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

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Background	Little is known about the joint effect of iodine deficiency and radiation exposure on the risk of thyroid cancer. No epidemiological studies have been published assessing the modifying effect of iodine deficiency on radiation-induced thyroid cancer following the Chernobyl accident.
Methods	A population sample of 3070 individuals (2590 ages 6–18, and 480 adults) from 75 settlements in the most highly contaminated regions of the Bryansk Oblast of Russia was identified and sampled for urinary iodine measurements in 1996, and iodine deficiency in each geopolitical unit (raion) was estimated. All cases of thyroid cancer were identified in those born 1968–1986 who were resident in the study area in May–June 1986 (34 histologically confirmed cases). The risk of thyroid cancer was examined in relation to population estimates of thyroid radiation dose and urinary iodine excretion level.
Results	The excess relative risk (ERR) of thyroid cancer was significantly associated with increasing thyroid radiation dose, and was inversely associated with urinary iodine excretion levels. There was a joint effect of radiation exposure and iodine deficiency. At 1 gray (Gy), the ERR in territories with severe iodine deficiency was approximately two times that in areas of normal iodine intake.
Conclusions	These findings suggest that elimination of iodine deficiency in areas affected by Chernobyl may be important in reducing the effects of radiation exposure on the thyroid. If confirmed by studies based on individuals, they may have implications for the use of stable iodine in the case of population exposure to radioactive iodine.
Keywords	Thyroid cancer, radiation, radioactive iodine, iodine deficiency, Chernobyl

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It is well established that exposure to ionizing radiation from external sources can result in the development of thyroid cancer.[1] Perhaps most informative are results from a pooled analysis of seven studies of external irradiation to the thyroid,[2] based on approximately 700 cases of thyroid cancer and nearly three million person-years of follow-up. These analyses revealed a significant linear dose-response relationship over a relatively broad range of doses, and that excess risk was highest from 15 to 29 years after exposure in childhood. Further, there was strong evidence of a decrease in risk with increasing age at

exposure, and some evidence that exposures received in two or more fractions were less carcinogenic than acute exposures. The carcinogenic effects of Iodine 131 (^{131}I) are much less well understood. There is little evidence from epidemiological studies of an increased risk of thyroid cancer following such exposures, although there have been relatively few studies of ^{131}I exposure, and most studies have focused on exposure in adults or in those receiving ^{131}I for therapeutic reasons for thyroid conditions such as Basedow's disease.[3] In recent years there has been increasing evidence to suggest an increased risk of thyroid cancer among people who were exposed as children and adolescents to radiation following the Chernobyl Power Station accident on 26 April 1986.[4–12]

In contrast to most other circumstances in which the effect of radiation exposure on the development of thyroid cancer has been investigated, almost all of the territories contaminated by radiation from Chernobyl in Belarus, Russia, and Ukraine are goitre endemic areas.[13,14] Although iodine deficiency has been found to be associated with the development of thyroid abnormalities, including thyroid cancer,[14,15] there is relatively little information available regarding the joint effect of iodine deficiency and radiation exposure on the risk of developing thyroid cancer. Iodine deficiency would likely affect the dose received by the thyroid gland at the time of exposure, as well as thyroid function after the radiation exposure. It has been suggested that iodine prophylaxis undertaken immediately after a radiological event is necessary in order to reduce accumulated radiation dose,[16] and others have suggested that such iodine prophylaxis can be of long-term benefit.[17,18] Although there has been some attention given to the possible influence of iodine deficiency on the risk of thyroid cancer following the Chernobyl accident,[19,20] no epidemiological studies designed to directly assess the potential modifying effect of iodine deficiency on radiation-induced thyroid cancer have been reported to date. The primary objective of the present study was to investigate the effect of iodine deficiency on the development of thyroid cancer in children and adolescents who were exposed to radioactive fallout as a result of the Chernobyl accident.

