Low-dose Ionizing Radiation: Overestimation of Effects and Overtreatment

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Abstract: - This article is a narrative review. The systematic approach is hardly applicable if more and less reliable data are intermingled due to bias, conflicts of interest, political and economical motives. The motives to overestimate Chernobyl consequences included financing, international help and cooperation. Certain writers exaggerating medical and ecological consequences of anthropogenic increase in the radiation background contribute to a strangulation of atomic energy. This is in the interests of fossil fuel producers. Nuclear power has returned to the agenda because of the concerns about energy demand and climate changes. Health burdens are the greatest for power stations based on coal and oil. The burdens are lower for natural gas and still lower for atomic energy. The same ranking applies to the greenhouse gas emissions and hence probably for the climate change. Among limitations of epidemiological studies are the dose-dependent selection and self-selection. It can be reasonably assumed that people knowing their higher doses would be more motivated to undergo medical checkups being at the same time given more attention. Therefore, diagnostics is on the average more efficient in people with higher doses. In this connection the literature on the post-Chernobyl thyroid and renal cancer, urinary bladder, cataracts and other lesions is reviewed here. Results of some Chernobyl-related studies should be re-interpreted, taking into account that many cancers found by the screening during the first decade after the accident, or brought from non-contaminated areas and recorded as Chernobyl victims, were in fact advanced neglected malignancies. The misinterpretation of such tumors as aggressive radiogenic cancers should not mislead towards overtreatment. Examples of the overtreatment are reviewed here. Ionizing radiation is a known carcinogen but there is no evidence of carcinogenicity below a certain level. Apparently, living organisms have adapted to the natural radiation background. The background has been decreasing during the time of life existence. The screening effect and increased attention of exposed people to their own health will probably result in new reports on the enhanced cancer and other health risks in areas with an elevated natural or anthropogenic radiation background. This will prove no causality. A promising approach to the research of dose-response relationships are lifelong animal experiments.

Key-Words: - Ionizing radiation, Chernobyl accident, East Urals radioactive trace, cancer

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1 Introduction

This article is a narrative review. The inter-study heterogeneity [1], a mixture of more and less reliable data assessed together is a limitation of systematic reviews and metaanalyses. The systematic approach is hardly applicable to the topic, where bias, conflicts of interest, politics and economics are intermingled. An impartial evaluation by an inside observer has advantages in this regard. After the Chernobyl accident (hereinafter accident), numerous publications appeared, where diseases among residents of contaminated territories were regarded to be radiogenic; some of such studies have been reviewed [2-6]. Certain data can be explained by artefacts e.g. more pronounced effects of lower doses compared to higher doses in some experimental and epidemiological research [7]. Potential motives to exaggerate Chernobyl consequences included financing, international help, scientific careers and cooperation. Later on, other motives have come to the fore: the strangulation of

nuclear industry and boosting of fossil fuel prices. Potential biases of epidemiological studies are known: unfounded classification of spontaneous conditions as radiation-induced, conclusions about incidence increase of diseases without adequate control, tendentious citation, misquoting of professional literature [2-6], data trimming and other varieties of scientific misconduct [3,8]. The publication bias should be mentioned: some studies with negative results were neither included in databases nor cited in reviews [9]. Other bias and confounders have been discussed [10-14]. Of particular importance are the dose-dependent selection, self-selection and recall bias noticed in various cohorts exposed to low-dose ionizing radiation [15-17]. It can be reasonably assumed that people knowing their higher doses would be more motivated to undergo medical checkups being at the same time given more attention. Therefore, diagnostics would be a priori more efficient in patients with higher doses. Apparently, certain writers exaggerating medical and ecological consequences of a slight anthropogenic increase in the radiation background contribute to a strangulation of the atomic energy. This is in the interests of fossil fuel producers. An ideological bias and/or conflict of interest seem to be present in many cases. Nuclear power has returned to the agenda because of the concerns about increasing global energy demand and climate changes. Health burdens are the greatest for power stations based on coal and oil. The burdens are inferior for natural gas and still lower for atomic energy. The same ranking applies to the greenhouse gas emissions and hence potentially for the climate change. Well-run nuclear plants pose less risk than fossil fuel power stations [18,19]. However, durable peace is needed because nuclear facilities are potential targets.

Among limitations of some epidemiological studies has been disregard for the natural radiation background. The following dose comparisons will be referred to in this review. Individual doses from the natural radiation background are expected to range from 1.0 to 10 mSv/a; some national averages are ≥10 mSv/a [20,21]. The average for Russian Federation (RF) is 3.36 mSv/a; the highest background is in the Altai region - 8.6 mSv/a [22]. According to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the average individual whole body dose to 6 million residents of the territories, officially recognized as contaminated by the Chernobyl fallout, was ~9 mSv received in the period 1986-2005 [23]. According to the data on solid cancers and leukemia from the Life Span Study (LSS) of atomic bomb survivors in Japan, there was a significant dose-effect association in the survivors who received ≤500 mSv but the statistical significance disappeared if only doses ≤200 mSv were considered [24,25]. The doses ≤100 mGy at low rates can induce adaptive responses, in particular, counteracting carcinogenesis [26].

