

Thyroid Autoantibodies and Thyroid Function in Subjects Exposed to Chernobyl Fallout during Childhood: Evidence for a Transient Radiation-Induced Elevation of Serum Thyroid Antibodies without an Increase in Thyroid Autoimmune Disease

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Context: An increase in the prevalence of thyroid autoantibodies (ATAs) was reported 6–8 yr after the Chernobyl accident in radiation-exposed children and adolescents.

Objective: Our objective was to reassess the effects of childhood radiation exposure on ATAs and thyroid function 13–15 yr after the accident.

Design and Setting: We measured the antithyroglobulin (TgAbs) and antithyroperoxidase (TPOAbs) antibodies and TSH in 1433 sera collected between 1999 and 2001 from 13- to 17-yr-old adolescents born between January 1982 and October 1986 in paired contaminated and noncontaminated villages of Belarus, Ukraine, and Russia. A total of 1441 sera was collected from age- and sex-matched controls living in Denmark and Sardinia (Italy). Free T₄ and free T₃ were measured when TSH was abnormal.

Results: TPOAb prevalence was higher in contaminated than in noncontaminated Belarusian children (6.4 vs. 2.4%; $P = 0.02$) but lower than previously reported (11%) in a different contaminated Belarus village. No difference in TPOAb prevalence was found in Ukrainian and Russian villages. TgAbs showed no difference between contaminated and noncontaminated Belarus and Ukraine, whereas in Russia they showed a relative increase in the exposed subjects with respect to the unexposed, who showed an unexpectedly lower prevalence of TgAbs. Besides radiation exposure, female gender was the only variable significantly correlated with ATAs in all groups. ATA prevalence in nonexposed villages of Belarus, Ukraine, and Russian Federation did not differ from that found in Sardinia and Denmark. With few exceptions, thyroid function was normal in all study groups.

Conclusions: TPOAb prevalence in adolescents exposed to radioactive fallout was still increased in Belarus 13–15 yr after the Chernobyl accident. This increase was less evident than previously reported and was not accompanied by thyroid dysfunction. Our data suggest that radioactive fallout elicited a transient autoimmune reaction, without triggering full-blown thyroid autoimmune disease. Longer observation periods are needed to exclude later effects. (*J Clin Endocrinol Metab* 93: 2729–2736, 2008)

The Chernobyl nuclear accident took place on April 26, 1986, and a large release of radionuclides occurred until May 5, 1986. A very large amount of radioactive iodine-131

(¹³¹I), and lesser amounts of short-lived iodine isotopes (iodine-129 and iodine-132 through iodine-135), were released intermittently over a period of 10 d after the accident.

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Abbreviations: AITD, Autoimmune thyroid disease; ATA, autoantibody; CIS, Commonwealth of Independent States; FT₃, free T₃; FT₄, free T₄; ¹³¹I, iodine-131; TgAb, antithyroglobulin antibody; TPOAb, antithyroperoxidase antibody.

The most contaminated areas were southern Belarus, northern Ukraine, and, to a lesser extent, southern Russian Federation. A large population was exposed to ionizing radiation, mostly from ingestion of radioiodine-contaminated food (particularly milk in children) and/or inhalation of radioactive isotopes dispersed in the environment (1). A few years after the nuclear accident, an enormous increase in the incidence of childhood thyroid carcinoma was observed in these areas, and the development of thyroid cancer was strictly related to the radioactive fallout exposure (2–3).

Besides thyroid carcinoma, it has been suggested that radiation exposure from the Chernobyl accident might also be responsible for an increased incidence of other thyroid diseases, particularly autoimmune thyroid disease (AITD) (4). In keeping with this notion, some years ago we showed a significant increase of serum antithyroperoxidase antibody (TPOAb) prevalence in a cohort of Belarusian children and adolescents exposed to Chernobyl fallout, but not in an unexposed control group (11.1 vs. 0.9%, respectively) (5). A higher prevalence of TPOAb was also observed by others in a group of Russian children and adolescents exposed to post-Chernobyl radioactive fallout (6). Quite recently, a significant association between the prevalence of TPOAb and the estimated ^{131}I thyroid dose has been reported in a large cohort of subjects from contaminated iodine-deficient territories of Ukraine (7), although, in the same cohort, no radiation-related increase of AITD was observed.

The aim of the present study was to verify the prevalence of circulating thyroid autoantibodies (ATAs) and thyroid dysfunction in the populations exposed to radiation 13–15 yr after the Chernobyl accident. The study was conducted in Belarusian, Ukrainian, and Russian subjects who were exposed or not exposed as young children or *in utero* at the time of the accident. As controls, we evaluated ATA prevalence in adolescents living in two different Western European areas: Sardinia (Italy) and Denmark.

