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CHERNOBYL-RELATED CANCER AND PRECANCEROUS LESIONS: INCIDENCE INCREASE VS. LATE DIAGNOSTICS

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□ The reported incidence of thyroid cancer in children and adolescents in Soviet Union before the Chernobyl accident was lower than in other developed countries. This is not clearly recognizable from the literature because comparisons of the high incidence figures 4 years after the accident and later have been made with those from the first years after the accident, when the registered incidence had already started to increase. Considering the low pre-accident registered incidence, there was an accumulated pool of undiagnosed thyroid tumors before the accident. The percentage of more advanced cancers, larger in size and less differentiated, was higher after the accident, when the pool of neglected cancers was diagnosed due to the screening and improved diagnostics. Some of these advanced tumors found by screening were interpreted as aggressive radiogenic cancers. The same tendency might be true also for other cancers, e.g. renal cell carcinoma. Furthermore, the screening-effect, false-positivity and registration of non-exposed patients as Chernobyl victims has obviously contributed to the registered incidence increase of malignancy.

Key words: thyroid cancer; ionizing radiation; Chernobyl

INTRODUCTION

The Chernobyl accident provides an example of considerable difference in diagnostic quality of many diseases, particularly, of thyroid cancer (TC), before and after the accident. TC was under-reported before the Chernobyl accident and more accurately diagnosed thereafter. This higher incidence of TC was attributed to the accident, although it was at least partially caused by more complete detection. There was also some over-estimation after the accident due to false-positivity and the diagnosis of borderline lesions as cancer (commented in Jargin 2010a). Many publications have been misleading. For example, in the manuscript by Yablokov *et al.* (2009), references to nonprofessional publications (newspapers, websites of unclear affiliation often with non working URLs, commercial editions etc.) were broadly used to support scientific views and conclusions, overestimating the medical consequences of the Chernobyl accident (commented in Jargin 2010b). In the authors' reply it was acknowledged that "sometimes references in the text do not correspond with those used in the list of references." (Yablokov and Nesterenko

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2010). This is only an example of Chernobyl overestimation in scientific literature; others have been discussed previously (Jargin 2013a, 2011a).

THYROID CANCER INCIDENCE BEFORE AND AFTER THE CHERNOBYL ACCIDENT

The registered incidence of thyroid cancer (TC) in children and adolescents in the former Soviet Union (SU) before the Chernobyl accident was lower than in other developed countries. This is not clearly recognizable from the literature because the high incidence figures 4 years after the accident and later have been compared with the figures from the first years after the accident, when the registered incidence had already started to increase. The following data were reported by Stsjazhko *et al.* (1995). In Belarus (population about 10 million) from 1981-85 the absolute number of TC diagnosed in children under 15 years old was 3 and the corresponding average annual rate per million children under 15 years was 0.3 (Stsjazhko *et al.* 1995). In Ukraine (population about 52 million) the absolute number of TC diagnosed in children under 15 years old was 25 and the corresponding average annual rate per million was 0.5 (Stsjazhko *et al.* 1995). For the northern regions of Ukraine (where contamination after the Chernobyl accident predominantly occurred) the lowest figures were reported with the absolute number of TC diagnosed in children under 15 being 1.0 with a corresponding average annual rate per million of 0.1 (Stsjazhko *et al.* 1995). The same figures were published by IARC (1999) with a reference to (Stsjazhko *et al.* 1995). The incidence of pediatric TC for 1986 (the year of the Chernobyl accident) and subsequent years was presented in the Tables 56 and 57 of the Annex J to the UNSCEAR 2000 Report. In 1986 in Belarus 3 cases were registered and 8 cases were registered in Ukraine (UNSCEAR 2000). The incidence rates, reported per 100,000 children under 15 years at diagnosis per year was 0.2 both for Belarus and Ukraine (UNSCEAR 2000). The UNSCEAR 2008 Report compares the enhanced TC annual incidence rates 4 years after the accident and later not with the pre-accident level but with the years 1986-90 (Annex D, pp. 60-61), when the incidence had already increased to around 5 cases per million per year. The time period was selected for comparison among others because “since 1986 and not earlier, specific data on thyroid cancer incidence have been specifically collected by local oncologists.” (UNSCEAR Secretariat, personal communication of 22 October 2013). It is stated on p. 60 of the Annex D to the UNSCEAR 2008 Report: “The background rate of TC among children under the age 10 years is approximately 2 to 4 cases per million per year”, which is higher than the above-cited figures from (IARC 1999; Stsjazhko *et al.* 1995) and UNSCEAR (2000). Moreover, the number of the registered cases in Ukraine presented in the Table D11 in the Annex D to the UNSCEAR 2008 Report is higher than the figures cited above (IARC 1999; Stsjazhko *et al.* 1995) and is 39 cases for the period 1982-85 rather than 25 cases for 1981-85. These higher

