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Дискуссии / Discussion

Overestimation of medical consequences of low-dose exposures to ionizing radiation

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Abstract

Overestimation of medical consequences of low-dose exposures to ionizing radiation contributes to the strangulation of nuclear energy production. Several examples of the overestimation are discussed here: the Chernobyl accident, East Urals Radioactive Trace and Semipalatinsk Nuclear Test Site. Results of certain studies of Chernobyl-related malignancies should be reassessed taking into account that some cases, classified as aggressive radiogenic cancers, were in fact late-stage malignancies. Associations of various markers with the tumor progression can become a field for future research and re-interpretation of data obtained in studies comparing malignancies from different regions. Reported correlations between low-dose exposures and non-malignant diseases call in question the cause-effect character of such correlations for cancer reported by the same and other researchers. The correlations may have been caused or influenced by bias, in particular, the dose-dependent selection and self-selection: individuals with higher dose estimates would be on average more motivated to undergo medical checkups and given more attention. Therefore, diagnostics tend to be more efficient in people with higher doses. Lifelong animal experiments are a promising approach to the research of dose-response relationships.

Key words: ionizing radiation, Chernobyl accident, East Urals radioactive trace, health services.

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Переоценка медицинских последствий воздействия малых доз ионизирующего излучения

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Резюме

Преувеличение медицинских последствий ионизирующего облучения в малых дозах препятствует развитию атомной энергетики. В этом обзоре преувеличение обсуждается на примерах аварии на Чернобыльской АЭС, Восточно-Уральского радиоактивного следа и Семипалатинского ядерного полигона. Результаты исследований злокачественных новообразований, связанных с Чернобылем, требуют переоценки с учетом того, что некоторые случаи, классифицированные как агрессивные радиогенные раки, на самом деле представляли собой опухоли на поздних стадиях. Ассоциации различных маркеров с опухолевой прогрессией могут стать темой дальнейших исследований и новой интерпретации данных, ранее полученных в исследованиях со сравнением злокачественных новообразований из различных регионов. Найденные зависимости между малыми дозами облучения и частотой неопухолевых заболеваний ставят под сомнение причинно-следственный характер таких ассоциаций

для рака. Причинами корреляций могли стать нерадиационные факторы, в особенности, дозозависимый отбор и самоотбор. Лица с высокими оценочными значениями доз в среднем более мотивированы для прохождения медицинских осмотров, где им уделяется больше внимания. Таким образом, эффективность диагностики иногда зависит от дозы. Перспективным подходом к исследованию зависимостей «доза–эффект» могут стать эксперименты на животных с оценкой средней продолжительности жизни.

Ключевые слова: ионизирующее излучение, авария на Чернобыльской АЭС, Восточно-Уральский радиоактивный след, здравоохранение.

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After the Chernobyl accident (CA) numerous publications appeared in which diseases among residents of contaminated territories were regarded to be radiogenic; some studies have been commented on previously [1–3]. Certain data can be explained as being due to artifacts e.g. reports of stronger biological effects of lower doses compared to higher doses in animal experiments and epidemiological studies. For example, doses ~ 12 mGy in mice were reportedly more efficient in inducing DNA and cell enzyme alterations than higher doses within a certain range (bimodal dependence) [4]. Among Chernobyl cleanup workers (liquidators), maximal deviations of some biochemical and blood-cell-related indices were observed at cumulative doses ≤ 150 mGy, decreasing at higher doses. The mortality among them was minimal at doses ~ 150 mGy. A similar bimodal dose-response relationship was reported for morbidity and mortality of some malignancies e.g. leukemia. The maximum frequency of disabilities among liquidators was noticed at the dose level of 79 mGy [4]. The biological relevance of such results appears questionable. Various kinds of bias can be found in the epidemiological research reporting elevated cancer risks from low radiation doses: interpretation of sporadic diseases as radiogenic, conclusions about incidence increase without adequate control [1], "forcing a positive slope to the relative risk dose-response curve" [5] etc. The publication bias should be mentioned: some studies with negative results were neither included in databases nor cited in reviews [6]. Other biases and confounders have been discussed [7–11]. Among limitations of some epidemiological studies has been disregard for the natural radiation background (NRB). The following dose comparisons are relevant to the rest of this review. Individual effective doses from NRB are generally expected to range from 1.0 to 10 mSv/year; some national averages exceed 10 mSv/year [12, 13]. The average for the Russian Federation is 3.35 mSv/year; the highest background among federal subjects is in the Altai Republic – 8.83 mSv/year [14]. The average individual whole-body dose to 6 million inhabitants of the territories, recognized as contaminated by the Chernobyl fallout, received from 1986 through 2005, was ~9 mSv [15]. For comparison, according to assessments of data on solid cancers and leukemia in the Life Span Study (LSS) of atomic bomb survivors in Japan, there was a significant positive dose-response correlation among all survivors who received < 500 mSv but the statistical significance vanished if only doses < 200 mSv were considered [16, 17]. The doses < 100 mGy at low rates may induce an adaptive response against neoplastic transformation [18]. More comparisons are at [19].

