); 1994:3–46.
- (9) Tsyb AF, Parshkov EM, Ivanov VK, Stepanenko VF, Matveenko EG, Skoropad YD. Disease indices of thyroid and their dose dependence in children and adolescents affected as a result of the Chernobyl accident. In: Nagataki S, ed. Nagasaki Symposium on Chernobyl: Update and Future. Elsevier Science, B.V. Amsterdam (The Netherlands); 1994:9–19.
- (10) Stsjazhko VA, Tsyb AF, Tronko ND, Souchkevitch G, Baverstock KF. Childhood thyroid cancer since accident at Chernobyl. *BMJ* 1995;310:108.
- (11) Abelin T, Averkin JI, Egger M, Egloff B, Furmanchuk AW, Gurtner F, et al. Thyroid cancer in Belarus post-Chernobyl: improved detection or increased incidence? *Soz Pravitivmed* 1994;39:189–97.
- (12) Likhtarev IA, Sobolev BG, Kairo IA, Tronko ND, Bogdanova TI, Oleinic VA, et al. Thyroid cancer in the Ukraine. *Nature* 1995;375:365.
- (13) 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.
- (14) 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.
- (15) Shibata Y, Yamashita S, Masyakin VB, Panasyuk GD, Nagataki S. 15 years after Chernobyl: new evidence of thyroid cancer. *Lancet* 2001;358:1965–6.
- (16) Davis S, Stepanenko V, Rivkind N, Kopecky KJ, Voilleque P, Shakhhtarin 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) Yamashita S, Shibata Y, eds. Chernobyl: a decade. Elsevier, Amsterdam (The Netherlands); 1997.
- (18) Cardis E, Amoros E, Kesminiene A. Observed and predicted thyroid cancer incidence following the Chernobyl accident—evidence for factors influencing susceptibility to radiation induced thyroid cancer. In: Thomas G, Karaoglou A Williams, ed. World Scientific Publishing, Singapore; 1999: p. 395–404.
- (19) Shakhhtarin VV, Tsyb AF, Stepanenko VF, Orlov MY, Kopecky KJ, Davis S. Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents in the Bryansk region of Russia following the Chernobyl power station accident. *Int J Epidemiol* 2003;32:584–91.
- (20) Astakhova LN, Cardis E, Shafarenko LV, Gorobets LN, Nalivko SA, Baverstock KF, et al. Additional documentation of thyroid cancer cases (Belarus): report of a survey, International Thyroid Project. 1995:95/001; International Agency for Research on Cancer, Lyon (France); 1995.
- (21) Cardis E, Okeanov AE. What’s Feasible and Desirable in the Epidemiologic Follow-Up of Chernobyl. 1996; First International Conference of the European Commission, Belarus, the Russian Federation and the Ukraine on the radiological consequences of the Chernobyl accident (Minsk, Belarus, 18–22 March 1996):835–50.
- (22) Gavrilin YI, Khrouch VT, Shinkarev SM, Krysenko NA, Skryabin AM, Bouville A, et al. Chernobyl accident: reconstruction of thyroid dose for inhabitants of the Republic of Belarus. *Health Phys* 1999;76:105–19.
- (23) Stepanenko VF, Voilleque PG, Gavrilin YI, Khrouch VT, Shinkarev SM, Orlov MY, et al. Estimating individual thyroid doses for a case-control study of childhood thyroid cancer in Bryansk Oblast, Russia. *Radiat Prot Dosimetry* 2004;108:143–60.
- (24) Gavrilin YI, Khrouch VT. Validation of semi-empirical model of the thyroid gland internal irradiation dose formation and selection of areas (x) at estimating thyroid doses for adults of rural regions [in Russian]. *Bulletin of Public Information Centre on Atomic Energy*, 1999;11:33–41 and 54.