figures are given with references to a “communication to the UNSCEAR Secretariat” and to (Tronko *et al.* 2002). However, this latter publication was not found in the available online databases, on the website of the International Journal of Radiation Medicine (edited in Ukraine): <http://www.physiciansofchernobyl.org.ua/magazine/eng/index.html> (accessed 5 January 2014), and could not be located in libraries. According to a personal communication (UNSCEAR Secretariat, 22 October 2013), UNSCEAR was provided with the hard copies of this paper. Apparently, this publication has never been accessible to the international scientific community. In the Russian Federation, TC was not registered separately until 1989 (Parshkov 2006), when screening after the Chernobyl accident had been initiated and the TC incidence began to increase rapidly.

The registered incidence of pediatric TC before the Chernobyl accident (1981-85) was low in comparison to other developed nations. TC is the most common tumor of endocrine glands in children and adolescents. Its incidence was generally estimated to be approximately 2-5 per million per year (Luster *et al.* 2007). The U.S. Cancer Registry SEER (Surveillance Epidemiology and End Results) reported an annual age-adjusted incidence rate, based on cases diagnosed in 2000-2004, to be 8.5 per 100,000 of which approximately 2.1% had been diagnosed in people under the age 20 (Luster *et al.* 2007). This corresponds to the annual incidence rate of around 1.8 per million. Data from a regional Tumor Registry in Würzburg, Germany were presented by Luster *et al.* (2007), where the age-adjusted incidence rate per 1 million per year for people under 20 years was equal to 2.0. Illustrative are the incidence rates of pediatric TC for different countries for the 1980s - early 1990s published by IARC (1999) and available online as a table in Demidchik *et al.* (2007), <http://www.scielo.br/img/revistas/abem/v51n5/a11tab1f.gif> (accessed 5 January 2014). An extract is presented here as Table 1.

It is visible from Table 1 that the incidence is generally higher in more developed countries, most likely due to the better diagnostics and cover-

TABLE 1. Thyroid cancer incidence in children 0-14 years old (IARC 1999; Demidchik *et al.* 2007).

Country (region)	Period	Crude incidence rate per million per year	Age standardized incidence rate
Belarus (commented in the text)	1981-85	0.3	-
Ukraine (northern regions; commented in the text)	1981-85	0.1	-
Bulgaria	1980-89	0.7	0.6
Canada	1982-91	1.6	1.4
Czech Republic	1980-89	1.1	0.9
Nigeria (Ibadan)	1983-92	0.2	0.2
Norway	1980-89	1.4	1.2

age of the population by medical checkups. Comparing these figures with those for Belarus and Ukraine (IARC 1999; Stsjazhko *et al.* 1995), cited above, it is evident that there must have been a pool of undiagnosed TC in the population of the former SU prior to the Chernobyl accident.