Materials and Methods

A territory of approximately 11 500 km^2 in the southwest portion of the Bryansk Oblast of the Russian Federation, defined by the ten administrative units (raions) most heavily contaminated by radioactive fallout from the Chernobyl accident, was chosen for study (Figure 1). These raions were selected because they encompass the area where people were most likely to have received the highest radiation exposures from Chernobyl, and because they are characterized by a relatively broad range and non-uniform pattern of radioactive contamination. The seven most highly contaminated raions, with Cesium 137 (^{137}Cs) contamination levels ranging from 1 to >40 Curies per square kilometre (Ci/km^2),[21,22] include Gordeevsky, Zlynkovsky, Klintsovsky, Klimovsky, Krasnogorsky, Novozybkovsky, and Starodubsky. The three relatively uncontaminated raions, with ^{137}Cs contamination levels under 1 Ci/km^2, include Surazhsky, Mglinsky, and Unechsky. In addition, there is a relatively large population (approximately 250 000) living in this area and information was available regarding the prevalence of endemic goitre. It is important to note, however, that knowledge of neither the distribution of iodine deficiency nor the prevalence of endemic goitre influenced the selection of the 10-raion study area. At the time the study area was defined, no urinary iodine concentration measurements had been made, and there was only limited information regarding the prevalence of endemic goitre in children and adolescents from some of the settlements in the contaminated raions. Such information was not complete, nor was it available from other raions that were less heavily contaminated. The operational details have been reported elsewhere,[23] but can be summarized as follows.

Within the study area, there were 428 settlements. Prior to selecting specific settlements for study, it was estimated that a total of 75 settlements would provide a sufficient number of people to characterize iodine sufficiency in the region, and would also be within practical and resource constraints. At least five settlements, including the raion centre, were selected for each raion. The choice of settlements other than the raion center was made at random. A settlement was eligible for inclusion in the study only if iodine prophylaxis had not been conducted in the settlement within the last year.

For each settlement, between 30 and 50 individuals were selected and invited to participate in the study. In cities and settlements with schools, study personnel identified students in three age groups (6–9, 10–14, and 15–17 years) and selected a sample of not less than 30 students such that the proportion in each age group was comparable to the distribution of the three age groups in that settlement or city. In settlements without a school, individuals were identified through the local medical ambulance station and included a wider range of age. Individuals who had taken thyroid medications or any iodine-containing medication within the last 3 months were excluded from the study. A total of 3070 individuals from 75 settlements were selected for inclusion (2590 aged 6–18, and 480 adults). This sample represents approximately 3.2% of the total number of children aged 6–18 years living in the 10-raion study area at the time. Virtually all those invited agreed to participate. Such a high degree of participation reflects in large part the fact that the research was introduced and carried out by local medical personnel who are well known and respected in the community, as well as a high degree of interest in personal health, and the fact that participation was simple and would provide useful information to the participant.

A morning sample of urine was collected from each individual in 2-ml plastic tubes and kept at –20°C until measurement. The degree and extent of iodine deficiency in each raion was estimated on the basis of these individual measurements of urinary iodine, performed in 1996 according to the cerium arsenate method.[24]

Based on the individual measurements in a settlement, the median urinary iodine value was determined for each settlement and used to divide the study area into four zones as follows: ≥10, 7.5–9.99, 5.0–7.49, and <5.0 µg/dl (Figure 2).

Population estimates were obtained from the Russian National Census of 1989 for each settlement, by age group and sex. A total of 119 785 people born between 1968 and 1986 were residing in the study area in 1986. Radiation dose to the thyroid from ^{131}I was estimated for residents of each settlement by year of birth, using semiempirical models described previously for reconstructing thyroid doses in the Russian Federation,[25] based on available results of human thyroid ^{131}I

Figure 1 Map of the Bryansk Oblast of the Russian Federation. Small subdivisions are raions. Box indicates the approximate study area

measurements. Key factors in the model include ^{137}Cs contamination levels in settlements, ^{131}I/^{137}Cs ratios in depositions within settlements, timing of the arrival of the radioactive cloud, type of fallout (wet or dry), pasture feeding patterns of dairy cattle, milk and leafy vegetable consumption, source of milk and leafy vegetables, location of food source, the use of countermeasures to reduce exposure, and an individual's age. The mean thyroid dose for those aged 6–18 was estimated for each settlement in the study area. These estimates were then averaged across settlements within each of the four zones as defined above by level of urinary iodine, taking into account the mean dose for each settlement and the number of people aged 6–18 in the settlement.

