0303-8408/94/040189-09 $ 1.50 + 0.20/0

Soz Präventivmed 1994; 39: 189–197

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Thyroid cancer in Belarus post-Chernobyl: Improved detection or increased incidence?

Summary

There is debate on whether the reported increase in the number of cases of childhood thyroid cancer in Belarus is real and attributable to radiation released following the Chernobyl nuclear accident, or rather an artefact due to incorrect histological diagnosis, more complete case reporting and mass screening of children after the accident. We have scrutinised the histological slides of 120 (75%) of the 160 cases reported among children aged up to 15 years to the Belarus tumour registry from 1986 to 1992 and examined time trends and geographical patterns in incidence and tumour characteristics. Incidence based on reported cases increased from 0.041 per 100.000 in 1986 to 2.548 in 1992. Carcinoma was confirmed in 94% of reviewed tumours. Except for one medullary carcinoma all histologies were of the papillary type. Most of the tumours had spread beyond the organ capsule and measured over 10 mm in diameter. There was a weak and statistically non-significant trend (p = 0.19) towards smaller tumours in the later years. The proportion of cases with lymphnode or distant metastasis remained unchanged. Incidence based on histologically confirmed cases was highest adjacent and to the west and north of Chernobyl, matching best estimates of iodine-131 contamination. Our data thus strongly suggest that the observed increase is real but more data are needed in order to assess the impact of mass screening and to clarify the possible association with radiation released at Chernobyl in 1986.

A pronounced increase in the number of thyroid cancer cases diagnosed among children in Belarus starting in 1988 and continuing through 1992 has been reported[1]. This has been attributed to radioiodines released following the accident which destroyed unit four of the Chernobyl reactor site on April 26, 1986, and which lead to radioactive contamination of large areas of the republic of Belarus[1,2]. Chernobyl is located in the Ukraine, near the Gomel district in the south-east of Belarus. The reported increase in childhood thyroid cancer occurred earlier than expected on the basis of much of the previous experience – in most studies of external radiation, a latent period of ten years or more has been documented[3]. On the other hand, reports of latent periods as short as 3 years can be found in the literature[4]. Patients with Graves' disease who were given therapeutic doses of iodine-131 have shown no increased risk of thyroid cancer[5]. It is therefore a matter of debate whether the excess observed among children in Belarus is real, and a number of alternative explanations have been put forward[6–8]. The increase could partly or entirely be attributable to false positive histological diagnoses or, conversely, be due to improved detection and more complete reporting of thyroid cancer cases because of increased awareness in the post-accident era. Furthermore, it has been argued that many of the reported cases could correspond to a dormant and thus clinically irrelevant type of carcinoma, occult papillary thyroid carcinoma, which has been described as a "normal finding" in autopsy studies[9].

We have re-examined the majority of histological slides and have assessed time trends and geographical patterns in tumour characteristics and incidence, in order to investigate the nature of this apparent epidemic of childhood thyroid cancer. Our objectives were to assess whether the excess could be artefactual due to (i) incorrect histological diagnoses, (ii) more complete case reporting in the post-Chernobyl era, or (iii) screening for thyroid tumours of large numbers of asymptomatic children in the years following the accident.

Material and methods

In Belarus, first medical contacts are with general policlinics, from which patients with suspected oncological conditions are referred to one of 12 specialized tumour clinics. These clinics, as well as all hospital departments throughout the country and the oncological centres in Minsk, are obliged by law to report all cases of neoplasms to a registry which was created in 1965 at the State Research Institute for Oncology and Medical Radiology in Lesnoj near Minsk (called in brief the Lesnoj Research Institute). Diagnoses are coded according to the 9th revision of the International Classification of Diseases (ICD-9)[10] and tumour stage is assessed using the TNM classification system[11]. Patient information includes name, age, sex, region (*oblast*) and district (*rayon*) of residence, date of diagnosis, reporting clinic and clinical follow-up data.