The percentage of more advanced cancers was higher amongst cases diagnosed for the first time after the Chernobyl accident. This is probably due to initial diagnosis of the pool of previously undiagnosed malignancies, modernization of histopathological laboratory equipment, as well as post-Chernobyl “radiation phobia” (Mould 2000) being at its highest. This is confirmed by the fact that the “first wave” TCs after the Chernobyl accident were on average larger in size and less structurally differentiated than those detected later (Williams *et al.* 2004). Supporting passages can be found in the recent monograph about Chernobyl-related TC (p. 76, translated from Russian): “If we assume that all tumors grow at approximately the same speed, those with a longer latency period must be bigger. In reality they were somewhat smaller” or “Tumors with a shorter latent period show more pronounced intra- and exrtathyroid spread.” (Abrosimov and Lushnikov 2006). Histologically, TCs in patients from contaminated territories were described as especially aggressive tumors, which was reported in many publications, some referenced in (Naing *et al.* 2009). However, Naing *et al.* (2009) concluded on the basis of a large cohort of patients with TC developed after radiotherapy for benign conditions that “thyroid cancers following external radiation exposure are not, on average, more aggressive than other thyroid cancers.” Comparisons with tumors in other developed countries indicated a higher percentage of extra-thyroidal extension in TC in Belarus and Russia (UNSCEAR 2000); and a higher percentage of lymph node metastases among pediatric TCs from Belarus in comparison with France and Italy was reported (Pacini *et al.* 1997). Table 2 shows figures reported by Tronko *et al.* (1999) on the basis of the TNM classification (Tumor-Nodes-Metastasis classification of malignant tumors) of TC in children younger than 14 years diagnosed in Ukraine before and after the Chernobyl accident. It shows that the most advanced stage (T4) was diagnosed in about 50 % of all 244 post-Chernobyl pedi-

TABLE 2. Thyroid carcinoma in children and adolescents in Ukraine before and after the Chernobyl accident: TNM Classification (Tronko *et al.* 1999). Number of patients (%).

TNM	1981–1985	1986–1990	1991–1995	1996–1996	Total
T1 (children)	–	–	4 (2,7)	1 (1,6)	5 (2,0)
T2 (children)	3 (100)	9 (31,0)	49 (32,4)	18 (28,6)	79 (32,4)
T3 (children)	–	6 (20,7)	27 (18,2)	6 (9,5)	39 (16,0)
T4 (children)	–	14 (48,3)	69 (46,3)	38 (60,3)	121 (49,6)
N2 (children)	1 (33,3)	9 (31,0)	45 (30,2)	22 (34,9)	77 (31,5)
T4 (adolescents)	3 (42,8)	5 (71,4)	18 (66,7)	10 (66,6)	36 (65,5)

atric TC cases. In adolescents, the percentage was even higher: 66-71 % (Table 2). To grow to a T4 stage, a tumor needs time. The high percentage of T4 cases can be partly explained by the screening effect of detection of previously undiagnosed cancers.

The increased incidence of TC after the Chernobyl accident was so substantial that an elevation of the background annual incidence rate by several cases per million would have a limited impact on the interpretation of this increase as a consequence of the accident. Considering the generally slow growth of papillary TC and the existence of latent/dormant cases, undiagnosed cases could have accumulated over many years. If the background annual incidence of pediatric (age up to 15 years) TC, as discussed above, was 2-4 cases per million, then the maximum size of the pool of undiagnosed TC would be 30-60 cases per million. If these were all diagnosed during the period of 5 years after the drastic incidence rise (1991-1995), then the maximum incidence rate (increased only due to this mechanism) would be around 8-16 cases per million per year. The reported figures were higher. The graph 3 by Balonov (2013), reproduced from UNSCEAR (2008), shows post-accident rates among people exposed as children and adolescents in Belarus increasing to the values between 30 (males, years 1991-95) and 120 (females, 2001-05) cases per million per year. Obviously, other mechanisms such as screening-effect, false-positivity, registration of dormant, latent, questionable TC, microcarcinomas and thyroid tumors of uncertain malignant potential as cancers, and other factors including false registration of non-exposed patients as Chernobyl victims, have additionally contributed to the drastic incidence increase; more details are in Jargin (2010a, 2011a). Ability of the screening to enhance registered TC incidence many times, even in the most developed countries, was known also before the Chernobyl accident (Jaworowski 2010).