Nuclear worker studies and radioactive contaminations in the Urals

Some dose-effect correlations may be attributed to a dose-dependent selection, self-selection and recall bias noticed in exposed cohorts [20–22]. It can be reasonably assumed that persons knowing their higher doses would be more motivated to undergo medical examinations being at the same time given more attention. Therefore, diagnostics would be a priori more efficient in people with higher doses. For example, the dose-dependent increase in incidence of cardio- and cerebrovascular diseases among Mayak Production Association (MPA) workers was not accompanied by a corresponding increase in mortality [23–26], which can be attributed to a recording of mild cases in people with higher doses. Moreover, the excess relative risk per unit dose (ERR/Gy) for leukemia, excluding chronic lymphocytic leukemia (CLL) among MPA workers using incidence data has been considerably higher than that using mortality data [27]. A more efficient detection of latent leukemia with occasional registration of unverified cases is a probable explanation. As for CLL, it is often accompanied by a lymph node enlargement thus less frequently remaining undiagnosed; therefore, the screening for CLL would result in decreased diagno-

sis than that for other leukemias. The inter-study heterogeneity [28], the mixture of more and less reliable data assessed together remains a problem of some systematic reviews and meta-analyses. As discussed previously [1], reported dose-effect relationships between low-dose low-rate exposures and non-neoplastic diseases call in question the causality of some reported relationships for cancer. Certain data on enhanced cancer risk after low-rate exposures appear doubtful. For example, a significantly increased risk of non-melanoma skin cancer was reported among MPA workers [29]. An observation bias was not excluded. The workers and probably some medical personnel knew individual work histories, wherefrom accumulated doses could be inferred, potentially influencing the diagnostic thoroughness. Skin doses were unknown [29]. Among A-bomb survivors, the non-melanoma skin cancer incidence dataset was consistent with a threshold at ~1 Sv [30]. The MPA workers were exposed mainly to γ-rays that have a relatively long penetration distance in tissues so the absorbed doses in the skin must have been correspondingly low. Not surprisingly, premalignant skin lesions and/or actinic keratoses were "very rare" [29]. Considering the above, a cause-effect relationship between radiation and skin tumors in the study [29] appears improbable. Results of some other studies have been discussed previously [1–3].

The conclusion of a recent review about nuclear workers reads as follows: "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" [27]. Neither NRB nor experiments are mentioned in this connection. Reliable data on the biological effects of low radiation doses can be obtained in large-scale animal experiments. Annual average doses from NRB should be indicated if cohorts from different regions 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 [31, 32], discussed in the next section. In the International Nuclear Workers Study (INWORKS), many workers received 2–4 mSv/year [27] i.e. around the global average from NRB. The mean cumulative doses in the INWORKS (red bone marrow – 17.6 mGy, colon – 19.2 mGy) protracted over years (follow-up 1950–2005) [33] are comparable with NRB. These and other considerations about INWORKS have been summarized previously: "Failure to account for natural background radiation exposure, the differences in which potentially dwarf the occupational exposures of the study cohort" [34].