2 Methods

The search of the international literature was performed predominantly using PUBMED/MEDLINE. Russian-language professional publications were searched in the electronic database eLIBRARY.ru. Books were found in the Russian State Library and other libraries. The data have been analyzed taking into account interviews with pathologists, radiologists and other experts in research centers and medical institutions including those on the territories formerly contaminated by the Chernobyl fallout.

3 Thyroid nodules

It is common knowledge that the incidence of thyroid cancer (TC) among people exposed at a young age increased after the Chernobyl accident. There has been no convincing evidence of a cause-effect relationship between radiation from the Chernobyl fallout and the frequency elevation of other cancers [23,27]. The dramatic increase of TC 4-5 years after the accident came as a surprise for the scientific community; it could be predicted neither from LSS nor from studies of medical exposures [28-37]. The bulk of evidence in support of relationships between radiation and TC incidence increase came from epidemiologic studies. Possible biases and confounding factors in such studies have been mentioned above.

Prior to the accident, the detection rate of pediatric TC had been lower in the former Soviet Union (SU) than in other developed countries [38,39]. Only 5 children were diagnosed with TC in Belarus in the period 1978-1985 [38]. During 1981-1985, the TC incidence in children ≤15 years old in the northern regions of Ukraine was 0.1 and in Belarus - 0.3 per million per year [39]. For comparison, the US Cancer Registry reported the total incidence rate of 85 per million per

year (2000-2004), ~2.1% diagnosed at the age ≤20 years. According to the Tumor Registry in Germany, the incidence was 69 in adults, 0.2 in children 0-9 years old, 0.4 in those 10-14 years old, 1.4 in adolescents 15-19 years and 2.0 per million per year in total for people ≤20 years old [40]. The TC incidence tends to increase with age: 0.43 (5-9 years old), 3.5 (10-14 years) and 15.6 (15-19 years) per million per year [41,42]. The predominant incidence elevation of TC in children and adolescents after the accident is attributable at least in part to the selection bias: children have been given more attention, they are accessible for the screening at schools and preschools; mass checkups were performed in the atmosphere of high alertness. Of note, the TC incidence in Belarus in people ≤18 years old has not declined to the basic level: it amounted to 15.7 cases/million/year in 2012 [43,44], although the radiation background is not elevated long since. It is known that screening can elevate the detection rate of TC many times due to a reservoir of clinically silent cancers and tumors with unknown malignant potential [10,45].

The state of facts discussed above tends to be obfuscated: "The background rate of TC among children under the age 10 was approximately two to four cases per million per year" [46]. The elevated TC incidence 4 years after the accident and later is compared by the UNSCEAR [46] not with the pre-accident level but with the period 1986-1990, when the incidence had already increased up to 4.1 cases/million/year in those exposed as children ≤10 years old and up to 5.4 in those exposed at ≤18 years [23]. The period 1986-1990 was used "since 1986 and not earlier, specific data on thyroid cancer incidence have been specifically collected by local oncologists" (UNSCEAR Secretariat, e-mail communication of October 2013). It was claimed that the frequency of sporadic TC in Belarus in the period 1971-1985 did not differ from international statistics [47] with the reference to [48], where no such data were found. It was stated that the background TC incidence in children ≤10 years old in Belarus and Ukraine was 2-4 cases per million per year [49], which disagrees with the statistics cited above [39]. The low detection rate before the accident indicates that there had been neglected cancers in the population. The screening after the accident found not only small nodules but also advanced cases interpreted as rapidly growing radiogenic malignancies developing after a short latent period. Besides, many people strived for recognition as Chernobyl victims to avail healthcare and other provisions [50]. For the lack of screening, cases from "clean" areas were probably on the average more advanced than those found on the contaminated territories. In accordance with this concept, TCs diagnosed in the first 10 years after the accident were larger and of higher grade than those detected later [51] as neglected cancers were sorted out thanks to the screening and high awareness of the population. As a result, first wave TCs after the accident were deemed comparatively poorly differentiated, aggressive and prone to metastasizing [52].