The UNSCEAR 2008 Report concluded that no cancer incidence increases, other than TC in patients exposed during childhood or adolescence, can be attributed to irradiation from the Chernobyl accident. However, the above considerations do not only pertain to TC. The following was stated about renal cell carcinoma (RCC): “Recent studies have shown that during the period subsequent to the nuclear Chernobyl accident (April 1986), an increase in morbidity (4.7 to 9.8 per 100,000 of the total population), aggressiveness, and proliferative activity of RCC from Ukrainian patients is recognized” (Morell-Quadreny *et al.* 2011). The increase in “aggressiveness” of the RCC was probably caused by detection in Ukraine of previously neglected cancers by means of improved diagnostic methods. In accordance with this hypothesis, the tumors from Ukraine had on average a higher histological grade than the control cases from Spain (Romanenko 2006a; Jargin 2007). In particular, “the dramatic increase of aggressivity and proliferative activity” was found in RCC

from Ukraine (Romanenko *et al.* 2000a), while “the majority of the high grade tumors occurred in the Ukrainian (rather than in the Spanish) groups” (Romanenko *et al.* 2001a), which can be explained by the on average earlier detection of malignancies in Spain.

Another illuminating report is that the chromosomal rearrangement of the tyrosine kinase proto-oncogene RET/PTC3 was found to be more frequent in TC of non-exposed patients from Ukraine (living outside the contaminated areas) than in TC from France: 64.7 % vs. 42.9 % (Di Cristofaro *et al.* 2005). This could have been caused by earlier tumor detection in France, because RET/PTC3 is probably a time-related marker (Jargin 2012b). Remarkable data were reported by the same researchers about thyroid adenoma. The RET rearrangements were found in 57.1 % of the adenomas in non-exposed patients from Ukraine and in absolutely 0 % of the adenomas from France (Di Cristofaro *et al.* 2005). This discrepancy can be explained by a remark from the same article that at a re-examination, in 8 from 14 of the adenomas from Ukraine (but in not one adenoma from France) were found groups of cells with “limited nuclear features of papillary cancers” (Di Cristofaro *et al.* 2005), which sounds strange for a pathologist and indicates uncertainty of the histopathological diagnostics.

Diagnostic uncertainty is a probable explanation for another paradox. In different groups of men with benign prostatic hyperplasia (BPH) and women with chronic cystitis, from the territories recognized as contaminated after the Chernobyl accident and the city of Kiev, severe urothelial dysplasia and carcinoma in situ (CIS) were found by bladder biopsy as frequently as in 56-92 % of all random cases (Romanenko *et al.* 2002, 2006b, 2009). Kiev (population about 3 million) did not count officially to the contaminated territories; average individual radiation doses remained there comparable with those from the natural radiation background (Borovikova *et al.* 1991; Likhtarev *et al.* 1992). The random selection mode was pointed out: “The Institute of Urology in Kiev during 1994-2006 collected all BPH patients who underwent suprapubic prostatectomy, and all these patients were included in our study in different years without exception” (Romanenko *et al.* 2009). Furthermore, the following was stated about patients with BPH studied by bladder biopsy: “Irradiation cystitis with multiple foci of severe urothelial dysplasia/CIS and some invasive transitional cell carcinoma were observed in 96/66, 76/56 and 56/8 % of patients in groups I, II and III respectively” (group III was from non-contaminated areas) (Romanenko and Fukushima 2000). In the handout by the same authors, distributed at the XXIII International Congress of the International Academy of Pathology (IAP) on 15-20 October 2000 in Nagoya, Japan, the following was written: “Histologically the different forms of proliferative cystitis, which were frequently combined and had features of irradiation cystitis with multiple