The following citations should be commented on: the "puzzling finding from INWORKS is that the primary ERR/Gy estimate for photon doses and all cancers except leukemia, which was adjusted for neutron monitoring status, 0.48 (95 % CI: 0.15, 0.85), reduced by ~ 60 % to 0.20 (95 % CI: –0.07, 0.51) when no such adjustment was made… A further perplexing result from INWORKS is that when the analysis was confined to the 83 % of workers who were not monitored for intakes of radionuclides, the ERR/Gy for all cancers except leukemia increased by 50 % to 0.72 (95 % CI: 0.21, 1.28); similar increases in external exposure risk estimates for workers not monitored for potential exposure to internal emitters when compared with those for workers who were monitored for internal exposures have been noted in other studies" [27]. The answer to the "puzzle" seems to be as follows. The workers monitored for intakes of radionuclides and those under the "neutron monitoring" received averagely more attention from medics. Consequently, there must have been fewer undiagnosed diseases among them. As a result, the mechanism of dose-dependent observation quality would be less efficient as fewer neglected cases are left to be preferentially found in persons with higher doses. Of note, 6 % of workers with doses > 100 mGy, received predominantly during earlier years (1960–1979), were influential in a downwards leverage of the dose-response. In the range of low doses, ERR/Gy for cancer in the INWORKS was even higher than in LSS [27, 33]. The LSS data originated from still earlier times. Apparently, the non-radiation-related dose-dependent mechanisms were less efficient in the remote past, when diagnostic possibilities were more limited. It can be speculated that modern methods and diversification with more differences between the superior and inferior diagnostic quality at a later time provided more opportunities for dose-dependent selection and self-selection. Moreover, excess deaths from solid cancer fitted under a simple linear excess relative rate model were higher in the INWORKS than in LSS among persons with mean colon doses 1–78.3 mGy, while in those with doses ≥ 143.1 mGy the aforesaid index was higher in the LSS [33]. A priori, the dose-response relationship must be stronger at > 200 mGy than at < 200 mGy. In the INWORKS, the tendency was vice versa [33]. Considering the above, both the dose-effect relationship at low doses and its weakening at higher doses were probably caused by non-radiation factors. Furthermore: "One main issue in the field of radiation protection is the validity of a linear extrapolation of risks at low doses, one aspect of what is known as the linear no-threshold hypothesis… this work provides support for the validity of a linear extrapolation of risks at low doses for solid cancer, and the current results do not suggest a reduction in ERR/Gy at low doses" [33]. According to the linear no-threshold (LNT) hypothesis, the risk

of cancer is proportional to the radiation dose; a dose-response correlation can be extrapolated down to low doses, where the relationship is unproven and can become inverted according to hormesis. By analogy with other environmental factors, an evolutionary adaptation to NRB can be reasonably assumed. Cells and organisms may have retained some capacity to repair the damage from higher radiation levels than today's NRB [35]. The experimental evidence in favor of hormesis and adaptive responses to ionizing radiation is considerable [36–39]; such evidence has been obtained also in humans [9, 40, 41]. In animal experiments, the doses associated with carcinogenicity have been generally higher than averages in nuclear workers and other peacetime exposed cohorts [39, 42–45]. Some assessments of LSS data do not support the LNT hypothesis being consistent with hormesis [46]. For solid cancers and leukemia, significant dose-response relationships were found in LSS after exposures to ≤ 500 mSv but not to ≤ 200 mSv [16, 17, 47]. The value 200 mSv has been mentioned in some reviews as a level, below which the cancer risk elevation is unproven [47, 48]. According to the UNSCEAR, a significant risk increase was observed at doses ≥ 100–200 mGy [49]. This value may be an underestimation due to biased epidemiological research.

Another citation to be commented on: "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 [50–52]. 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" [33]. The argumentation about DDREF on the basis of INWORKS is unconvincing as the radiogenic nature of diseases under discussion is unproven. Some models suggested that protracted exposures are between 2.0 and infinitely times safer than acute exposures at comparable doses. The latter corresponds to a threshold or hormesis concept. However, risk estimates should be based primarily on direct comparisons of data from acute and protracted exposures, rather than on models [53].