The counting of tumors with uncertain malignant potential and microcarcinomas among cancers, overdiagnosis and registration of non-irradiated individuals as radiation-exposed, have contributed to the increased TC frequency after the accident [4-6]. The prevalence of papillary thyroid microcarcinoma was estimated at 1/200 people after their thirties [53], their detection by screening would enhance the registered TC incidence. Statements like the following may be confusing: "77% of primary tumors were larger than 1 cm, suggesting that these were not incidental TCs detected by screening" [54]. Note that the screening found not only small nodules but also large TCs, neglected because of the incomplete population coverage by medical checkups before the accident. Accordingly, the "first wave" TCs after the accident tended to be larger and less differentiated than those diagnosed at a later date [51]. Considering the misclassification of advanced TCs as aggressive radiogenic malignancies, some markers of supposedly radiogenic cancers must characterize, on the average, a later stage of the tumor progression [4,5]. As example of such marker, the Ret/PTC3 chromosomal rearrangement has been discussed previously [55,56]. Predictably,

the mass screening in the areas where pediatric TC had been rarely diagnosed before, in the atmosphere of enhanced alertness, resulted in an elevation of the detection rate. As for the lower (albeit enhanced as mentioned above [43,44]) TC incidence in people born after the accident, the data pertaining to them originated from later time, when the quality of diagnostics improved, radiophobia declined, and there were no motives to artificially enhance the figures.

A recent example is a study comparing 359 papillary TCs from patients exposed to the Chernobyl fallout with 81 TCs from patients born ≥9 months after the accident [57]. The "study population included a substantial number of papillary TCs occurring after <100 mGy." The study reported "…radiation dose-related increases in DNA double-strand breaks in human TCs developing after the CA… Non-homologous end-joining (NHEJ) the most important repair mechanism… increased likelihood of fusion versus point mutation drivers" [57]. These findings could be expected in advance: mutations tend to accumulate with the tumor progression. The double-strand breaks with imperfect repair come along with the genome diversity [58]. The NHEJ repair pathway is potentially mutagenic [59,60]. Interestingly, no association of the radiation exposure with transcriptomic and epigenomic markers was found [57]. This indicates that the latter markers are not immediately linked to the tumor progression. On the contrary, epigenetic mechanisms have been associated with favorable (hormetic) effects of low-dose exposures. There has been evidence indicating that epigenetic mechanisms are involved in the radiation-induced life prolongation of experimental animals [61]. As for the controls born after the accident [57], the data pertaining to them originated from a later time, when the pool of neglected cases had been exhausted by the screening. Considering the above, the average stage and grade of TCs in the exposed group must have been higher than those among the controls due to non-radiation-related reasons. The causative role of low-dose radiation e.g. "a dose-dependent carcinogenic effect of radiation derived primarily from DNA double-strand breaks" [57] is therefore unproven. The notion that the "…increased detection of pre-existing papillary TCs in the population that may not become clinically evident until later, if at all, due to intensive screening and heightened awareness of thyroid cancer risk in Ukraine" [57] had been put forth earlier [4,5]. The articles [4,5] were not cited in [57]. In conclusion of this section, results of some Chernobyl-related studies should be re-interpreted, taking into account that many cancers found by the screening during the first decade after the accident, or brought from clean areas and recorded as Chernobyl victims, were in fact advanced neglected malignancies. The misinterpretation of such tumors as aggressive cancers should not mislead towards overtreatment (discussed below).

4 Kidney and urinary bladder

The series of studies [62-68], discussed previously [69], compared renal-cell carcinomas from Ukraine, including territories contaminated by the Chernobyl fallout, with those from Spain and Colombia. The cancers from Ukraine were on the average of a higher histological grade than the controls from abroad. In the most recent research, microvessel density in the tumor tissue from patients residing both in "highly" and in "low contaminated areas of Ukraine" was significantly higher than in cases from Spain and Colombia ($p<0.01$). The difference between both aforesaid groups from Ukraine was statistically insignificant. The increased angiogenesis was associated with a higher immunohistochemical expression of the marker VEGF (vascular endothelial growth factor) [68]. The authors concluded that irradiation causes an increase in the microvessel density, which is in turn associated with a de-differentiation and worse prognosis of renal cancer [66,68,70]. The proposed increase in "aggressivity" of both TC (discussed in the preceding section) and renal cancer after the accident [62,71] can be explained by finding of undiagnosed advanced tumors, misinterpreted as radiogenic cancers with the "rapid onset and aggressive development" [71]. Similarly to TC, the special features of renal cancer from the former SU must have been caused by late cancer detection.

In view of the above dose comparisons, radiation doses from the natural background should be specified in studies where patients or specimens from different parts of the world are compared. The doses in a control group may turn out to be comparable with those in the "exposed" group, for

example, in Spain vs. Kiev [67]. The average individual dose from the natural background in Spain is ~5 mSv/a [72,73]. The mean whole-body dose in Kiev was estimated at ≤10 mSv in 1986, declining in subsequent years [74]. No doses were quoted in the papers [62-68]; it is only claimed with a self-reference: "This observation also supports the prevailing suspicion [66] that in Ukraine the radiation contamination levels were similar within and beyond the officially-established 80-km extent of radiation contamination around Chernobyl [75]" [68]. The report [75] is not in the public domain.