The histological slides of 120 children aged up to 15 years who were diagnosed as having thyroid cancer from 1986 to 1992 and who had undergone thyroid surgery were re-examined by a pathologist of the Lesnoj Research Institute (A.W.F.) and by two senior Swiss pathologists (B.E., C.R.). The International Classification of Thyroid Tumours[12] was used for histological grouping. Tumour size had been measured and invasion of neighbouring tissues and lymph nodes assessed immediately following surgery. Detailed procedures are described elsewhere[13].

Incidence rates based on population data obtained from the Belarus State Commission for Statistics, together with Poisson 95% confidence intervals, were calculated for the ten-year period preceding the accident at the Chernobyl nuclear power plant and for each year from 1986 to 1992. Comparison rates from Eastern Europe, Scandinavia and the United States were computed based on cancer registry data published by the World Health Organisation[14]. Incidence rates by *oblast* and, in some instances, by *rayon* were calculated for 1990 and 1991 combined and compared to patterns of radio-iodine contamination on May 10, 1986, as estimated by the Belarus Centre for Radiation Control and Environmental Radiation Surveillance on the basis of radionuclide emission and meteorological data.

Results

As shown in Table 1 the number of cases of childhood thyroid cancer reported to the registry increased from an average of 1 case per year during the ten-year period preceding the accident to 27 cases in 1990, 55 in 1991 and 66 in 1992. Incidence based on reported cases averaged 0.041 per 100,000 person-years (95% confidence intervals 0.019–0.078) during the decade preceding the accident, but had increased to 2.548 per 100,000 (1.94–3.28) by 1992; that is, a 62 times higher rate. The incidence of childhood thyroid cancer reported from Eastern European registries are comparable with the pre-accident rates from Belarus. The rates reported from the big Scandinavian and U.S. registries are still about 13 times below the rate reported from Belarus for 1992.

Among the 120 histological slides which were reviewed by outside pathologists carcinoma was confirmed in 113, corresponding to 94% of reviewed cases. Up to 1991, 93% of reported cases could be reviewed by our team, but this figure dropped to 41% in 1992 (Table 1). Overall, the 120 slides reviewed represent 75% of all 160 cases reported from 1986 to 1992. All cancers were of the papillary type except for one which was of the medullary type.

The characteristics of the 86 histologically confirmed cases diagnosed from 1986 to 1991 are shown in Table 2. Among these, all underwent thyroidectomy or hemithyroidectomy except for 1 patient who only had a node removed. Sixty percent of children were below 10 years of age at diagnosis. There was a slight female preponderance. The majority of cases were diagnosed in Gomel. Sixty-two percent of tumours had spread beyond the capsule, 65% had invaded cervical lymph nodes and (including follow-up information) 13% had spread to the lungs. On histological review, one case was reclassified from T2 to T4. The 1992 cases are not included in Table 2 because only a small proportion which may not be representative was available for independent assessment.

Because of incomplete data for the pre-accident cases no direct comparisons can be made. However, it is known that only 1 out of the 9 cases (11%) diagnosed in the ten-year period preceding the accident was below 10 years of age at diagnosis, a significantly ($p = 0.011$ by Fisher exact test) lower proportion than among the cases diagnosed from 1986 to 1991 (60%). Forty-four (51%) of the 86 cases with confirmed histology were a few months to 4 years old at the time of the accident. Among the cases diagnosed from 1988 onwards none was born after 1986.