Earlier studies reported no increase in the cancer incidence at doses ≤ 520 mSv or generally among MPA workers. The existence of a threshold was regarded as possible [54–57]. A reduction of cancer mortality in the exposed cohort was found compared to a control population [55]. The frequency of incapacity for work was found to be independent of the cumulative dose [58]. The risk of leukemia per 1 Gy was reportedly 3.5 times lower in the Techa river cohort than in LSS i.e. effectiveness of the acute exposure was higher than that of protracted or fractionated exposures, as expected [59, 60]. It was noticed that the relative risk of solid cancers in the Techa river cohort increased with the age at exposure and attained age, whereas among A-bomb survivors it tended to decrease [60, 61]. The risk elevation with the age is typical for spontaneous cancer. No significant increase in cancer morbidity and mortality was found in residents of the territories contaminated due to the 1957 Kyshtym accident i.e. the East Urals Radioactive Trace (EURT) [60]. Later on, an increased excess relative risk of solid cancer incidence and mortality was reported in the EURT cohort [62]. The earlier publication [55] showed a reduction in cancer mortality in the exposed cohort when compared to a control population. The later publication [62] did not compare the mortality of the irradiated cohort with control but fitted the data to the LNT model. In more recent publications it was pointed out that the cancer risk or "carcinogenic efficiency" of chronic exposures in the Techa river and EURT cohorts is comparable with or not lower than that of acute exposure in A-bomb survivors both for leukemia and solid cancers [62–66].

Elevated risks of non-malignant diseases – cardiovascular, respiratory, digestive – have been found in Chernobyl, MPA and Techa river populations [23, 25, 67–80]. For example, the average dose from external γ-radiation was ~ 0.54 Gy in men and 0.44 Gy in women in a study, where the frequency of lower extremity arterial disease was found to correlate with the cumulative external dose [80]. The frequency of atherosclerosis 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 α-radiation [75]. Among MPA workers with total absorbed external γ-ray doses > 0.1 Gy the incidence of cerebrovascular diseases (CVD) was significantly higher compared to those exposed to lower doses; the same for 0.01 Gy alpha-particle dose to the liver from incorporated plutonium [74]. The excess relative risk of CVD per dose unit in MPA workers was reportedly even higher than in LSS [23, 74, 78], where the bias could have also been operative. Risks of cardiovascular diseases and, in particular, of ischemic heart disease, were found in the Techa River cohort to be higher than in LSS [77]. Remarkably, the dose-dependent incidence increase in CVD and ischemic heart disease among MPA workers was not accompanied by an increase in mortality [24–26], which can be attributed to the dose-dependent diagnostic efficiency with the recording of mild and borderline cases in exposed people. According to

the same research group, the incidence of CVD was significantly increased among MPA workers with cumulative external doses ≥ 0.1 Gy [74, 81]. For comparison, the UNSCEAR could not make any conclusions about immediate causal relationships between doses ≤ 1–2 Gy and the excess incidence of cardiovascular or generally non-malignant diseases [82]. According to the ICRP, "there are excess risks of heart disease for patients receiving radiotherapy with estimated average heart doses of 1–2 Gy (single dose equivalent, after correction for dose fractionation effects)" [83]. The value of 1–2 Gy may be an underestimation due to bias in epidemiological studies. It is known that patients may develop cardiovascular diseases after radiotherapy with doses to the heart ~ 40 Gy. Lower doses were discussed [83–86], being still much higher than averages for the MPA, Techa River and Chernobyl cohorts. The doses associated with heart injury in experimental animals have also been higher than in the above-named cohorts [83, 87, 88]. In some experiments and epidemiological studies, low doses were protective against atherosclerosis [83]. Of note, an earlier study found no association between individual cumulative doses and the frequency of ischemic heart disease [89]. In the past, long-term observations found no special features of cardiovascular diseases in MPA workers compared to the general population [90].