By analogy with TC, the tendency of underreporting exists also for renal cancer [76]. Some neglected cases, found by the screening, self-reported or brought from clean territories and misclassified as Chernobyl victims, were interpreted as rapidly growing radiogenic malignancies. As mentioned above, renal cancers from Ukraine tended to be less differentiated than Spanish cases. Ukrainian specimens more often demonstrated the de-differentiated sarcomatoid histology: 62 from 236 (26.3%) of Ukrainian vs. 11 from 112 (9.8%) of Spanish cases ($p<0.001$) [62]; the statistically significant difference was confirmed later on [64]. The following citations are illustrative: "The dramatic increase of aggressivity and proliferative activity" was found in renal cell carcinomas from Ukraine, while "the majority of the high grade tumors occurred in the Ukrainian (rather than in the Spanish) groups" [62]. These differences are explainable by an earlier, on the average, cancer diagnostics in Spain and finding by the screening of advanced cases in Ukraine.

Certain markers of renal cancer from the former SU compared to those from other parts of the world need a re-interpretation e.g. the absence of significant differences in the expression of ubiquitin [67]. Considering that renal cancers from Ukraine were higher-grade than those from Spain, these data indicate that ubiquitination does not correlate with the neoplastic progression. On the other hand, VEGF was found significantly more often in clear-cell renal carcinomas from Ukraine than in those from Spain and Colombia [68]. The assertions that the expression of VEGF in renal cell carcinomas and its serum level was related to the tumor stage and grade [68] agrees with the literature [70,77-79]. It can be generalized onto other markers, where significant differences between Spanish and Ukrainian cases were detected, especially the factor kappa B (NF-kappa-B), its p50 and p65 subunits [64]. The ≥10% positivity of the tumor cells for p50 was detected in 25 from 59 (42.4%) of specimens from Ukraine and in 4 from 19 (21.1%) in those from Spain. The ≥50% cell positivity for p65 was found, correspondingly, in 18 from 59 (30.1%) and 1 from 19 (5.3%) of the cases ($p<0.05$) [64]. These data are not surprising as activated NF-kappa-B is considered to be a promoter of neoplastic progression [80-85]. By analogy with chromosomal fusions Ret/PTC3 in papillary TC [55,56], there is probably an association between the tumor de-differentiation and those markers, where differences between the Ukrainian and Spanish groups were found. This is a promising field for research and re-interpretation of data already obtained in studies comparing malignancies from different regions. Some markers may reflect the diagnostic efficiency and thus characterize healthcare services in different countries [86].

5 Malignant vs. benign conditions

As discussed above, the diagnosis of diseases is a priori more likely in people with higher doses. The dose-dependent incidence increase of cardio- and cerebrovascular diseases among employees of the Mayak Production Association (MPA) and residents of the Techa river valley was not accompanied by a proportionate elevation of mortality [87-92]. This discrepancy can be attributed to a diagnosis of mild, borderline and unverified cases in patients with relatively high doses. Furthermore, the excess relative risk (ERR) per unit dose for leukemia (except chronic lymphocytic leukemia) among MPA workers based on the incidence figures was considerably higher than that based on mortality [93]. A more efficient detection of latent cases is a probable mechanism. As for lymphocytic leukemia, it is often accompanied by lymphadenopathy hence remaining comparatively rarely undiagnosed. Accordingly, the screening effect must be less pronounced in lymphocytic than in other leukemias.

Elevated risks of non-malignant diseases (cardio- and cerebrovascular, respiratory, digestive and others) have been found in Chernobyl, MPA and Techa river cohorts [90,94-106]. For example, the average dose from external gamma-radiation was ~0.54 Gy in males and 0.44 Gy in females in a study, where the frequency of lower extremity arterial disease was found to correlate with the cumulative external dose [100]. The atherosclerosis frequency was significantly higher in MPA workers with doses ≥0.5 Gy than among those with lower doses; the same for ≥0.025 Gy liver dose of internal alpha-radiation [97]. The risk of cerebrovascular diseases per unit dose among MPA workers was reported to be even higher than that in LSS