In order to investigate whether there was an effect of screening activities on tumour and patient

Location/ year	No of cases: Reported	Histology reviewed (% of reported)		Histology confirmed (% of reviewed)		Incidence (95% Confidence Intervals) per 100,000 person-years based on reported cases	
Belarus *pre-Chernobyl*							
1976–1985	9	na		na		0.041	(0.019–0.078)
Belarus *post-Chernobyl*							
1986	2	1	(50%)	1	(100%)	0.083	(0.010–0.300)
1987	3	3	(100%)	0	(0%)	0.124	(0.026–0.362)
1988	7	5	(71%)	3	(60%)	0.290	(0.117–0.598)
1989	6	6	(100%)	6	(100%)	0.249	(0.091–0.542)
1990	27	23	(85%)	23	(100%)	1.148	(0.757–1.670)
1991	55	55	(100%)	53	(96%)	2.335	(1.759–3.039)
1992	60	27	(45%)	27	(100%)	2.548	(1.944–3.280)
1986–1992	160	120	(75%)	113	(97%)		
International comparison							
Eastern Europe[1]	21	na		na		0.072	(0.045–0.110)
Scandinavia[2]	41	na		na		0.194	(0.139–0.263)
U.S.A. SEER (Whites)[3]	37	na		na		0.194	(0.137–0.268)

na: not available

[1] Bohemia and Moravia 1983–1887; Slovakia 1983–1987; Estonia 1983–1987; Latvia 1983–1987; Cracow 1983–1986; Lower Slesia 1983–1986; Nowy Sacz 1983–1986; Opole 1985–1987; Warsaw 1983–1987[14]
[2] Denmark 1983–1987; Finland 1982–1986; Norway 1983–1987; Sweden 1983–1987[14]
[3] U.S.A., SEER (Surveillance, Epidemiology and End Results Program): Alameda County, San Francisco Bay Area, Connecticut, Atlanta, Hawaii, Iowa, Detroit, New Mexico, Utah, Seattle (Whites) 1883–1987[14].

Table 1. *Incidence of thyroid cancer in children below 15 years of age in Belarus 1976–1985 (pre-Chernobyl), 1986–1992 (post-Chernobyl) and international comparison rates*

characteristics, the cases diagnosed in the period before screening began (1986 to 1989) were compared with the cases reported in 1990 and 1991 (Table 3). No statistically significant differences are evident although there is a trend towards younger age, more diagnoses in Gomel *oblast*, and smaller tumours during the later years when screening of children at schools and clinics took place. The severity of disease at diagnosis as judged from lymph node involvement and distant metastasis was similar in the two periods.

Figure 1a shows incidence rates for childhood thyroid cancer for 1990 and 1991 combined by *oblast* or groups of districts. The highest rate is observed in the districts adjacent to Chernobyl but high rates are seen in all of Gomel and in the neighbouring districts of Mogilev and Brest to the north and west respectively. The geographical distribution of childhood thyroid cancer incidence thus roughly corresponds with the contamination pattern shown in Figure 1b, although no

Characteristic	year 1986 (n = 1)	1987 (n = 0)	1988 (n = 3)	1989 (n = 6)	1990 (n = 23)	1991 (n = 53)	total (n = 86)	
Age (years)								
0–4	0	–	0	1	2	0	3	(3.5%)
5–9	0	–	2	1	15	31	49	(56.9%)
10–14	1	–	1	4	6	22	34	(39.6%)
Sex								
F	1	–	2	2	10	34	49	(57.0%)
M	0	–	1	4	13	19	37	(43.0%)
Residence at diagnosis								
Gomel	1	–	1	2	11	37	52	(60.5%)
Brest	0	–	1	1	5	4	11	(12.8%)
Minsk	0	–	0	1	3	5	9	(10.5%)
Mogilev	0	–	0	0	3	2	5	(5.8%)
Grodno	0	–	1	2	0	3	6	(7.0%)
Vitebsk	0	–	0	0	1	2	3	(3.5%)
TNM classification								
T (tumour)								
<1 cm (T1)	0	–	0	0	2	9	11	(12.8%)
1–4 cm (T2)	0	–	2	2	7	8	19	(22.1%)
>4 cm (T3)	0	–	1	0	1	1	3	(3.5%)
beyond capsule (T4)	1	–	0	4	13	35	53	(61.6%)
N (lymph node metastasis)								
none (N0)	0	–	2	2	7	19	28	(32.6%)
ipsilateral (N1a)	1	–	0	3	7	20	31	(36.0%)
other (N1b)	0	–	1	1	9	14	25	(29.1%)
M (distant metastasis)								
none (M0)	1	–	3	5	19	47	75	(87.2%)
yes (M1)*	0	–	0	1	4	6	11	(12.8%)

* all lung metastasis, including follow-up information

Table 2. *Characteristics of 86 histologically confirmed thyroid cancer cases below 15 years of age in Belarus, 1986–1991*

increase in incidence is noticeable in Grodno *oblast* despite fairly high contamination levels.