All cases of thyroid cancer that occurred among people born between 1968 and 1986 who were resident in the study area in May–June 1986 were identified from the Bryansk Oblast Oncologic Dispensary, a medical institution of the Oblast government that operates the Bryansk Oblast Cancer Registry. The registry relies on active surveillance to achieve population-based reporting and registration. All those residing in the Oblast suspected of having cancer are referred either to the Oncologic

Dispensary or another specially designated hospital. When a diagnosis of cancer is made outside of the Dispensary, the institution is required by law to submit notification to the Bryansk Oblast Cancer Registry.

A total of 34 cases of thyroid cancer were identified. The diagnosis was confirmed in 30 cases by an international panel of five experts in thyroid pathology (Dr V Troshin, Bryansk Diagnostic Center in Bryansk; Prof. E Lushnikov and Dr A Abrosimov, Medical Radiological Research Center in Obninsk; Prof. G Frank, National Hematology Center in Moscow; and Prof. D Williams, Cambridge University). An additional three cases were reviewed and confirmed by pathologists from the Moscow Oncology Research Center. One case was diagnosed at the Research Institute of Radiation Medicine in Minsk, Belarus.

The risk of thyroid cancer was examined in relation to thyroid radiation dose and urinary iodine excretion level as follows. The observed number of thyroid cancer cases (O) was determined for the residents living in each of the four geographical zones at the time of the accident. The corresponding expected numbers of thyroid cancer cases (E) were calculated using Russian national age- and sex-specific rates among people
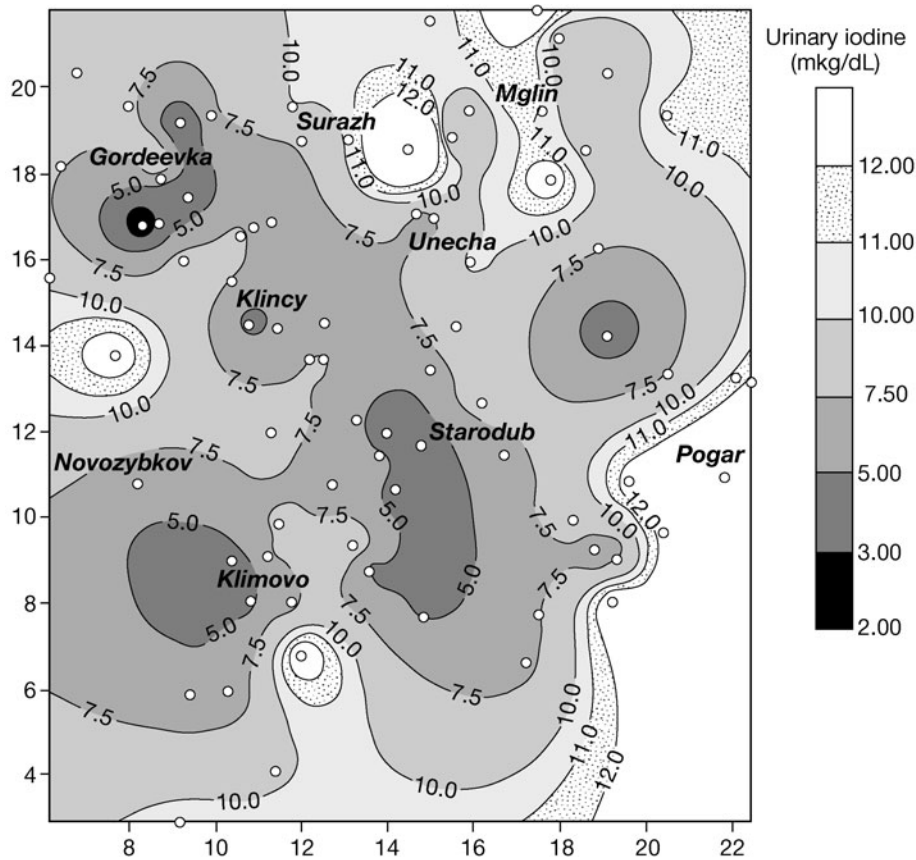
Figure 2 Median urinary iodine levels, shown as isolines, based on individual measurements in settlements (white dots)