Similar tendencies have been noticed in regard to radiation-related cataracts. Correlations between the cumulative dose and cataract incidence in the MPA cohort [91, 92] have been doubted [26, 93], which pertains by inference also to another study [94]. A threshold for chronic exposures is regarded to be uncertain for lack of evidence [95]. Reportedly, the risk increase in all dose categories starting from 0.25–0.50 Sv was significant compared to the reference category 0–0.25 Sv. Average doses were 0.54 ± 0.061 Gy in men and 0.46 ± 0.01 Gy in women [94]. Dose-effect relationships were found for cataracts; but the well-known correlation of the latter with diabetes mellitus was not confirmed [26, 91, 94], which questions the biological relevance of the results. There were no significant associations of the radiation dose with cataract removal surgeries [96], which is indicative of bias: cataracts including mild cases were diagnosed earlier in exposed individuals due to increased attention to their own health and/or attention on the part of medics (dose-dependent selection and self-selection). Earlier publications asserted that radiation-induced cataracts developed in MPA workers only after exposures ≥ 4 Sv [97]. A review of data from Russia indicated that chronic exposures ≤ 2 Gy were not associated with cataracts [83, 90, 98]. According to the UNSCEAR, a "minimum of 3–5 Gy are required to produce significant opacities in animals which are normally not prone to cataract development, as is the case for man… Minimum stationary opacities have been observed after single doses of 1–2 Gy. More dose is required when fractionated. The threshold for cataract for occupational exposure or long-term fractionation is in the range of 6-14 Gy" [99]. Later on, lower thresholds and the no-threshold model of cataract development have been discussed [100–103]. Based predominantly on epidemiological research, the International Commission on Radiological Protection (ICRP) revised preceding recommendations and proposed a threshold of 0.5 Gy for the development of cataracts [83, 103, 104]. However, not all epidemiological studies support this lower threshold [83]. The dose-dependent diagnostic efficiency and self-reporting associated with a better awareness of the problem, with a longer work history and hence with a cumulative dose, may explain the above-average risk of cataracts found among radiologic technologists [105, 106]. A discrepancy has been noticed between the data on the cataract history and cataract surgery, whereas risks for the latter were lower and generally not significant [106]. As mentioned above, a similar pattern of significant excess relative risk (ERR) for cataract morbidity but not surgery has been reported in MPA workers [96, 106, 107]. This agrees with the concept of a dose-dependent diagnostic efficiency with the recording of mild cases not requiring surgery in persons with higher doses. Among cohorts studied for radiation-associated cataracts, a significant ERR for cataract surgery has been reported only in the LSS cohort [102, 106, 108, 109], where the effect of acute exposure could have been significant. In animal experiments, the doses were higher than the averages in Chernobyl, MPA and Techa river populations. Some experiments in rodents investigated low doses and suggested that genetic factors have an influence on the susceptibility to radiation-induced lens opacities [83, 104, 110]. Effects of low doses are not a priori denied here. Cataracts can be caused by radiation; but doses and dose rates associated with risks, i.e., potential thresholds should be further investigated. The number of studies that provide biological and mechanistic evidence at doses < 2 Gy is small [105, 111].

Doubtful correlations between low-dose exposures and non-malignant diseases call in question the cause-effect character of such correlations for malignancies [64, 112–117]. The correlations may be caused or influenced by bias, in particular, the dose-dependent selection and self-selection noticed in exposed populations [20–22]. Individuals with higher doses are probably generally more motivated to undergo medical checkups and given more attention. Even in blind studies e.g. of MPA workers, the

subjects and probably also some medical personnel knew individual employment histories, from which cumulated doses could be inferred, potentially influencing the self-reporting and diagnostic thoroughness. Considering the above, diagnostics must be a priori more efficient in people with higher dose estimates.

Post-Chernobyl cancer vs. control

Studies of Chernobyl-related renal-cell carcinoma (RCC) with control from overseas are discussed here in comparison with thyroid cancer (TC). The series of studies [31, 32, 118–122], in particular, the last study [31], compared RCC tissue specimens from Ukraine (including the area of Chernobyl contamination) with those from Spain and Colombia. RCCs from Ukraine tended to be less differentiated than the controls from overseas. In the last study, the microvessel density in the RCC tissue from patients residing both in "highly" and "low contaminated areas of Ukraine" was considerably higher than in RCC from Spain and Colombia ($p < 0.01$). The difference between the two Ukrainian groups was statistically insignificant. The increased level of angiogenesis was associated with a higher expression of the immunohistochemical marker VEGF (vascular endothelial growth factor) [31]. It has been suggested that the radiation exposure leads to an increase in the microvessel density, which in turn is associated with a lower level of differentiation (higher tumor grade) and a less favorable prognosis of RCC [31, 122, 123].