Discussion

The nature of the reported increase of childhood thyroid cancer has been the subject of intense debate. Some believe that the excess is real and most likely attributable to radiation released following the nuclear accident at Chernobyl, while their opponents have dismissed it as an artefact.

We have examined three key questions which are at the heart of this debate. First, could the observed increases be spurious due to false positive histological diagnoses? Based on the data presented here and on data published earlier[13], this possibility can clearly be ruled out. In over 90% of reviewed cases the histological diagnosis was confirmed by an international team consisting of a senior pathologist from the Lesnoj Research Institute and two senior Swiss pathologists.

Secondly, could the increase be due to more complete case reporting in the post-accident era? Both the leading American and European cancer registries (the SEER-programme in the United States and the Scandinavian registries) report a childhood thyroid cancer incidence rate of 0.19 cases per 100,000 per year (95% confidence interval: 0.14–0.27 and 0.14–0.26)[14], and this rate is significantly lower than the rates reported for Belarus in 1990, 1991 and 1992 ($p<0.05$, $p<0.0001$ respectively). Improved reporting could thus only explain a small part of the increase observed in Belarus.

Thirdly, could a large proportion of the Belarus cases correspond to dormant and thus irrelevant occult papillary carcinoma (OPC) detected by screening? Autopsy studies have shown that OPC is indeed very common in adults. In 8 series comprising 1.759 autopsies OPC was found in 17.6%[9] and a recent autopsy study from Belarus reported a prevalence of 8.8% among 215 autopsies[15]. Conversely, OPC appears to be rare in children but no large autopsy series exists in this age group. The limited data which are available indicate that OPC is present in less than 5% of children[16]. However, even if only one out of a hundred children were affected, this could lead to a spurious epidemic of thyroid cancer if OPC was detectable by screening and if a large enough number of children were screened. The exact number of children screened is unknown but it is certain that many children were indeed examined for thyroid disease by palpation or ultrasonography. These activities were concentrated in the southern, most heavily contaminated regions of Belarus, from which the majority of cases have been reported.

A number of observations make it nevertheless unlikely that OPC detected by screening is behind the observed increase in childhood thyroid cancer in more than a minority of cases. In the autopsy studies mentioned earlier OPC was detected by serially and transversally cutting the thyroid at 2- to 3-mm intervals. Eighty-one percent of occult tumours measured less than 3 mm in diameter and 96% measured below 10 mm[9]. The same holds true for a study from Belarus: 46% of OPCs were up to 1 mm in size and only one (4%) was larger than 5 mm[15]. It is therefore unlikely that more than a small proportion of occult tumours would be detectable by screening. Furthermore, the histological features found in Belarus are far from typical for OPC. Among the histologically confirmed cases diagnosed in 1990 and 1991, 70% measured more than 10 mm, 62% showed extracapsular growth and 66% lymph node metastasis, and after follow-up, 13% had distant metastasis of the lung. During the