Patients and Methods

Study groups

Recruitment of subjects to be enrolled in the present study was randomly performed in the largest school of the selected villages of Belarus, Ukraine, and Russia. A total of 2874 sera was collected and analyzed: 1433 sera were taken between 1999 and 2001 (13–15 yr after the Chernobyl accident) in school-attending adolescents aged 13–17 yr, born from 4 yr before (1982) to 6 months after the accident (October 1986) in Belarus (n = 541), Russia (n = 322), and Ukraine (n = 570). In each country, two villages were selected for blood collection: one contaminated by post-Chernobyl radiation fallout and the other not contaminated (Fig. 1), according to the level of contamination registered by the local authorities (8). At the time of the accident, iodine deficiency was prevalent in both contaminated and noncontaminated areas. The degree of iodine deficiency was defined as moderate-severe in Belarus, mild-moderate in Ukraine, and mild in Russia, with no major difference between the contaminated and noncontaminated villages (1, 9).

As control populations, 1441 sera were collected in Denmark (n = 645) and Sardinia (n = 796) from school-attending adolescents matched for age and sex. These two populations have been chosen as

uncontaminated control groups of children living in Western European areas with documented mild iodine deficiency at the study (10–12).

As a consequence of the continuous resettlement of many subjects, especially in the contaminated areas, it was not possible to examine the same Belarusian cohort analyzed in the previous study (5). We collected sera from 283 Belarusian adolescents living in Lelchitsy village and 258 subjects of the same age living in Braslav. It is worth noting that both Lelchitsy, the contaminated village of the present study, and Hoiniki, the contaminated village of the previous report, belong to Gomel oblast, which was the most exposed to post-Chernobyl radioactive fallout. In contrast, Braslav belongs to Vitebsk oblast, which is known as being noncontaminated. The Lelchitsy group consisted of 120 (42.4%) boys and 163 (57.6%) girls, aged 13–17 yr at the time of observation. At the time of the accident, they were either *in utero* (45 individuals) or already born (238 cases), with a mean age of 18.2 ± 11.5 months (range 1–43). The Braslav group (not exposed) included 119 (46.1%) males and 139 (53.9%) females with ages ranging from 15–17 yr. At the time of the accident, 13 subjects were *in utero*, and 245 were already born, with a mean age of 9.6 ± 5.9 months (range 1–23).

In Ukraine, we analyzed 336 adolescents living in Korosten village (located 140 km northwest of Kiev), which was exposed to post-Chernobyl radioactive fallout, and an unexposed group of 234 adolescents of the same age, living in Borispol (located 30 km southeast from Kiev). The Korosten group consisted of 183 (54.5%) males and 153 (45.5%) females, aged 13–17 yr at the study. At the time of the accident, their mean age was 16.3 ± 8.6 months (range 4–74), and five individuals were *in utero*. The Borispol group included 98 (41.5%) boys and 136 (58.5%) girls, aged 14–17 yr. At the time of the accident, they were either *in utero* (60 individuals) or already born (174 cases), with a mean age of 12.2 ± 8.5 months (range 1–36).

In Russia, we evaluated 185 adolescents from the exposed village of Klinty in the Bryansk oblast. The unexposed group consisted of 137 adolescents of the same age from Maloarchangelsk in the Orel oblast. In the Klinty group, 91 (49.7%) were males, and 94 (50.3%) were females, aged 13–17 yr at the time of observation. The Maloarchangelsk group included 55 (40.1%) males and 82 (59.9%) females, aged 7–16 yr at the study. At the time of the accident, their mean age was 19.2 ± 12.1 months (range 1–45) in the Klinty group (26 subjects were *in utero*) and 10.4 ± 19.1 months (range 1–30) in the Maloarchangelsk group (10 subjects were *in utero*).

As shown in Table 1, sex distribution, mean and median age at observation, and the number of subjects exposed and not exposed were similar in the group of contaminated and noncontaminated children and adolescents in each country. Control subjects from Sardinia and Denmark were similar to those of the Commonwealth of Independent States (CIS) study groups both for sex and age at observation.

Parents and/or guardians of both adolescents from CIS and Western European countries signed informed consent. The study on healthy children was approved by the local ethical committees (KF no. V200, 1996/90, in Denmark and Italy) and conducted in accordance with the Second Helsinki Declaration.

Antithyroglobulin antibody (TgAb), TPOAb, and TSH measurement

Measurements of TgAb, TPOAb, and TSH were centralized in the Pisa laboratory (Italy).

Serum free T_4 (FT4) and free T_3 (FT3) measurements were performed in sera with abnormal TSH concentration (both $< 0.4 \mu\text{U/ml}$ or $> 3.4 \mu\text{U/ml}$).