It was pointed out in the preceding comment that the difference in the RCC grade between Spain and Ukraine can be explained by more efficient and early cancer diagnostics in Spain [124]. The proposed increase in the "aggressivity" of both RCC and TC after the radioactive contamination in the Chernobyl area [118, 125] apparently resulted from detection by the screening of old neglected malignancies, interpreted as radiogenic cancers with the "rapid onset and aggressive development" [125]. The screening detected not only small nodules but also advanced TCs, not diagnosed because of the incomplete coverage of the population by medical checkups prior to CA. This predictable phenomenon was confirmed by the fact that the "first wave" TCs after CA were on average larger and higher-grade than those diagnosed later as neglected cancers were gradually sorted out by the screening [126]. In view of the dose comparisons, radiation can hardly be a cause of differences between "exposed" and control groups from other countries. Average annual doses from NRB have been overviewed in the Introduction. The doses from NRB should be specified in studies where cohorts from different countries are compared; otherwise, doses among controls may turn out to be not significantly different from those in the "exposed" cohort e.g. in patients from Spain vs. those from Kiev [32, 121]. The average annual individual dose from NRB in Spain is ~5 mSv [127, 128]. According to an estimate, the mean whole-body individual dose to inhabitants of Kiev from all sources was ≤ 10 mSv in 1986, decreasing thereafter [129]. No dose estimates were given in the articles [31, 118–122, 131]; it is only written with a self-reference: "This observation also supports the prevailing suspicion [122] that in Ukraine the radiation contamination levels were similar within and beyond the officially-established 80-km extent of radiation contamination around Chernobyl [131]" [31]. The source [131], a Ukrainian Ministry report, has been unavailable.

The Chernobyl disaster gives an example of a considerable difference in diagnostic quality before and after the event. There has been no convincing evidence of cause-effect relationships between radiation exposures from CA and the incidence increase of cancers other than TC in residents of contaminated territories exposed at a young age [22]. TC and some other cancers were generally under-reported in the Soviet Union. Mechanisms of the registered TC incidence increase included the screening and improved medical surveillance after CA [15]. According to the UNSCEAR, "the background rate of thyroid cancer among children under the age of 10 was approximately two to four cases per million per year" [132]. The UNSCEAR 2008 Report compares the enhanced TC incidence rates 4 years after the accident and later not with the pre-accident level but with the years 1986–1990 (Annex D, pp. 60–61), when the incidence had increased up to 4.1 cases per million per year in people exposed at the age of <10 years and up to 5.4 – in those exposed at <18 years [15]. The period 1986–1990 was chosen for comparison "since 1986 and not earlier, specific data on thyroid cancer incidence have been specifically collected by local oncologists" (UNSCEAR Secretariat, e-mail correspondence of 22 October 2013). According to another source, the incidence of TC among people younger than 15 years in the North of Ukraine (overlapping with the contaminated area) was 0.1 and in Belarus – 0.3 cases/million/year from 1981 through 1985 [133]; more details are in [1]. Only 5 children were diagnosed with thyroid malignancies in Belarus during the period 1978–1985, the detection rate of pediatric TC prior to CA being lower than that in other developed countries [134]. This indicates that there were undiagnosed cases in the population. The underreporting tendency is known also for renal malignancies [135]. Some

advanced cancers, detected by the screening, self-reported in conditions of increased public awareness after CA, or brought from other areas and registered as Chernobyl victims, were misinterpreted as rapidly growing radiogenic malignancies [1, 2]. Many people strived for recognition as Chernobyl victims to gain access to health care provisions [136]. Cases brought from non-contaminated areas must have been on the average more advanced as there was no extensive screening there.