0–29 years old during 1991, 1992, and 1993. Thus, the unit of analysis is the urinary iodine excretion zone (four). The excess relative risk (ERR) was calculated as ERR = (O – E)/E. An estimate of the radiogenic risk in each zone was then calculated as ERR_{Rad} = ERR/Dm, where Dm is the zone's estimated average thyroid dose. The linear ERR model was examined to investigate whether ERR varied according to estimated average radiation dose: $ERR(Dm) = \beta_1 \times Dm$. Note that this regression model has no intercept term, so that ERR(0) = 0. The effect of iodine deficiency on risk of radiogenic thyroid cancer was investigated using a simple linear regression model $ERR_{Rad}(I) = \alpha+ + \beta_2 \times I$, where I is the estimated average urinary iodine excretion in µg/dl. We also examined a combined model for the joint effects of iodine deficiency and radiation dose on the risk of thyroid cancer, in which the ERR is a linear function of mean dose, with the risk coefficient a linear function of the mean urinary iodine excretion level, i.e. $ERR(D_m, I) = (\alpha + \beta_2 I)D_m$, where ERR, D_m and I are the excess relative risk, mean dose, and mean urinary iodine excretion levels, respectively, and α and β_2 are the regression parameters to be estimated.

Results

Table 1 displays, for each zone defined by settlement urinary iodine values, the numbers of settlements investigated and people examined, along with the mean and median urinary iodine excretion level. At the time of the accident, 65% of the

study cohort lived in the two zones characterized by mild iodine deficiency (5.0–9.99 µg/dl). These two zones contain 49 of the 75 settlements investigated. Another 7% of the cohort lived in the zone with severe iodine deficiency (<5.0 µg/dl), within which eight settlements were investigated. The remaining 27% of the cohort lived in the iodine sufficient zone (⩾10 µg/dl; 18 settlements investigated). The town of Klimovo and the large settlement of Gordeevka are located in the area of moderate iodine deficiency. The towns of Surazh, Mglin, and Unecha are located in the area of normal iodine intake.

Of the 34 cases of thyroid cancer, 20 occurred in females and 14 in males (female/male ratio = 1.4). Papillary thyroid carcinoma accounted for more than 90% of the cases (12 of 14 (86%) in males, 19 of 20 (95%) in females). Cases ranged from 5 to 25 years of age at diagnosis (median 16 years).

Figure 3 displays the contour map of iodine excretion levels, overlaid with a map of estimated average thyroid radiation doses to adults. Adult doses are used in this instance because they are based on measurements, whereas the doses to children are adjusted estimates based on conversion factors applied to the adult doses. The primary purpose of the comparison shown in Figure 3 is to demonstrate the geographical relationship between iodine excretion levels and thyroid radiation dose. Estimates for adults are adequate for this purpose. It is clear from this map that various combinations of iodine deficiency and thyroid radiation dose occur in this geographical area. In children the relationship between thyroid dose and iodine

Table 1 Population characteristics and urinary iodine excretion in territories of different levels of iodine deficiency in southwestern raions of the Bryansk Oblast