- (25) Lozovsky LN. Iodine on soils of Belarussia [in Russian]. 1971; Doctoral Thesis. Moscow, MSU, 223.
- (26) Vinogradov AP. Geochemical situation in the areas of thyroid goiter [in Russian]. *Izvestia Akademii nauk SSSR, ser geogr i geofiz* 1946;10:341–56.
- (27) Kovalsky, VV. Biological role of iodine [in Russian]. In: *Biological role of iodine*. Eds. Kovalsky V.V., Blokhina R.I., Katalymov M.V., Kolomijtseva M.G., Litvin I.I., Rish M.A., Veslukhin R.V. Moscow, Kolos, 1972: 32.
- (28) BEIR V. Committee on the Biological Effects of Ionizing Radiation. The effects on population of exposure to low levels of ionizing radiation. National Academy of Sciences, Washington (DC); 1990.
- (29) Direct estimates of cancer mortality due to low doses of ionising radiation: an international study. IARC Study Group on Cancer Risk among Nuclear Industry Workers. *Lancet* 1994;344:1039–43.
- (30) Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat Res* 2003;160:381–407.
- (31) EPICURE (Computer Package). Hirossoft International; 2002.
- (32) Parkin DM, Kramarova E, Draper GJ, Masuyer E, Michaelis J, Neglia J, et al, eds. *International Incidence of Childhood Cancer, Vol. II*. IARC Scientific Publication No. 144, International Agency for Research on Cancer, Lyon (France); 1998.
- (33) Astakhova LN, ed. *Children's thyroid gland: consequences of the Chernobyl accident* [in Russian]. Ministry of Public Health of Belarus, Minsk; 1996.
- (34) Gembicki M, Stozharov AN, Arinchin AN, Moschik KV, Petrenko S, Khmara IM, et al. Iodine deficiency in Belarusian children as a possible factor stimulating the irradiation of the thyroid gland during the Chernobyl catastrophe. *Environ Health Perspect* 1997;105 Suppl 6:1487–90.
- (35) Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. *Am J Med* 1993;94:524–32.
- (36) Zanzonico PB, Becker D. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by ¹³¹I from radioactive fallout. *Health Phys* 2000;78:660–7.

NOTES

This study was made possible by contracts FI4C-CT96–0014 and ERBIC15-CT96–0308 from the European Union (Nuclear Fission Safety and INCO-Copernicus Programmes) and a contract from the Sasakawa Memorial Health Foundation (Chernobyl Sasakawa Health and Medical Cooperation Project). The Study Group is grateful to the Ministries of Public Health and the Regional Departments of Health in Belarus and the Russian Federation for support of the study, to the former head doctor of Gomel Specialised Dispensary (Dr. V. Vorobey) and the head doctor of Mogilev Diagnostic Centre (Dr. T. Krupnik) for their assistance and that of their staff in organizing interviews and clinical examinations of study subjects, and the ZAGS and address bureaus in Gomel and Mogilev regions for assistance in selecting and tracing subjects.

We especially thank all of the study subjects who agreed to participate in the study and are grateful to the study interviewers. We also gratefully acknowledge the contributions of Drs. A. Ye. Okeanov, N. Bazoulko (Minsk, Belarus), A. Konogorov (Canada), and E. Amoros (France) who participated in the feasibility study and took part in the design and start of implementation of this study; Dr. V. Pitkevitch (deceased), who assisted in the development of the dosimetry questionnaire; Dr. V. Stepanenko (MRRC of RAMS, Obninsk, the Russian Federation) for helpful discussions concerning the content of the dosimetry questionnaire; Drs. A. Bratilova (St. Petersburg, the Russian Federation) and S. Shinkarev (Moscow, the Russian Federation), who contributed to the development and testing of the dose reconstruction method; Drs. Keith Baverstock (University of Kuopio, Finland) and Silvia Franceschi (IARC, Lyon) for useful discussion and comments either in the design and/or conduct of the study; Mrs. N. Krutovskikh and H. Tardy (Lyon, France) for assistance with the verification of data from the questionnaires; and Ms. L. Richardson and Dr. I. Deltour for useful discussions about the results and their presentation.

Manuscript received September 24, 2004; revised January 19, 2005; accepted April 5, 2005.