By analogy with TC, the registered increase in the incidence of RCC in Ukraine following CA [31, 118, 120, 122] was probably caused by improved diagnostics [124]. As mentioned above, RCCs from Ukraine tended to be less differentiated than those from Spain. RCCs from Ukraine showed sarcomatoid i.e. poorly differentiated pattern more frequently: 62 of 236 (26.3 %) of Ukrainian vs. 11 of 112 (9.8 %) of Spanish cases ($p < 0.001$) [118]; the significant difference was confirmed by the subsequent study [120]. In this connection, the following comments should be following citations should be commented noted: "The dramatic increase of aggressivity and proliferative activity" was found in RCC from Ukraine, while "the majority of the high-grade tumors occurred in the Ukrainian (rather than in the Spanish) groups" [118]. These differences can be attributed to detection by the screening of advanced cases in Ukraine. The misinterpretation of such cases as aggressive radiogenic cancers could have been conducive to overtreatment. The concept of enhanced aggressiveness of post-Chernobyl RCC can have unfavorable consequences if surgeons get the message that cancers from radio-contaminated areas tend to be more aggressive than usual while surrounding renal tissues harbor "proliferative atypical nephropathy with tubular epithelial nuclear atypia and carcinoma in situ" [119]. Based on this premise, surgeons might decide to perform nephrectomy more often than the clinically indicated kidney-preserving procedure. By analogy, the misinterpretation of advanced TCs as rapidly growing radiogenic malignancies had implications for the therapy. In the 1990s, thyroid surgery in some clinical centers in Belarus and Ukraine became more radical [137–139]. The overdiagnosis and overtreatment of post-Chernobyl urinary bladder lesions in Ukraine have been discussed previously [140].

Some molecular-genetic characteristics of RCC from Ukraine vs. those from Spain and Colombia need a re-interpretation e.g. the absence of significant differences in the expression of ubiquitin [121]. Considering that RCCs from Ukraine were averagely more advanced than Spanish cases, these data indicate that ubiquitin is not associated with the progression of RCC. In contrast, VEGF was found more frequently in clear-cell RCC from Ukraine than in the specimens from Spain and Colombia [31]. The statement that "in RCC the level of serum VEGF has been shown to be closely related to the stage and grade of RCC, and the expression of VEGF to be significantly associated with tumor stage" [31] was supported by the reference [125]. Other studies also reported associations between the VEGF expression and microvascular density, nuclear grade, tumor size, stage, and prognosis of RCC [141–144]. The study under discussion also "demonstrated a close relationship between VEGF expression and the stage of clear-cell RCC" [31]. The same considerations probably pertain to other markers, where substantial differences were found between the Spanish and Ukrainian RCCs, in particular, the transcriptional nuclear factor kappa B (NF-kappa-B), its p50 and especially p65 subunits [120]. The > 10 % cell positivity for p50 was found in 25 from 59 (42.4 %) of specimens from Ukrainian vs. 4 from 19 (21.1 %) of Spanish patients; the > 50 % p65 positivity was found, correspondingly, in 18 from 59 (30.1 %) vs. 1 from 19 (5.3 %) of the specimens ($p < 0.05$) [120]. In line with the concept discussed here, activated NF-kappa-B is considered to be a biomarker and promoter of cancer progression [145–150]. By analogy with RET/PTC3 chromosomal rearrangements in papillary TC discussed previously [151], there may be a relationship between the tumor progression and those markers of RCC, where differences between the Ukrainian and Spanish cohorts were found. In particular, the higher microvessel density and VEGF expression in the Ukrainian specimens vs. those from Spain and Colombia [31] can be explained by the earlier cancer diagnosis compared to Ukraine on average. Associations of various markers with the tumor progression (disease duration, tumor size, stage and grade, metastases etc.) is a potential field for the future research and re-interpretation of the data already obtained in studies comparing malignancies from different parts of the world.

Another recent example is the study making a comparison between 359 papillary TCs from patients who underwent radiation exposure from CA and the control group – 81 TCs from patients born > 9 months after CA [152]. 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" [152]. These findings are not surprising: DNA alterations tend to accumulate with tumor progression. Double-strand breaks with error-prone repair contribute to the genome diversity

in cancer cells [153]. The NHEJ repair pathway is potentially mutagenic [154]. Some aberrant gene fusions drive the tumor progression [155]. At the same time, no association of radiation exposure with transcriptomic and epigenomic features was found [152]. This indicates that the latter markers are to a lesser degree associated with the neoplastic progression than DNA lesions. As for individuals born after CA (the control group in [152]), the data pertaining to them originated from a later period, when the quality of diagnostics improved while the reservoir of advanced neglected cancers was partly exhausted by the screening. Therefore, the average stage and grade of TCs in the exposed group must have been a priori higher than those among the controls. The causative role of low-dose radiation e.g. "a dose-dependent carcinogenic effect of radiation derived primarily from DNA double-strand breaks" [152] is unproven in the studied population. The concept 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" [152] was discussed in several preceding papers [1, 2] that are not cited in [152]. The study [152] is well-designed, but the authors should think about re-interpretation of their results.