[87,89,103]. In the Techa River cohort, the risk of cardiovascular conditions including ischemic heart disease was found to be higher than in LSS [91], where the exposure was acute and expectedly more efficient than that protracted over years. As mentioned above, the dose-dependent incidence increase of cerebrovascular and ischemic heart disease among MPA employees was not accompanied by an increase in mortality. This can be attributed to a dose-dependent diagnostic efficiency with recording of mild and borderline cases in people with higher doses. According to the same scientists, the incidence of cerebrovascular diseases was significantly increased among MPA workers with cumulative external doses ≥0.1 Gy [89,107]. Based on the data from the MPA cohort, a "specific pathogenesis of radiation induced cerebrovascular diseases" after low-dose exposures was expounded [107]. In comparison, the UNSCEAR could not make any conclusions about causal relationships between doses ≤1-2 Gy and the excess incidence of cardiovascular or non-malignant diseases in general [108]. According to the International Commission on Radiological Protection (ICRP), there is an excess risk of heart disease after radiotherapy with heart doses ~1-2 Gy [109]. The value 1-2 Gy may be an undervaluation due to bias in epidemiological research. It is known that cardiovascular derangements can appear after radiotherapy with doses to the heart ~40 Gy. Lower doses were discussed [109-112] being, however, still much higher than averages for the MPA facility, Techa River and Chernobyl populations. There may be factors others than radiation e.g. chemotherapy [113] and stress, leading to cardiac derangements or symptoms in patients under radiotherapy. Besides, oncologic patients are probably better examined than the general population. The doses associated with a heart injury in experimental animals have also been much higher than average doses in the aforesaid populations [109,114,115]. In some experiments and epidemiological studies, low doses were associated with decreased risks of vascular disease [109]. In accordance with the hypothesis discussed in the next paragraph, an earlier study from the same institution found no associations between individual cumulative doses and the frequency of ischemic heart disease [116]. In the past, long-term observations found no differences of cardiovascular diseases in MPA workers compared to the general population [117]. There are intriguing data on the association between radiotherapy (~0.1 Gy) for tinea capitis and the risk of carotid stenosis. The irradiated subjects were significantly older, more frequently hypertensive, had higher glycated hemoglobin and alkaline phosphatase levels than healthy controls [118]. It can be speculated that a cause-effect relationship of these findings was not with radiation but with a predisposition to skin mycosis or symptoms such as itching.

The tendency to overestimate health risks from low-dose exposures in the MPA facility and Techa river cohorts has been noticed since approximately the year 2005. Earlier studies reported no increase in the cancer incidence at doses ≤520 mSv or generally in all MPA workers. Existence of a threshold was deemed possible [116,117,119-122]. The risk of leukemia per 1 Gy was reported to be 3.5 times lower in the Techa river cohort than in LSS i.e. effectiveness of the acute exposure was expectedly higher than that of protracted exposures [123,124]. The relative risk of solid cancers in the Techa river cohort increased with age, whereas in LSS it decreased [124,125]. The risk elevation with age is typical for spontaneous cancer. No significant increase in cancer morbidity and mortality was found in residents of the territories contaminated after the 1957 Kyshtym accident i.e. the East Urals Radioactive Trace [124]. Later on, the same researchers reported elevated cancer incidence and mortality among exposed people in the Urals [126]. In more recent publications, the same scientists concluded that the "carcinogenic efficiency" of chronic exposures in the Urals is not lower than that of acute exposure in LSS [126-129]. It can be surmised that a directive aimed at a strangulation of the nuclear energy and boosting of fossil fuel prices was behind these changes in the attitude. Politically motivated manipulations of statistics in the Soviet and post-Soviet science are known [6,11].

The author agrees with Prof. Mark P. Little that some research "should therefore probably not be used for epidemiologic analysis, in particular for the Russian worker studies considered here [99,101,102,104]" [130]. Certain data on the enhanced cancer risk after low-rate exposures are indeed doubtful. For example, a significantly increased risk of non-melanoma skin cancer was reported among MPA workers [131]. The workers and probably some medics were informed about individual work histories, whence total doses could be estimated, potentially affecting the extent of examinations and self-reporting. An observation

bias is hardly avoidable under such conditions. In LSS, the non-melanoma skin cancer dataset was compatible with a threshold at ~1 Gy [132]. Skin doses were unknown in the study [131]. The MPA employees were exposed mainly to gamma rays that have a long penetration distance, so that energies absorbed within the skin were correspondingly low. It comes as no surprise that premalignant skin lesions such as actinic keratosis were "very rare" [131]. Considering the above, a cause-effect relationship between radiation and skin tumors in [131] is unproven. Risk estimates by the same researchers [95] were found to be significantly higher than those by other experts [133].

Concluding the recent review on nuclear workers, Prof. Richard Wakeford writes: "Ultimately, it will be powerful epidemiological studies examining exposure conditions of direct relevance to radiological protection against low-level radiation exposure that will provide the most reliable evidence" [93]. Neither the radiation background nor experiments are mentioned in this connection. Reliable information on the effects of low radiation doses can be obtained in large-scale animal experiments. Annual average doses from the background should be indicated when patients from different parts of the world are compared; otherwise exposures in a control group may turn out to be not significantly different from those in "exposed" cohorts e.g. from Spain and Colombia vs. Ukraine (discussed above) [64,68]. In the International Nuclear Workers Study (INWORKS), many workers received 2-4 mSv/a [93]. This corresponds to doses from the natural background. The mean cumulative doses (red bone marrow - 17.6 mGy, colon - 19.2 mGy) protracted over years (follow-up period 1950-2005) [134] are also consistent with the natural background. These and other considerations about INWORKS have been published: "Failure to account for natural background radiation exposure, the differences in which potentially dwarf the occupational exposures of the study cohort" [135]. Analogous considerations were formulated also earlier [136].