Urinary iodine excretion category (µg/dl)	Population (1986)		No. of settlements investigated	No. people examined		Urinary iodine excretion level (µg/dl)	
	No.	%		No.	%	Mean ± SD	Median
<5.0	8325	7%	8	441	5%	3.51 ± 1.02	3.64
5.0–7.49	60 442	50	26	920	2	6.41 ± 0.90	6.42
7.5–9.99	18 178	15	23	862	5	8.56 ± 0.85	8.72
≥10.0	32 840	27	18	847	3	12.88 ± 2.53	12.94
Total	119 785	100	75	3070	3		
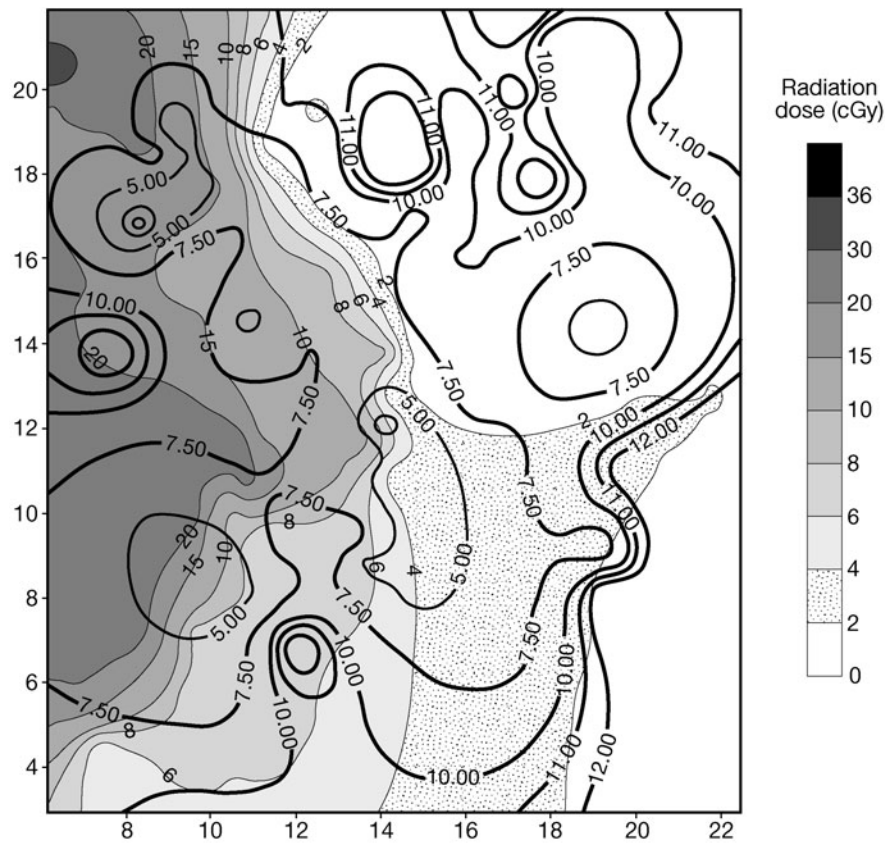
Figure 3 Estimated average radiation doses (in centigray [cGy]) to the thyroid in adults from Chernobyl radiation, and urinary iodine excretion levels (shown as isolines) in the Bryansk study area. Adult doses are displayed because they are based on measurements, whereas the doses to children are adjusted estimates based on conversion factors applied to the adult doses, and are thus preferable in demonstrating the geographical relationship between iodine excretion levels and thyroid radiation dose

deficiency may be more complicated than depicted in Figure 3 because thyroid dose to a child depends to a greater degree on age at the time of the accident. Estimated thyroid doses from radioiodines in children and adolescents residing in the areas under study varied from several centigray (cGy) to 240 cGy, with an average estimated dose of 75 cGy.

Table 2 displays the estimated collective and mean radiation dose from ^{131}I, as well as information regarding the incidence of thyroid cancer, for each of the four zones, along with the observed and expected numbers of thyroid cancer cases and

estimates of excess risk. Overall, the rate of thyroid cancer in the study area was approximately 5.5 times the rate expected on the basis of national rates, corresponding to an ERR of 4.4. The excess was highest in the territories characterized by the lowest levels of urinary iodine excretion (ERR in the two lowest iodine excretion zones = 5.9 and 6.6), and there was a clear trend of decreasing excess of thyroid cancer with increasing level of urinary iodine excretion.