Both TgAb and TPOAb were determined by immunoradiometric assays [Biocode, ICN Pharmaceuticals, Sclessin, Belgium, normal range 0–50 U/ml (coefficient of variation 4–9%); and DiaSorin, Saluggia, Italy, normal range 0–10 IU/ml (coefficient of variation 4–9%), respectively]. According to the technical specifications of the methods, TgAbs were considered slightly increased when their con-

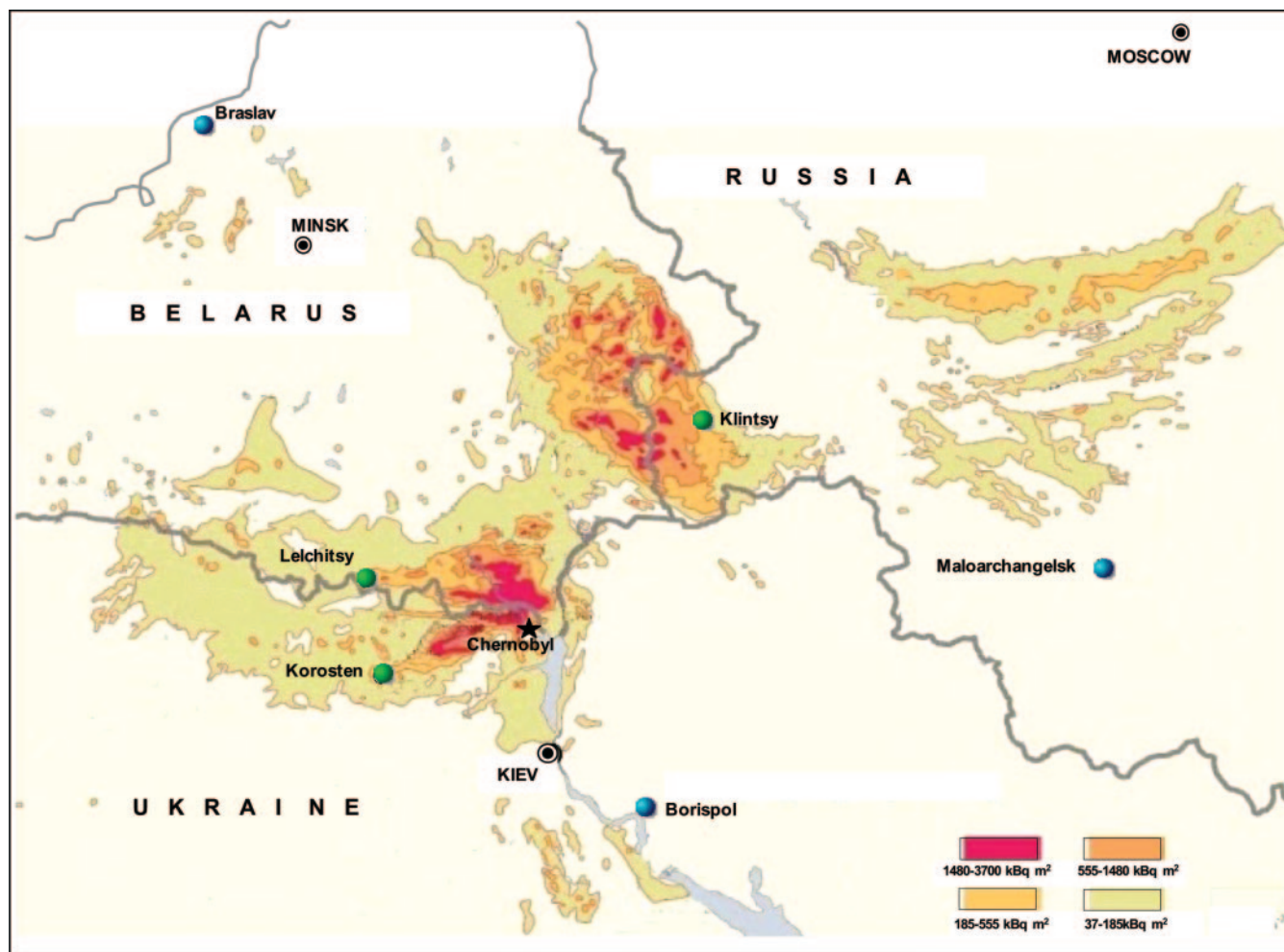


FIG. 1. Map of Belarus, Ukraine, and part of Russian Federation showing the primary area around Chernobyl contaminated by the radioactive fallout. Different colors indicate the different levels of radiation exposure. The contaminated villages of Lelechitsy in Belarus, Korosten in Ukraine, and Klinty in Russian Federation are indicated with a green dot. The noncontaminated villages of Braslav in Belarus, Borispol in Ukraine, and Maloarchangelsk in Russian Federation are indicated with a blue dot.

centrations were more than or equal to 50 and less than 100 IU/ml, moderately increased when more than or equal to 100 and less than 300 IU/ml, and highly increased when more than or equal to 300 IU/ml. Similarly, TPOAbs were considered slightly elevated when their levels were more than or equal to 10 and less than 20 IU/ml, moderately elevated when more than or equal to 20 and less than 100 IU/ml, and highly elevated when more than or equal to 100 IU/ml. All cases with slightly, moderately, and highly elevated ATA titers were considered as positive.

Serum TSH was detected using an ultrasensitive commercial chemiluminescent method (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA; normal range 0.4–3.4 μ U/ml).

Serum FT4 and FT3 were determined by a chemiluminescent method (Vitros System, Ortho-Clinical Diagnostics, Johnson & Johnson, Amersham, Bucks, UK; normal ranges 7–17 and 2.7–5.7 pg/ml, respectively).