Another citation should commented: "A second important issue in the field of radiation protection is the hypothesis of a reduction of radiation-associated cancer risk per unit dose at low dose-rates [137-139]. Such a hypothesis was derived from observations of biological results, and has been implemented in the system of radiation protection by the introduction of a dose and dose-rate effectiveness factor (DDREF)… For solid cancer mortality, summary estimates of ERR/Gy derived from the LSS and INWORKS were similar in magnitude, a finding that does not support the conclusion of a reduction of ERR/Gy at low dose-rates" [134]. The argumentation about DDREF on the basis of INWORKS and other nuclear worker studies is unconvincing as radiogenic nature of diseases under discussion is unproven [140]. Certain mathematical models suggested that protracted exposures are between 2.0 and infinitely times safer than acute exposures at comparable doses [141] (i.e. DDREF up to infinity). The latter corresponds to a threshold or hormesis concept.

In conclusion of this section, doubtful correlations between low-dose exposures and non-malignant conditions call into question the cause-effect character of such relationships for cancer reported by the same and other researchers [71,128,142-146]. It is known that correlations can be caused by non-radiation factors, systematic errors and biases, in particular, the dose-dependent selection and self-selection.

6 Cataracts

Results of the studies reporting correlations between the cumulative radiation dose and cataract incidence among MPA workers [147-149] have been questioned [150,151]. The risk in higher dose groups starting from 0.25-0.50 Sv was found to be significantly higher than that in the control group with doses ≤0.25 Sv. The average doses were 0.54±0.061 Gy in males and 0.46±0.01 Gy in females [149]. Dose-effect relationships were claimed for cataracts; but the well-known association of the latter with diabetes mellitus was not confirmed [148-150]. This called into question the biological relevance of other results by the same researchers. Supposedly after the criticism [150], the data on diabetes did not reappear in a subsequent article [152]. Remarkably, there were no significant associations of the radiation dose with cataract surgeries [153]. The cataracts including mild cases not requiring surgery were probably diagnosed on the average more efficiently in individuals with higher doses due to an increased attention to their own health and/or attention on the part of medics. Earlier publications with participation of the same researchers asserted that radiation-induced cataracts developed among MPA workers only after exposures ≥4 Gy [154]. According to the UNSCEAR 1982 Report, a minimum of 3-5 Gy is required to produce significant opacities in animals

which are, like humans, not prone to the cataract development. More dose is needed when fractionated. The threshold for chronic exposures was supposed to be in the range 6-14 Gy. Later on, lower thresholds and the no-threshold model have been discussed. Based predominantly on epidemiological studies, the International Commission on Radiological Protection revised preceding recommendations and proposed a threshold of 0.5 Gy for low linear energy transfer radiation [155]. However, some epidemiological studies do not support this lower threshold for cataracts [155]. "A threshold for highly fractionated or protracted exposure was judged as <0.5 Gy mainly from one paper [156] on cataracts at 12-14 years after exposure in Chernobyl clean-up workers" [157], where a possibility of "underestimation of uncertainties" in dosimetry was acknowledged [156]. Objectivity of some Chernobyl-related studies has been questioned [2-6]. A threshold for chronic exposures is regarded to be uncertain for lack of evidence [157]. In the study of radiologic technologists, the cumulative occupational exposure was associated with self-reported cataracts, but not with the cataract surgery [158]. "The population of radiologic technologists… is medically literate" [158]. The self-reporting might have been related to a professional awareness associated with a longer work experience and hence with a cumulative dose. The data on radiologic technologists agree with the concept of a dose-dependent diagnostic efficiency and registration of mild cases not needing surgery. A significantly increased risk of the cataract surgery as a function of radiation dose has hitherto been reported only in LSS [159], where the effect of acute exposure could have been indeed significant. Of note, the reports [152,153] on "a clear and significant increased ERR/Sv in females compared to males" among MPA workers were designated as "the most striking study observing sex effects relating to radiation-induced cataract incidence" [160]. The sex differences can be attributed to a gender-related attitude in the Russian healthcare. It is well known that middle-aged and elderly men visit health care centers (polyclinics) on the average less frequently than women. Middle-aged men sometimes encounter an unfriendly attitude in governmental medical institutions especially if supposed to be alcoholics. Some of them don't seek medical help if they have symptoms or chronic disease. This is probably one of the causes of the relatively short life expectancy. Besides, aged women are often more attentive than men to their own health at least in RF. A higher frequency of cataracts in females than in males was found also in a study of the Techa river cohort [161]. Another observation was made in the same study: the higher frequency of cataracts in Slavic (353 from 2227, 15.9%) than in Turkic people (327 from 4116, 7.9%); the figures are from the paper [161], percentages calculated by the author of this review. The difference seems to be camouflaged in the text: "Standardized cataract incidence rates in Tatars and Bashkirs were 6% higher than those in Slavs" [161]. The "incidence rates" were calculated using not the sample sizes (2227 and 4116) but the total number of individuals with cataracts (353+327) that produced uninterruptable results [161]. Most probably, the difference was caused by a dependence of diagnostic thoroughness on the ethnicity. Comparable inter-ethnic differences were noticed previously [162]: a sixfold higher mortality from circulatory diseases among Turkic people compared to Slavs in the Techa river cohort [91]. It is known that cardiovascular diseases have been habitually written in the former Soviet Union on death certificates in unclear (unexamined) cases [163]. The aforesaid questions the etiological role of radiation in [147-149,152,153,156,161,163].