Further, the radiogenic risk ERR_{Rad} decreases with increasing urinary iodine excretion level as well. In the group with

Table 2 Collective and mean thyroid radiation dose from [131]Iodine (^{131}I) and thyroid cancer incidence among people born during 1968–1986, residing in areas with different levels of iodine deficiency in the Bryansk Oblast of Russia

Urinary iodine excretion category (μg/dl)	Thyroid dose (Gy)[a]		Thyroid cancer cases					
	Collective dose	Mean dose (D_m)	Observed (O)	Expected (E)	ERR = (O − E)/E		ERR_{Rad} = ERR / D_m[b]	
					Estimate	95% CI	Estimate	95% CI
<5.0	2043	0.245	3	0.43	5.9	(0.4, 19.2)	24.1	(1.7, 78.3)
5.0–7.49	21 889	0.362	24	3.15	6.6	(3.9, 10.3)	18.3	(10.7, 28.6)
7.5–9.99	3617	0.199	4	0.95	3.2	(0.2, 9.8)	16.2	(0.8, 49.3)
≥10	1903	0.058	3	1.71	0.8	(−0.6, 4.1)	13.0	(−11.0, 71.2)
Total	29 452	0.246	34	6.24	4.4	(2.8, 6.6)	18.1	(11.3, 26.9)

[a] gray.

[b] ERR = excess relative risk, ERR_{Rad} = radiation-related ERR (per Gy).

severe iodine deficiency (<5.0 μg/dl), the radiogenic risk (ERR_{Rad}) is = 24.1/Gy, nearly twice the estimate of 13.0/Gy observed in the iodine sufficient group (≥10.0 μg/dl). In a linear regression model relating radiogenic risk to urinary iodine excretion (I), $ERR_{Rad}(I) = \alpha + \beta_2 \times I$, radiogenic risk decreased significantly with $\beta_2 = -1.14$ (95% CI: −1.58, −0.70).

The results in Table 2 also show that although mean doses vary within a relatively small range (0.058–0.362 Gy), there is a significant relationship between increasing mean radiation dose and increasing ERR. Specifically, for the linear ERR model the estimate of radiogenic risk per Gy is $\beta_1 = 19.4$/Gy (95% CI: 16.0, 22.7). Using this estimate implies that the RR is 1 + ERR(1) = 20.4 (95% CI: 17.0, 23.7) at 1 Gy, and 5.8 (95% CI: 4.9, 6.6) at the overall average dose of 0.246 Gy.

For the combined model $ERR(D_m, I) = (\alpha + \beta_2 I)D_m$, the unweighted least squares was −1.53 (95% CI −2.14, 0.93), which is significantly less than zero ($P = 0.038$). Note that this estimate of β_2 is similar to that obtained from the regression of ERR_{Rad} on urinary iodine excretion in the two-step analysis described above; its negative value again indicating that the radiation effect increased with increasing iodine deficiency (i.e. with decreasing urinary iodine excretion). The weighted least squares estimate of β_2, calculated for the combined model with weights inversely proportional to estimates of the variance of ERR, i.e. (1 + ERR)/E where E is the expected number of cases from Table 2, was similar to that above (results not shown).

Discussion

Findings of this study indicate that the development of thyroid cancer in people exposed to ^{131}I from the Chernobyl accident in childhood and adolescence may depend on both thyroid radiation dose and the level of iodine deficiency at the time of exposure. There was a trend of decreasing risk of thyroid cancer with increasing level of urinary iodine excretion, and of increasing risk of thyroid cancer with increasing mean radiation dose. Thus, the present study provides some initial evidence of a potential modifying effect of iodine deficiency on thyroid cancer risk after radiation exposure from Chernobyl.

However, it is important to recognize that the study has a number of limitations. First, it is ecologic in design, and the analysis is limited by the fact that it is based on approximations of both radiation dose and iodine deficiency. The number of study units is four, and the unit of analysis is defined by level of urinary iodine excretion in groups of individuals from 10 geographical regions (raions) representing the areas most contaminated from Chernobyl radiation. Thus, the estimates of risk in this study are not derived from individual estimates of radiation dose or iodine deficiency. Inclusion of additional raions would have added little additional statistical power to the analysis, as there was relatively little radiation exposure outside the selected 10 raions. A more informative approach would be to evaluate the modifying effect of iodine deficiency on the dose-response relationship derived from individual estimates of radiation dose. Such work is underway.