Statistical analysis

We performed all statistical analyses using the SPSS 12.0 software package (SPSS, Inc. Chicago, IL). To describe the prevalence of ATA in exposed and nonexposed groups, we constructed crosstabs for each country and tested for unequal distribution with the global χ^2 statistic. We performed multiple logistic regression analyses to evaluate the influence of different covariates (gender, age, date of birth, and ra-

diation exposure) on the prevalence of ATA by considering the prevalence of ATA as the outcome variable. All covariates were evaluated as main effects in the regression models, and the odds ratios for each of them were adjusted for all other covariates in the model. *P* values less than 0.05 were considered statistically significant.

Results

Prevalence of ATA in contaminated and noncontaminated villages of CIS countries

As shown in Fig. 2, in Belarus the prevalence of TPOAb was significantly higher in the exposed Lelechitsy village (18 of 283; 6.4%) compared with the nonexposed Braslav village (six of 258; 2.4%; *P* = 0.02). The prevalence of TgAb was also found to be higher [15 of 283 (5.3%) in Lelechitsy *vs.* seven of 258 (2.7%) in Braslav], although the difference did not reach the level of statistical significance. When the results of TPOAb and TgAb were pooled together, the prevalence of adolescents with positive TPO or TgAb was higher in the contaminated village [24 of 283 (8.5%) in Lelechitsy *vs.* 13 of 258 (5.0%) in Braslav], but, again, the difference was not significant. As

TABLE 1. Epidemiological features of study groups from CIS countries (Belarus, Ukraine, and Russian Federation) and control groups from western countries (Sardinia and Denmark)

	Contaminated (no. of cases)		No. of males (%)	No. of females (%)	Mean age \pm SD at observation (range)/median	P value
	Yes	No				
Belarus						
Leltchitsy	283		120 (42.4)	163 (57.6)	14.3 \pm 1.2 yr (13–17)/15	NS
Braslav		258	119 (46.1)	139 (53.9)	15.8 \pm 0.7 yr (15–17)/16	
Ukraine						
Korosten	336		183 (54.5)	153 (45.5)	14.5 \pm 0.7 yr (13–17)/15	NS
Borispol		234	98 (41.5)	136 (58.5)	14.9 \pm 0.9 yr (14–17)/14	
Russia						
Klintsy	185		91 (49.7)	94 (50.3)	14.7 \pm 1.2 yr (13–17)/15	NS
Maloarchangelsk		137	55 (40.1)	82 (59.9)	14.4 \pm 1.6 yr (13–16)/14	
Sardinia		796	429 (53.9)	367 (46.1)	13.0 \pm 1.0 yr (11–17)/13	
Denmark		645	268 (41.6)	377 (58.4)	13.3 \pm 3.6 yr (6–19)/13	

NS, Not significant.

shown in Table 2, multivariate logistic regression analysis showed that among all the variables examined (e.g. ^{131}I exposure, sex, age at accident, age at study), only ^{131}I exposure and female gender were significantly correlated with TPOAb presence ($P = 0.021$, $P = 0.007$, respectively).

As shown in Fig. 3, in Ukraine, the prevalence of TPOAb was slightly but not significantly higher in the contaminated subjects of Korosten village (25 of 336; 7.7%) compared with those of the noncontaminated Borispol village (10 of 234; 4.3%). No difference was found in the prevalence of positive TgAb individuals living in the exposed village (eight of 336; 2.5%) and in those living in the nonexposed village (10 of 234; 4.3%), and the combination of positive TPOAb and/or TgAb was essentially similar in adolescents living in the two villages [Korosten (30 of 336; 8.9%) and Borispol (19 of 234; 8.1%)].

Multivariate logistic regression analysis showed that, among all the variables examined, only female gender was significantly

(or nearly significantly) correlated with both TPOAb and TgAb presence (Table 2).

In Russia, the prevalence of TPOAb alone was low in both villages and did not differ in the exposed (four of 185; 2.2%) and nonexposed individuals (four of 137; 2.9%) living in Klintsy and Maloarchangelsk, respectively (Fig. 4). The prevalence of TgAb alone in the exposed village of Klintsy was significantly higher ($P = 0.03$) than in the nonexposed village of Maloarchangelsk [nine of 185 (4.9%) vs. one of 137 (0.7%)], but the relevance of radiation in this finding is uncertain because the TgAb prevalence in Maloarchangelsk was significantly lower than the TgAb prevalence found in all other contaminated or noncontaminated CIS villages, or in the control Western European areas. There was no difference between the two villages when the TPOAbs and/or TgAbs were considered [11 of 185 (5.9%) vs. five of 137 (3.6%)]. As shown in Table 2, multivariate logistic regression analysis showed, as in Ukraine, that among all the variables examined, only female gender was significantly correlated with both TPOAb and TgAb presence.

As far as the levels of ATA are concerned, in Belarus, six of 18 positive TPOAb subjects from the exposed village and one of six from the nonexposed village had highly elevated levels of TPOAb, but no influence of the ATA levels was found in the regression analysis. Similarly, no difference in the levels of both TPOAb in Ukraine and Russia and TgAb in the three CIS countries was found (data not shown).