In conclusion of this section, ionizing radiation is a proven cataractogen [157] but doses and dose rates associated with risks, i.e. potential thresholds, should be further investigated. The number of studies that provide explicit biological and mechanistic evidence at doses ≤2 Gy is indeed "very small" [159]. Reliable information can be obtained in animal experiments.

7 Overtreatment of radiation-related lesions

The misinterpretation of neglected advanced cases as rapidly progressive cancers supported the concept that radiogenic TCs are more aggressive than sporadic ones [51,164-166]. This had consequences for the practice: during the 1990s, thyroid surgery in some institutions of the former SU adopted more radical methods. The following was recommended for the post-Chernobyl pediatric TC: "Radical thyroid surgery including total thyroidectomy combined with neck dissection followed by radioiodine ablation" [38] and/or radiotherapy

~40 Gy [167]. Some experts regarded subtotal thyroidectomy to be "oncologically not justified" and recommended total thyroidectomy with prophylactic neck dissection [168-171]. Less extensive resections were regarded to be "only acceptable in exceptional cases of very small solitary intrathyroidal carcinomas without evidence of neck lymph node involvement on surgical revision" [172]. It was stated in a recent monograph that a bilateral neck dissection must be performed for all TCs independently of their size, histological pattern and lymph node status [173]. This approach is at variance with a more conservative treatment of TC in other countries.

The sources [174-176] were cited in support of the claim: "The most prevailing opinion calls for total thyroidectomy regardless of tumor size and histopathology" [172]. The citation is imprecise: the subtotal thyroidectomy was used or recommended in these studies, in some of them along with total thyroidectomy [174-176]. The sources [176-178] were inexactly cited in the article [169], where the total thyroidectomy with bilateral neck dissection is recommended for all types of pediatric TC. Apparently, the total thyroidectomy was overused also in radiation-exposed thyroid patients in the Urals [179]. The radical procedure is associated with complication risks especially if combined with the neck dissection: hypoparathyroidism, recurrent laryngeal nerve damage, Horner syndrome and pulmonary fibrosis [180,181]. Many thyroid patients were young females potentially concerned about cosmetic aspects. The overall survival rate was very high in young people with differentiated TCs regardless of the extent of surgery [182]. This indicates that the radicalism has been sometimes excessive. Reasonable remarks were published in a review: "After the Chernobyl and Fukushima nuclear accidents, thyroid cancer screening was implemented mainly for children, leading to case over-diagnosis;" "The existence of a natural reservoir of latent thyroid carcinomas, together with advancements in diagnostic practices leading to case overdiagnosis explain, at least partially, the rise in TC incidence in many countries;" "Total thyroidectomy, as performed after the Chernobyl accident, implies patients must live the rest of their lives with thyroid hormone supplementation. Additional treatment using radioactive iodine-131 therapy in some cases may result in potentially short- or long-term adverse effects" [183]. This concept had been formulated also earlier [184-187]. The articles [184-187] were not cited in [183].

Mechanisms of TC false-positivity have been discussed in detail previously; among others, the misinterpretation of nuclear pleomorphism as a malignancy criterion of thyroid nodules [187]. Potentially misleading histological images from Russian handbooks were reproduced and commented [5,187,188]. The post-Chernobyl radiophobia [72] contributed to the overdiagnosis of cancer. This can be illustrated by the following citation (from Russian): "Practically all thyroid nodules, independently of their size, were regarded at that time in children as potentially malignant tumors, requiring an urgent surgery" [189]. It should be stressed in this connection that early detection and treatment is not a golden rule for thyroid nodules as the screening is not regarded to be harmless for asymptomatic patients, for children in particular [53]. Epidemiologists have issued a warning regarding overdiagnosis and overtreatment of patients with thyroid neoplasm. It is essential to exclude adenoma and indolent borderline/precursor tumors that can be treated by excision [190]. As mentioned above, the iatrogenic morbidity is considerable. Finally, the psychological effect and stigmatization as a cancer patient is an unfavorable consequence of the thyroid screening [53].