Second, a possible limitation arises from the potential effect of population movement in and out of the region since the Chernobyl accident. If the population of the study area has changed substantially, the results of the iodine survey may less accurately represent the circumstances at the time of the accident. However, it is generally thought that there has been relatively little population movement in and out of this region since the accident. Unofficial estimates from the Bryansk Oblast Health Department indicate that in- and out-migration since the accident is less than 5%. Furthermore, there were no special measures taken to provide iodine to the Bryansk Oblast population, nor were there any known significant changes in availability of iodine through dietary sources between the times of the Chernobyl accident and the survey in 1996. Although stable iodine prophylaxis was not provided to the region's population after the Chernobyl accident, a total of 18 people in 6 settlements who were found during the survey to have received stable iodine prophylaxis following the Chernobyl accident were excluded from the urine sampling. Thus, the survey results should reasonably reflect the relatively stable degrees of iodine sufficiency in the underlying population of this region.

Third, the average dose in iodine-deficient areas, as estimated here, may be an underestimate because it does not take into account the degree of iodine deficiency or sufficiency in the area. In effect, all areas are assumed to be iodine sufficient. Thus, in areas where there is actually a degree of iodine deficiency, individuals will uptake more ^{131}I than those in iodine-sufficient areas. Consequently, actual doses to the thyroid will be higher than estimated here. Under such circumstances, estimates of excess risk per unit dose (Gy) will be overestimates. This could explain, in part, the relationship observed in the present study.

Finally, the expected values were computed using incidence data for the whole of Russia, whereas the study is limited to a

specific area where the level of diagnostic attention to thyroid cancer is probably higher than for Russia as a whole. If this resulted in artificially low expected values, the resulting estimate of the relationship between radiation exposure and thyroid cancer incidence could be biased. It is not clear, however, that if such were the case it would necessarily bias the estimate of the interaction between iodine deficiency and radiation exposure.

In summary, these results are preliminary and based on population estimates of radiation dose and iodine deficiency. Although findings from an ecologic study such as this are limited in providing evidence that would be sufficient to serve as a basis for making recommendations in case of a radiation emergency, they nevertheless suggest that elimination of iodine deficiency in areas contaminated by radiation from the Chernobyl accident could be important in reducing the long-term effects of radiation exposure on the thyroid gland. Iodine saturation of the thyroid gland is thought to modify the risk of radiation-induced thyroid cancer. Risk may be enhanced when the excretion of radioactive iodine is limited due to reduced thyroid hormone synthesis and blocked thyroid hormone secretion.[26] If these findings are borne out by more detailed studies based on individuals, they may have important implications in considering the prophylactic use of stable iodine in the case of potential population exposure to radioactive iodine. Future studies based on individual estimates of radiation dose and iodine deficiency would help to clarify this relationship.

Acknowledgements

KEY MESSAGES

- There is little known about the joint effect of iodine deficiency and radiation exposure on the risk of thyroid cancer.
- This study assessed iodine deficiency in a geographical region of Russia contaminated by radiation fallout from the Chernobyl accident, based on individual urinary iodine excretion measurements in a sample of 3070 individuals (85% children and adolescents).
- All cases of thyroid cancer were identified in those born 1968–1986 who were resident in the study area at the time of the accident.
- The risk of thyroid cancer was examined in relation to population estimates of thyroid radiation dose and urinary iodine excretion level.
- The risk of thyroid cancer was significantly associated with increasing thyroid radiation dose, and was inversely associated with urinary iodine excretion levels. There was also a joint effect of radiation exposure and iodine deficiency.
- Although preliminary, these findings suggest that elimination of iodine deficiency in areas affected by Chernobyl may be important in reducing the effects of radiation exposure on the thyroid.

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