ATA prevalence in uncontaminated Western European regions

The combined prevalence of ATA in adolescents living in the two western countries (Sardinia and Denmark) was very similar (5.3 and 5.6%, respectively). As shown in Table 3, no significant difference was found between the prevalence of TgAb and/or TPOAb in the Sardinia and Denmark control groups when compared with the exposed and nonexposed villages of Belarus, Ukraine, and Russia, except for a higher prevalence of TPOAb in the exposed Ukrainian village of

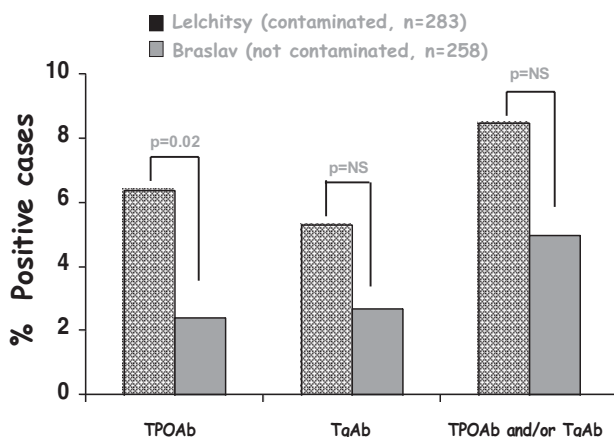


FIG. 2. Prevalence of thyroid ATAs in the contaminated and noncontaminated Belarusian villages. The prevalence of TPOAbs alone was significantly higher in subjects living in the contaminated Lechitsy village than in those living in the noncontaminated Braslav village. A slightly, but not significantly, higher prevalence of TgAbs alone and/or with TPOAb was also observed in subjects living in the contaminated village. NS, Not significant.

TABLE 2. Multivariate logistic regression analysis of all examined variables: ¹³¹I exposure, sex, age at diagnosis, and age at the accident

Variables	TgAb		TPOAb		TgAb and/or TPOAb	
	P value	Relative risk	P value	Relative risk	P value	Relative risk
Belarus						
¹³¹ I exposure (yes)	0.192	2.1	0.021 ^a	1.9	0.874	1.1
Sex (female)	0.304	1.6	0.007 ^a	2.0	0.312	1.4
Age at diagnosis	0.056	1.4	0.344	1.1	0.160	1.2
Date of birth with respect to accident (before vs. after)	0.447	0.6	0.657	0.8	0.611	0.7
Ukraine						
¹³¹ I exposure (yes)	0.491	0.6	0.131	2.0	0.486	1.3
Sex (female)	0.011 ^a	5.0	0.071 ^a	2.0	0.006 ^a	2.5
Age at diagnosis	0.302	0.6	0.613	1.1	0.730	0.9
Date of birth with respect to accident (before vs. after)	0.490	0.6	0.624	1.5	0.623	0.8
Russia						
¹³¹ I exposure (yes)	0.056	9.1	0.355	1.8	0.110	2.5
Sex (female)	0.035 ^a	5.0	0.051 ^a	5.0	0.012 ^a	5.0
Age at diagnosis	0.814	0.9	0.892	0.9	0.802	0.9
Date of birth with respect to accident (before vs. after)	0.965	1.0	0.107	0.2	0.540	0.6

^a P < 0.05 (statistically significant).

Korosten (25 of 336; 7.4%) when compared with Denmark (17 of 645; 2.6%).

Thyroid function in the CIS and Western Europe study groups

The mean and median values of serum TSH were similar among all study groups, independent of the levels of radioiodine contamination, iodine status, and country of residence. In the majority of cases, serum TSH levels were in the normal range (0.4–3.4 μU/ml). Among subjects with positive ATA, a serum TSH value slightly above the normal range, associated with normal FT4 and FT3 (subclinical hypothyroidism), was found in one Belarusian adolescent from the exposed village of Lelchitsy, in four subjects from the exposed Russian village (Klintsy), and in two subjects from the nonexposed Russian

village (Maloarchangelsk). The serum TSH range of the seven subjects with subclinical hypothyroidism was 3.7–7.0 μU/ml. In Ukraine, one subject from Korosten (exposed village) had slightly elevated FT3 and FT4 with suppressed TSH, suggesting overt hyperthyroidism.

Discussion

In this study we analyzed the ATA prevalence and thyroid function in 1434 adolescents who were young children or still *in utero* at the time of the Chernobyl nuclear accident, and were living in both radiation-exposed and nonexposed vil-

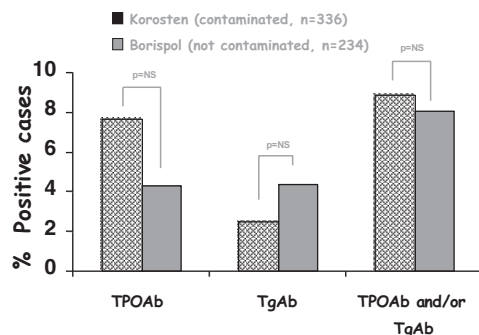


FIG. 3. Prevalence of thyroid ATAs in the contaminated and noncontaminated Ukrainian villages. The prevalence of TPOAbs alone was slightly, but not significantly, higher in subjects living in the contaminated Korosten village than those living in the noncontaminated Borispol village. No difference was observed in the prevalence of positive TgAbs alone and/or with TPOAb. NS, Not significant.