In regard to renal cancer, the concept of enhanced aggressiveness of post-Chernobyl cases can have unfavorable consequences if surgeons get the message that cancers from radio-contaminated areas tend to be more aggressive than regular ones, while surrounding renal tissues harbor "proliferative atypical nephropathy with tubular epithelial nuclear atypia and carcinoma in situ" [63]. Based on this information, surgeons may decide in favor of nephrectomy more often than clinically

indicated instead of a kidney-preserving procedure.

The same scientists who participated in the renal cancer research discussed above [62-66], found in several groups of patients with benign prostatic hyperplasia or cystitis, residing in Kiev or on territories recognized as contaminated after the accident, severe urothelial dysplasia and/or carcinoma in situ in 56-96 % of consecutive cases [191-196]. In earlier studies, the frequency of severe urothelial dysplasia and carcinoma in situ was 66-73% (contaminated areas) and 56-64% of randomly selective patients (Kiev). This is ~1300 times more than the incidence of bladder cancer in Ukraine (43.1/100,000) discussed by the same writers [192,195,196]. These figures are obviously unrealistic and indicative of the false-positivity. The microphotographs from the papers [191,192] were reproduced in [197]: the histological slides are visibly thick, the nuclei are stained insufficiently. Neither cancer nor severe dysplasia is identifiable. The inadequate fixation, processing-related artefacts and electrocoagulation apparently contributed to the poor quality of specimens. The false-positivity entailed excessive manipulation and overtreatment. The "Chernobyl cystitis" or "irradiation cystitis" characterized by the "reactive epithelial proliferation associated with hemorrhage, fibrin deposits, fibrinoid vascular changes, and multinuclear stromal cells" [196], was probably caused or maintained by repeated cystoscopies, "mapping" biopsies and electrocoagulation. Accordingly, some markers, especially those associated with inflammation and proliferation (mitogen-activated protein kinases, growth factors, TGF-β1, NF-κB, p38) as well as the "marked activation of angiogenesis" [192] characterized chronic inflammation sometimes of iatrogenic etiology. Looking at the images from [198,199] (reproduced in [197]), it seems that false-positive diagnoses of malignant and premalignant bladder lesions by the same experts occurred as early as in the 1980s.

8 Conclusion

The medical surveillance of populations exposed to low-dose ionizing radiation is important; but more consideration should be given to potential bias, especially to the screening effect, dose-dependent selection and self-selection, conflicts of interests, policies of certain companies and governments. Well-conducted epidemiological studies can account for biases. However, this has not always been the case especially in the former SU [2,6]. Epidemiological studies of Chernobyl victims would not add much reliable information due to inexact dose reconstructions and registration of unexposed individuals as exposed. Some dose-effect correlations can be attributed to a recall bias: cancer patients tend to recollect radiation-related circumstances better than healthy people [200]. The higher the average dose estimate, the greater would be a probability to undergo screening or a medical checkup. The following citation is enlightening: "The tumors were randomly selected (successive cases) from the laboratories of Kiev and Valencia… The tumors were clearly more aggressive in the Ukrainian population in comparison with the Valencian cases" [201]. The explanation is on the surface: the more efficient and early diagnostics in Valencia. Considering the results of [68], the same must be true for Colombia.

Radiation is a known carcinogen but there is no evidence of carcinogenicity below a certain threshold. Apparently, living organisms have undergone an evolutionary adaptation to the natural radiation background analogously to other environmental factors: various chemical substances and elements, ultraviolet rays, products of water radiolysis, etc. Natural selection is a slow process; the adaptation to a changing factor would thus correspond to some average of historic levels. The natural radiation background has been decreasing during the time of life existence [202]. Of note, DNA damage and repair are in a dynamic equilibrium, and there must be an optimum of the radiation impact. Accordingly, there is experimental evidence in favor of radiation hormesis i.e. biphasic dose response [11,13,203-206].

The screening effect and increased attention of exposed people to their own health will

probably cause new reports on the enhanced cancer and other health risks in areas with an elevated natural or anthropogenic radiation background. In this connection, the following claims appear counterproductive: "When considering the effects of irradiation on human health, it is necessary to clearly distinguish between the effects of increased background radiation to which adaptation can occur over many generations at the population level and the effects of irradiation as a result of accidents or medical procedures" [203]. What is significant, is the dose, dose rate and the type of radiation, while its source natural vs. anthropogenic is by itself non-relevant [207]. A promising approach to the research of dose-response relationships are lifelong animal experiments. The life duration is a sensitive endpoint attributable to radiation exposures [208] that can quantify the net harm or potential benefit according to the concept of hormesis. Most importantly, speculations about extraordinary aggressiveness of radiogenic cancers should not be conductive to an overtreatment [197,209,210].

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