Characteristic	**period** 1986–1989 (*No or little screening*) n = 10	1990–1991 (*Screening*) n = 76	**p***
Age (years)			
0–4	1 (10%)	2 (2%)	0.13
5–9	3 (30%)	46 (61%)	
10–14	6 (60%)	28 (37%)	
Sex			0.9
F	5 (50%)	44 (58%)	
M	5 (50%)	32 (42%)	
Place of residence			0.29
Gomel	4 (40%)	48 (63%)	
Other	6 (60%)	28 (37%)	
TNM classification			
T (tumour)			0.19
< 1 cm (T1)	0 (0%)	11 (14%)	
1–4 cm (T2)	4 (40%)	15 (20%)	
>4 cm (T3)	1 (10%)	2 (3%)	
beyond capsule (T4)	5 (50%)	48 (63%)	
N (lymph node metastasis)			0.8
none (N0)	4 (40%)	26 (34%)	
ipsilateral (N1a)	4 (40%)	27 (36%)	
other (N1b)	2 (20%)	23 (30%)	
M (distant metastasis)			1.0
none (M0)	9 (90%)	66 (85%)	
yes (M1)**	1 (10%)	10 (15%)	

* by Student's t-test, Fisher's exact test or continuity adjusted chi-square test
** all metastasis of the lung

Table 3. *Comparison of thyroid cancer cases diagnosed 1986–1989 (no or little screening) with cases diagnosed 1990 and 1991 (some screening)*

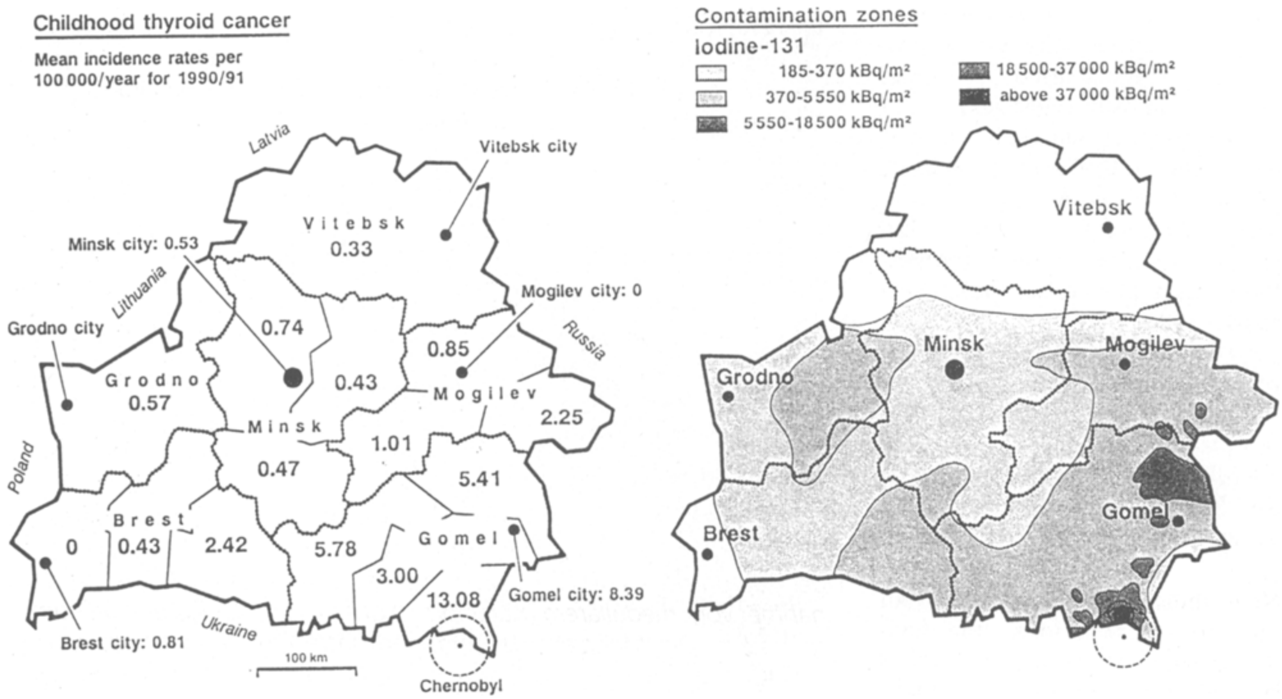

Figure 1. *Incidence of thyroid cancer in children up to 15 years of age per 100,000 person-years for 1990 and 1991 combined (Figure 1a) and iodine-131 contamination map of Belarus (Figure 1b). Belarus is divided into oblasts (..........); the southern oblasts were further divided into groups of districts (-------). The circle around Chernobyl indicates a 30 km radius*

follow-up period one child died from lung metastasis. These findings are very comparable to those for a series of childhood thyroid cancer patients treated in France[17].