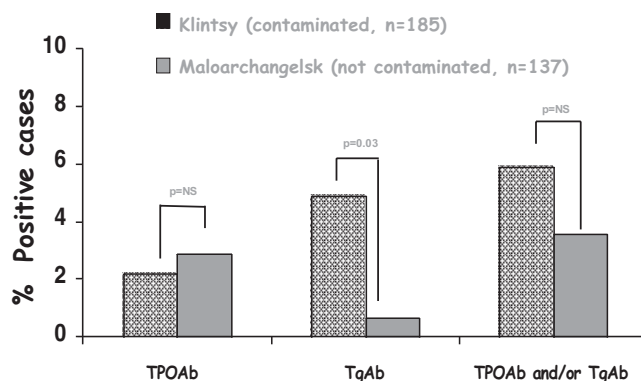


FIG. 4. Prevalence of thyroid ATAs in the contaminated and noncontaminated Russian villages. The prevalence of TPOAbs alone and/or with TgAbs was low and not different in exposed and nonexposed subjects. The prevalence of TgAb alone was significantly higher in the exposed village of Klintsy than in the nonexposed village of Maloarchangelsk. NS, Not significant.

TABLE 3. Prevalence of serum thyroid antibodies in Sardinia and Denmark with respect to CIS villages

	Sardinia	Denmark	Belarus		Ukraine		Russia	
			Lelechitsy ^a	Braslav	Korosten ^a	Borispol	Klintsy ^a	Maloarchangelsk
TPOAb	4.1%	2.6% ^b	6.2%	2.4%	7.4% ^b	4.3%	4.0%	2.9%
TgAb	2.3%	3.9%	5.5%	2.7%	2.5%	4.4%	5.1%	0.7%
TPOAb/TgAb	5.3%	5.6%	8.6%	5.0%	8.9%	8.0%	6.9%	3.6%

^a Contaminated villages.

^b $P = 0.0004$ (statistically significant).

lages of Belarus, Ukraine, and Russian Federation. The same analysis was performed on two groups of sex- and age-matched subjects living in Sardinia and Denmark, two Western European areas of mild iodine deficiency that were not exposed to radiation. Together, a total of 2874 sera were measured, and data on ATA prevalence and thyroid function were analyzed with regard to radiation exposure, sex, age at the time of the accident, and the geographical area of residence.

A significantly higher prevalence of TPOAb was found in radiation-exposed Belarusian subjects 13–15 yr after the Chernobyl accident. This finding confirms, although at a lower level of significance (see below for further discussion), the results of our previous study performed in 1998 in a cohort of radiation-exposed Belarusian children (5). TPOAb prevalence was also higher (although not significantly) in radiation-exposed Ukrainian but not in Russian adolescents. The different TPOAb prevalence found in the contaminated areas of the three CIS countries is reminiscent of a similar gradient in the post-Chernobyl thyroid carcinoma incidence (Belarus > Ukraine > Russia), which has been explained on the basis of different radiation exposures (13–15). As far as TgAb prevalence is concerned, there was no difference between contaminated and noncontaminated villages, with the exception of Russia, where the prevalence of TgAb was higher in the contaminated (Klintsy) than in the noncontaminated (Maloarchangelsk) village. This finding appeared mostly due to an unexpectedly low TgAb prevalence in Maloarchangelsk subjects (0.7%), a value significantly lower than that observed in any other CIS or Western European area. Thus, it would appear that TPOAb alone primarily contributes to the higher prevalence of ATA in radiation-exposed subjects, consistent with previous data reported by us (5) in Belarusian children and Vermiglio *et al.* (6) in Russian children. Recently, a study on the risk quantification of developing ATA after ¹³¹I exposure in a large cohort of 12,240 Ukrainian subjects has been published (7). The authors did not find any significant relationship between thyroid ¹³¹I dose exposures, individually estimated, and the prevalence of different degrees of *a priori* defined AITDs 12–14 yr after the Chernobyl accident. However, the presence of TPOAb alone (in the absence of signs of AITD) was weakly but significantly associated with estimated ¹³¹I thyroid irradiation, especially for moderately elevated TPOAb levels. The present study and previous studies (5, 7)

provide concordant evidence supporting the concept that circulating TPOAbs may appear as a consequence of radiation exposure.