areas of severe dysplasia and carcinoma in situ (CIS), sometimes associated with small transitional-cell carcinoma (TCC), occurred in 97 % of patients from the radiocontaminated areas of Ukraine.” Such a high prevalence of severe dysplasia and CIS in randomly selected BPH patients is obviously unrealistic and indicative of the false-positivity that probably resulted in overtreatment and over-manipulation including cystoscopies with biopsies, which, among others, could have caused transmission of infection such as hepatitis C or G (Saludes *et al.* 2013; Vanhems *et al.* 2003). It cannot be excluded that the so-called “Chernobyl cystitis” or “irradiation cystitis” (Romanenko *et al.* 2001b; 2009), characterized not only by urothelial dysplasia and CIS but also by “reactive epithelial proliferation associated with hemorrhage, fibrin deposits, fibrinoid vascular changes, and multinuclear stromal cells” (Romanenko *et al.* 2001b) was at least in part caused and/or maintained by repeated cystoscopies with mapping biopsies, electrocoagulation etc. The concept of “Chernobyl cystitis”, reported by the same authors to be widespread in contaminated territories and Kiev, has probably fostered radiophobia and facilitated recruitment of subjects for the studies. Some histopathological images from (Romanenko 1982; Romanenko *et al.* 1985, 2000b, 2009; Samsonov 1993; Paltsev and Anichkov 2005), potentially conducive to false-positivity, were commented by Jargin (2013b, c, 2011b).

The above and previously published (Jargin 2011a, 2012a, b) arguments question the cause-effect relationship between radiation and cancer incidence increase after the Chernobyl accident. With regard to TC, such relationship cannot be excluded, although it is known that the registered incidence has increased also due to the factors unrelated to radiation (UNSCEAR 2008). Such a high incidence and short induction period have not been experienced in other exposed populations (IARC 2001). In addition to the screening-effect and improved registration and reporting (Cardis 2007), the following mechanisms obviously contributed to the dramatic increase of TC after the Chernobyl accident: registration as Chernobyl victims of patients brought from non-contaminated areas, classification of questionable and borderline lesions as cancers as well as some percentage of false-positivity. Mechanisms of false-positivity have been discussed previously (Jargin 2009, 2010a). Iodine deficiency, and goiter associated with it, was also a contributing factor (IARC 2001) because more thyroid nodules have been found by the screening, providing more opportunities for the overdiagnosis of malignancy. Data about verification by expert commissions of post-Chernobyl pediatric TC in Russia provided evidence for false-positivity; more details are in Jargin (2010a). Remarkable observations about post-Chernobyl attitude to thyroid nodules can be found in Russian-language professional literature (translation): “Practically all nodular thyroid lesions in children, independently of their size, were regarded as potentially malignant neo-

plasms, requiring urgent surgical operation” and “Aggressiveness of surgeons contributed to the shortening of the minimal latent period.” (Parshkov 2006) As discussed above, false-positivity also occurred in regard to the lesions of the urinary bladder (Jargin 2013b). False-positive cases, not covered by verifications, have remained undisclosed, the more so that some archives of histological specimens and paraffin blocks were in a poor condition.

Some special features of the Chernobyl-related pediatric TC should be addressed. Nearly all of them were of papillary type with relatively high frequency of the solid and/or follicular pattern (IARC 2001). A reason thereof is that the diagnostics of follicular TC sometimes requires numerous high-quality histological sections from the capsular area of a nodule, not usually done because of technical reasons and insufficient awareness of the minimally invasive follicular carcinoma, absent in Russian-language literature of that time. Therefore, if papillary TC was sometimes over-diagnosed, follicular TC must have been under-diagnosed. Furthermore, it is known from practice that more advanced papillary TCs often contain solid and/or follicular structures, while the tumors are usually graded and classified according to the least differentiated or most malignant components. Finally, regarding the absence of significant TC increase in children born after the Chernobyl accident, the data pertaining to them originated from a later period, when quality of diagnostics had improved, “radiation phobia” (Mould 2000) had subsided, and there were no motives to enhance the figures (see Jargin 2010a, 2011a).

In conclusion, the medical consequences of the Chernobyl accident have been overestimated. Realization of this fact is of importance for the correct assessment of the dose-response relationship with regard to the low doses of ionizing radiation (Calabrese 2013a, b), carcinogenicity of radioiodine and other radionuclides, for a more realistic attitude to the radiation safety norms and for the future of nuclear energy.

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