The reports to the registry thus appear to reflect a real increase in incidence of childhood thyroid cancer, although this conclusion should be further supported by studies specifically addressing the question of screening. Is this increase compatible with causation by radiation from the nuclear accident? Radioactive iodines accumulate in the thyroid gland and the risk of developing radiation-induced thyroid cancer will thus depend on levels of exposure to radioiodines. Individual radioiodine doses are difficult to reconstruct, given the short half-life of radioactive iodine isotopes, and attempts at developing such estimates are still in progress. However, geographical comparisons are already possible. The regional distribution of iodine-131 contamination as estimated for May 10, 1986, by the Belarus Centre for Radiation Control and Environmental Radiation Surveillance, is shown in the figure. A similar map had already been produced from data of the Lawrence Livermore National Laboratory in 1986[18]. The geographical distribution of childhood thyroid cancer incidence roughly corresponds to this contamination pattern.

The age distribution of the cases also supports a causal link with the accident. In the pre-accident era, only 1 out of 10 children was below the age of 10 years at diagnosis, but this proportion increased to over 50% among the cases reported in 1990 and 1991. Fifty-four percent of the latter were less than 5 years old in 1986, but none of the cases diagnosed between 1988 and 1991 were born after 1986. These data are compatible with causation by radiation and with a higher susceptibility among younger children. No increase in thyroid cancer had been seen in adult patients after iodine-131 treatment, but external radiation to the thyroid is more carcinogenic in infants than in adults and the same may be true for internal radiation from iodine-131[4, 19]. Finally, papillary histology has been shown to be associated with radiation exposure[3].

In conclusion, our analysis of available data supports the notion that there is a real increase in childhood thyroid cancer in Belarus which is causally related to the Chernobyl nuclear accident, as tumour properties make it unlikely that more than a minority of cases correspond to occult carcinoma detected by screening. This interpretation corresponds to that of a recent consensus opinion of an international Panel of Thyroid Experts formed by the Commission of the European Community[20], to which some of our analyses had already been made available. It is also compatible with preliminary findings from the Chernobyl Sasakawa Project, where systematic ultrasonic screening of children led to the discovery of seven cancer cases in the contaminated Gomel *oblast* (6.129 children screened), but so far none in Mogilev *oblast*, which was much less contaminated by iodine-131 (6.496 children screened)[21].

Nevertheless, as is evident from numerous discussions, the evidence will not be generally considered as conclusive, and further analyses including data on the extent of screening activities, the mode of diagnosis of reported cases, and the place of residence of the patients around the time of the Chernobyl accident are needed, as are studies attempting to establish exposure levels, dose-response relationships for Chernobyl-related thyroid cancer and possible modifying factors including endemic iodine deficiency.

In the meantime, the ongoing debate should not distract those who are in a position to help from providing urgently needed medical and humanitarian assistance to the increasing number of Belarus children in whom thyroid cancer has been diagnosed.

Zusammenfassung

Schilddrüsenkrebs in Belarus nach Tschernobyl: Verbesserte Erkennung oder erhöhte Inzidenz?