In the present study, the combined TPOAb and TgAb prevalence found in the Belarus exposed adolescents (8.5%) is much lower than that previously reported in radiation-exposed Belarusian children (19.5%). The reason for this discrepancy is not immediately clear, but it is consistent with the hypothesis that it may be explained by the different time interval elapsed after radiation exposure (6–8 yr in the previous study; 13–15 yr in the present study). It is, in fact, conceivable that a thyroid autoimmune reaction (revealed by serum ATA appearance) triggered by thyroid ¹³¹I exposure at the time of Chernobyl accident might undergo a progressive attenuation, a phenomenon similar to the transient increase in circulating ATA in Graves' disease after therapeutic ¹³¹I administration (16–21).

It is worth noting that in addition to ¹³¹I exposure, only female gender provided a significant independent risk of developing ATA both in exposed and nonexposed adolescents. In our previous study on Belarusian children exposed to radiation, the difference in ATA prevalence between females and males was more evident in the children exposed after puberty (5). This observation is not unexpected, given the greater susceptibility of postpubertal females in developing ATA (10, 22).

No differences were found in the ATA prevalence when exposed and nonexposed villages of CIS countries (Belarus, Ukraine, and Russian Federation) were compared with the Sardinia and Denmark control groups. Despite their different ethnic origins, these populations are apparently similar regarding the prevalence of ATA in children and the adolescent population.

Iodine deficiency as a possible environmental modifier was not specifically addressed in this study. However, it has been previously demonstrated that the risk of post-Chernobyl radiation-related cancer was three times higher in iodine-deficient areas than elsewhere (1), and we cannot exclude a favoring role of iodine deficiency in the development of a thyroid autoimmune phenomenon.

In conclusion, the present study indicates that 13–15 yr after the Chernobyl nuclear accident, the prevalence of TPOAb in Belarusian adolescents exposed during childhood to radioactive fallout is still increased when compared with

that of unexposed subjects, but the difference is remarkably less evident than that found earlier in a contaminated Belarusian village 6–8 yr after the accident. No clear radiation effect on ATA prevalence is found in Ukraine and Russia, where the estimated radiation exposure was lower than in Belarus. This suggests that the thyroid autoimmune reaction elicited by radiation was transient with no effect on thyroid function after 13–15 yr. However, because it was shown that autoimmune hypothyroidism can naturally occur over decades (23), we cannot exclude that thyroid dysfunctions related to radiation exposure may develop in a later period. In this regard, the studies on atomic bomb survivors clearly indicate the necessity to monitor for a long period the exposed subjects because thyroid disorders such as autoimmune and nonautoimmune hypothyroidism may be observed 40 yr or more after the explosion (24, 25). In this respect, further studies on the post-Chernobyl radiation-exposed population should be conducted to assess thyroid autoimmunity and thyroid function in a longer period of time.