Semipalatinsk Nuclear Test Site

The Semipalatinsk Nuclear Test Site (SNTS) is the place where 456 nuclear explosions were carried out between 1949 and 1989 [156]. It was suggested that the radiation background in the area has been additionally influenced by the Lop Nor nuclear test site in China [157], which, considering the distance > 1300 km, is hardly of any significance. Settlements affected by the 1949 test were located northeast of the test site, notably, Dolon discussed below. Apparently, the mortality and morbidity increase was arbitrarily ascribed to radiation exposures e.g. in [158]. The tendency to overestimate medical consequences of enhanced background radiation in the Semipalatinsk area and of nuclear testing, in general, was discussed previously [159–161]. Yuri Dubrova claimed that "according to the results of numerous studies the doses for the families living in the Semipalatinsk District of Kazakhstan have been estimated as 0.5 Sv and higher" [162] with reference to [163]. In the abstract of the latter article, it is, however, written: "The village of Dolon, in particular, has been identified for many years as the most highly exposed location in the vicinity of the test site. Previous publications cited external doses of more than 2 Gy to residents of Dolon while an expert group assembled by the WHO in 1997 estimated that external doses were likely to have been less than 0.5 Gy" [163]. Other researchers reported lower doses for Dolon residents [157]. The single historical measurement in Dolon is deemed uncertain being likely performed at the axis of the radioactive trace about 1.5–1.6 km northwest of Dolon, while the width of the cloud was narrow [164, 165]. The dose estimates based on this measurement are supposed to be the maximum external doses rather than average doses to Dolon inhabitants [164], while in other settlements the doses were much lower. The average individual dose estimates in settlements near SNTS, received in the period 1949–1953, have been estimated as follows: Dolon 1600 mGy, Abai (Karaul) 370, Kainar – 240, Sarzhal 200, some other villages presumably 5–20 Semipalatinsk city ≤ 5.6 mGy. In the period 1971–1990 annual individual doses in the area were below 5 mGy [166]. For comparison, in 2008 the annual individual dose within STS was 0.073–0.749 mSv, outside STS – 0.036–0.37 mSv [167], which is a negligible addition to NRB.

Conclusion

The medical surveillance of populations exposed to low-dose ionizing radiation is important; but more consideration should be given to potential bias e.g. screening effect, dose-dependent selection and self-selection. Among others, "the very high rates of circulatory disease" [168] in some cohorts may be caused by the overdiagnosis tendency of cardiovascular diseases in unclear post- and antemortem cases, which is a confounding factor. In the author's opinion, epidemiological studies of populations exposed to the Chernobyl fallout would hardly add much reliable information, among others, because of inexact dose reconstructions and counting of unexposed people as exposed. Furthermore, dose-effect correlations can be explained by a recall bias: cancer patients tend to recollect radiation-related circumstances better than healthy people [169]. It can be reasonably assumed that patients with advanced cancers would recollect such circumstances better than practically healthy individuals with small nodules. The higher the average dose estimate, the greater would be the probability to undergo a medical examination. Certain features of post-Chernobyl TC would be a priori more prevalent in populations with higher dose estimates and/or residing on more contaminated territories. One of such features is the relatively high percentage of advanced neglected cancers detected by the screening after CA and misinterpreted as aggressive radiogenic malignancies [1, 2]. The screening effect and increased attention of exposed people to their own health will probably result in new reports on elevated cancer and other

health risks in areas with enhanced natural or anthropogenic radiation background. Lifelong animal experiments are a promising approach to the research of dose-response relationships. The life duration is known to be a sensitive endpoint attributable to radiation exposures [43], which can measure the net harm or potential benefit (within a certain range according to the concept of hormesis [37]) from low-dose exposures. Last but not the least, suppositions about enhanced aggressiveness of malignancies from radiocontaminated areas may be conducive to an overtreatment [139, 140].

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