Es wird diskutiert, ob die berichtete Zunahme von Fällen kindlichen Schilddrüsenkarzinoms in Belarus echt und der Strahlung in der Folge des Nuklearunfalls von Tschernobyl zuzuschreiben ist, oder ob es sich um einen Artefakt handelt, indem nach dem Unfall falsche histologische Diagnosen gestellt wurden, die Berichterstattung über die Fälle vollständiger wurde oder Massenfrüherfassungsaktivitäten bei Kindern durchgeführt wurden. Wir haben die histologischen Präparate von 120 (75%) der 160 Fälle von Schilddrüsenkarzinom bei Kindern bis zu 15 Jahren überprüft, die zwischen 1986 und 1992 dem Krebsregister von Belarus gemeldet worden sind, sowie die zeitliche Entwicklung und geographische Verteilung der aufgetretenen Fälle und deren Merkmale analysiert. Gestützt auf die gemeldeten Fälle nahm die Inzidenzrate von 0,041 pro 100000 im Jahre 1986 auf 2,548 im Jahre 1992 zu. In 94% der überprüften Fälle wurde Krebs als Diagnose bestätigt. Mit einer Ausnahme von medullärem Karzinom wurden nur papilläre Karzinome gefunden. Die Mehrzahl der Tumoren hatte die Organkapsel durchbrochen und massen über 10 mm im Durchmesser. Im Laufe der Zeit fand sich ein schwacher und statistisch nicht signifikanter Trend (p = 0,19) in Richtung kleinerer Tumoren. Der Anteil von Tumoren mit Lymphknoten- und entfernten Metastasen blieb unverändert. Gestützt auf die histologisch bestätigten Fälle war die Inzidenz angrenzend an Tschernobyl und in westlicher und nördlicher Richtung am höchsten, was auch der Kontamination mit Jod-131 entspricht. Unsere Daten weisen damit deutlich darauf hin, dass die beobachtete Zunahme echt ist, doch werden noch weitere Daten benötigt, um das Ausmass des Einflusses des Massenscreening abzuschätzen und die mögliche Beziehung mit der im Jahre 1986 in Tschernobyl freigesetzten radioaktiven Strahlung abzuklären.

Résumé

Le cancer de la thyroïde en Belarus après Tchernobyl: Détection améliorée ou incidence accrue?

La question est posée de savoir si l'augmentation du nombre de cas de cancer de la thyroïde observée chez les enfants en Belarus est réelle et à attribuer à l'irradiation relâchée suivant l'accident nucléaire de Tchernobyl, ou si elle reflète un phénomène artificiel dû à un diagnostique histologique erroné, une déclaration de cas plus complète ou le résultat des campagnes de dépistage qui ont suivi l'accident. Nous avons examiné les préparations histologiques de 120 (75%) des 160 cas survenus chez les enfants de moins de 15 ans rapportés entre 1986 et 1992 au registre des tumeurs de la république de Belarus, et analysé les chronologiques et les distributions géographiques de l'incidence et des caractéristiques des tumeurs. L'incidence des cas déclarés a augmenté de 0,041 par 100 000 en 1986 à 2,548 en 1992. Le diagnostique de carcinome a été confirmé dans 94% des tumeurs re-examinées. A l'exeption d'un seul cas de carcinome médullaire, toutes les histologies étaient du type papillaire. La plupart des tumeurs s'étandaient au delà de la capsule de l'organe, et avaient un diamètre supérieur à 10 mm. Pour les années les plus récentes, les tumeurs mesurées au moment du diagnostique sont devenues légèrement et non-significativement (p = 0,19) plus petites. La proportion des tumeurs ayant développé des métastases lymphatiques ou pulmonaires n'a pas changé. L'augmentation de l'incidence des cas confirmés a été particulièrement importante dans le voisinage, ainsi que dans l'ouest et le nord de Tchernobyl, ce qui correspond assez bien à la distribution de la contamination par l'iode-131. Nos données suggèrent donc fortement que l'augmentation observée et réelle. Néanmoins, d'avantage de données sur le dépistage en masse sont nécessaires pour clarifier l'association possible avec l'irradiation consécutive à Tchernobyl en 1986.

Acknowledgements

Thanks are due to Dr. K.V. Kasakov, Minister of Health of Belarus, for supporting international collaboration in Chernobyl-related health research, Professor E.P. Demidchik for entrusting us with the epidemiological analysis of the first childhood thyroid cancer data, the Swiss Federal Office of Public Health for financial support and Christian Langenegger for the art work.

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