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References

- Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, Drozdovitch V, Maceika E, Zvonova I, Vlassov O, Bouville A, Goukko G, Hoshi M, Abrosimov A, Anoshko J, Astakhova L, Chekin S, Demidchik E, Galanti R, Ito M, Korobova E, Lushnikov E, Maksoutov M, Masyakin V, Nerovnia A, Parshin V, Parshkov E, Piliptsevich N, Pinchera A, Polyakov S, Shabeka N, Suonio E, Tenet V, Tsyb A, Yamashita S, Williams D 2005 Risk of thyroid cancer after exposure to ¹³¹I in childhood. *J Natl Cancer Inst* 97: 724–732
- Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D 1992 Thyroid cancer after Chernobyl. *Nature* 359:21–22
- Demidchik E, Kazakov VS, Astakhova LN, Okeanov AE, Demidchik YE 1994 Thyroid cancer in children after the Chernobyl accident: clinical and epidemiological evaluation of 251 cases in the Republic of Belarus. In: Nagasaki S, ed. Nagasaki symposium on Chernobyl: update and future. Amsterdam: Elsevier; 21
- Eheman CR, Garbe P, Tuttle M 2003 Autoimmune thyroid disease associated with environmental thyroidal irradiation. *Thyroid* 13:453–464
- Pacini F, Vorontsova T, Molinaro E, Kuchinskaya E, Agate L, Shavrova E, Astakhova L, Chiovato L, Pinchera A 1998 Prevalence of thyroid autoantibodies in children and adolescents from Belarus exposed to the Chernobyl radioactive fallout. *Lancet* 352:763–766
- Vermiglio F, Castagna MG, Volnova E, Lo Priesti VP, Vincenzo P, Moleti M, Violi MA, Artemisia A, Trimarchi F 1999 Post-Chernobyl increased prevalence of humoral thyroid autoimmunity in children and adolescents from a moderately iodine-deficient area in Russia. *Thyroid* 9:781–786
- Tronko MD, Brenner AV, Olijnyk VA, Robbins J, Epstein OV, McConnell RJ, Bogdanova TI, Fink DJ, Likhtarev IA, Lubin JH, Markov VV, Bouville AC, Terekhova GM, Zablotska LB, Shpak VM, Brill AB, Tereshchenko VP, Masnyk IJ, Ron E, Hatch M, Howe GR 2006 Autoimmune thyroiditis and exposure to iodine 131 in the Ukrainian cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident: results from the first screening cycle (1998–2000). *J Clin Endocrinol Metab* 91:4344–4351
- Balnov M, Jacob P, Likhtarev I, Minenko V 1996 Pathways, levels, and trends of population exposure after the Chernobyl accident. In: The radiological consequences of the Chernobyl accident. Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. EUR 16544EN. Brussels-Luxembourg: European Commission; 235–249
- Tronko M, Kravchenko V, Fink D, Hatch M, Turchin V, McConnell R, Shpak V, Brenner A, Robbins J, Lusanchuk I, Howe G 2005 Iodine excretion in regions of Ukraine affected by the Chernobyl accident: experience of the Ukrainian-American cohort study of thyroid cancer and other thyroid diseases. *Thyroid* 15:1291–1297
- Loviselli A, Velluzzi F, Mossa P, Cambosu MA, Secci G, Atzeni F, Taberlet A, Balestrieri A, Martino E, Grasso L, Songini M, Bottazzo GF, Mariotti S, Sardinian Schoolchildren Study Group 2001 The Sardinian autoimmunity study: 3. Studies on circulating antithyroid antibodies in Sardinian schoolchildren: relationship to goiter prevalence and thyroid function. *Thyroid* 11:849–857
- Laurberg P 2003 Iodine deficiency disorders in Denmark. *J Endocrinol Invest* 26(Suppl 9):17
- Laurberg P, Jorgensen T, Perrild H, Ovesen L, Knudsen N, Pedersen IB, Rasmussen LB, Carlø A, Vejbjerg P 2006 The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol [Erratum]* (2006) 155:643] 155:219–228
- Demidchik E, Kazakov VS, Astakhova LN, Okeanov AE, Demidchik YE 1994 Thyroid cancer in children after the Chernobyl accident: clinical and epidemiological evaluation of 251 cases in the Republic of Belarus. In: Nagasaki S, ed. Nagasaki symposium on Chernobyl: update and future. Amsterdam: Elsevier; 21–30
- Tronko N, Bogdanova T, Kommisarenko I, Bolshova E, Oleynic V, Tereshchenko V, Epshtein Y, Chebotarev V 1996 Thyroid cancer in children and adolescents in Ukraine after the Chernobyl accident (1986–1995). In: Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. The radiological consequences of the Chernobyl accident. Brussels: European Commission; 683–690
- Tsyb AF, Parshkov EM, Shaktarin VV, Stepanenko VF, Skvortsov VF, Chebotareva IV 1996 Thyroid cancer in children and adolescents of Bryansk and Kaluga regions. In: Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. The radiological consequences of the Chernobyl accident. Brussels: European Commission; 691–698
- Chiovato L, Santini F, Vitti P, Bendinelli G, Pinchera A 1994 Appearance of thyroid stimulating antibody and Graves' disease after radioiodine therapy for toxic nodular goitre. *Clin Endocrinol (Oxf)* 40:803–806
- Mariotti S, Martino E, Francesconi M, Ceccarelli C, Grasso L, Lippi F, Banchieri L, Pinchera A 1986 Serum thyroid autoantibodies as a risk factor for development of hypothyroidism after radioactive iodine therapy for single thyroid 'hot' nodule. *Acta Endocrinol (Copenh)* 113:500–507
- Einhorn J, Fagraeus A, Jonsson J 1965 Thyroid antibodies after 131-I treatment for hyperthyroidism. *J Clin Endocrinol Metab* 25:1218–1224
- Fenzi GF, Hashaizume K, Roubush CP, De Groot LJ 1979 Changes in thyroid stimulating immunoglobulins during antithyroid therapy. *J Clin Endocrinol Metab* 48:572–576
- O'Gorman P, Staffueth JS, Ballentyne MR 1964 Antibody response to thyroid irradiation. *J Clin Endocrinol Metab* 24:1072–1075
- Pinchera A, Liberti P, Martino E, Fenzi GF, Grasso L, Rovis L, Banchieri L 1969 Effects of antithyroid therapy on the long-acting thyroid stimulator and the antithyroglobulin antibodies. *J Clin Endocrinol Metab* 29:231–238
- Chiovato L, Lapi P, Fiore E, Tonacchera M, Pinchera A 1993 Thyroid autoimmunity and female gender. *J Endocrinol Invest* 16:373–401
- Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F,

- Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F 1995 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Wickham Survey. *Clin Endocrinol (Oxf)* 43:55–68
24. Nagataki S, Shibata Y, Inoue S, Yokoyama N, Izumi M, Shimaoka K 1994 Thyroid disease among atomic bomb survivors. *JAMA* 272:364–370
25. Imaizumi M, Usa T, Tominaga T, Neriishi K, Akahoshi M, Nakashima E, Ashizawa K, Hida A, Soda M, Fujiwara S, Yamada M, Ejima E, Yokoyama N, Okubo M, Sugino K, Suzuki G, Maeda R, Nagataki S, Eguchi K 2006 Radiation dose-response relationships for thyroid nodules and autoimmune thyroid diseases in Hiroshima and Nagasaki atomic bomb survivors 55–58 years after radiation exposure. *JAMA* 295:1011–1022