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Markers of Radiogenic Cancer vs. Tumor Progression: an Overview of Chernobyl Studies

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Keywords: Renal cell carcinoma; Cancer grading; Ionizing radiation; Chernobyl; Thyroid cancer; Health services

Abstract

Differences in the histological grade of malignancies may reflect diagnostic quality, that is, averagely earlier or later tumor detection in a given country. Studies of Chernobyl-related renal-cell carcinoma with a control from Spain and Colombia are discussed here in comparison with thyroid cancer research. It is concluded that suppositions about averagely higher grade and enhanced aggressiveness of malignancies from the areas previously contaminated by the Chernobyl fallout are unfounded and can lead to overtreatment. Results of many studies of Chernobyl-related malignancies are valuable; but conclusions should be reassessed taking into account that some cases, classified as aggressive radiogenic cancers, were in fact late-stage neglected malignancies. Associations of various markers with the tumor progression can become a field for the future research and re-interpretation of data obtained in studies comparing malignancies from different countries. Some markers may reflect efficiency of healthcare services.

Abbreviations

RCC: renal-cell carcinoma; **TC:** thyroid cancer; **PTC:** papillary thyroid carcinoma; **VEGF:** vascular endothelial growth factor; **SU:** Soviet Union; CA, Chernobyl accident; **mSv:** millisievert; **mGy:** milligray; **UNSCEAR:** United Nations Scientific Committee on the Effects of Atomic Radiation; **NF:** nuclear factor; **RET:** rearranged during transfection; **PTC:** papillary thyroid carcinoma; **TGF:** transforming growth factor; **IAEA:** International Atomic Energy Agency; **NHEJ:** ron-homologous end-joining.

Introduction

A tendency to overestimate health risks from low doses of ionizing radiation has been discussed previously [1,2]. Apparently, certain scientists exaggerating medical and ecological consequences of the anthropogenic increase in the radiation background contribute to a strangulation of the atomic energy, which would agree with the interests of fossil fuel producers. Nuclear power has returned to the agenda because of the concerns about increasing global energy demand and climate changes. Health burdens are greatest for power stations based on coal and oil. The burdens are smaller for natural gas and still lower for nuclear power. The same ranking applies also to the greenhouse gas emissions and thus probably to climate changes [3].

Studies of Chernobyl-related clear-cell renal-cell carcinoma (RCC) with a control from other countries are discussed here in comparison with thyroid cancer (TC). The series of studies [4-10], in particular, the last study [10], compared RCC tissue specimens from Ukraine (including the area of Chernobyl contamination) with those from Spain and Colombia. In brief, RCCs from Ukraine tended to be less differentiated than the overseas controls [4-10]. In the last study, the microvessel density in the RCC tissue from patients residing both in "highly" and in "low contaminated areas of Ukraine" was considerably higher than in RCC from Spain and Colombia ($p<0.01$). The difference between both Ukrainian groups was statistically insignificant. The increased level of angiogenesis was associated with a higher expression of the immunohistochemical marker VEGF [10]. It has been assumed that the radiation exposure leads to an increase in the microvessel density, which in turn is associated with a lower level of differentiation (higher grade) and less favorable prognosis of RCC [9,10,11].

It was pointed out in the preceding comment that the difference in the RCC grade between Spain and Ukraine can be explained by a more efficient and early cancer diagnostics in Spain [12]. The proposed increase in the "aggressivity" of both RCC and TC after the radioactive contamination in the Chernobyl area [4,13] apparently resulted from detection by the screening of old neglected malignancies, interpreted as radiogenic tumors with the "rapid onset and aggressive development" [13]. The screening detected not only small nodules but also advanced TCs, neglected 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 [14] because neglected cancers were gradually sorted out by the screening. The hypothesis presented here is that radiation exposure as a cause of differences between "exposed" and control groups from abroad is improbable. As previously discussed in regard to TC, the differences are caused at least in part by the averagely later cancer diagnostics in the former Soviet Union (SU) [1].

Dose Comparisons

Individual effective doses from the natural background radiation are generally expected to range from 1.0 to 10 mSv/year; some national averages exceed 10 mSv/year [15,16]. 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 [17]. 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 [18]. For comparison, according to assessments of data on solid cancers and leukemia among survivors of atomic explosions in Japan, there was a significant positive dose response correlation among all survivors who received <500 mSv

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but the statistical significance vanished if only doses <200 mSv were considered [19,20]. Doses <100 mGy at low rates may induce adaptive response against neoplastic transformation [21]. Annual average doses from natural radiation should be specified in papers where cohorts from different geographical regions 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 [6,8]. The average annual individual dose from the background radiation in Spain is ~5 mSv [22,23]. According to an estimate, the mean whole-body individual dose to inhabitants of Kiev from all sources was ≤10 mSv in 1986, decreasing thereafter [24]. No dose estimates were given in the articles [4-10]; it is only written with a self-reference: "This observation also supports the prevailing suspicion [9] that in Ukraine the radiation contamination levels were similar within and beyond the officially-established 80-km extent of radiation contamination around Chernobyl [25]" [10]. The source [25], a Ministry report, has been unavailable.

Radiation Effects vs. Late Detection

The Chernobyl accident (CA) provides an example of considerable difference in diagnostic quality before and after the accident. There has been no convincing evidence of cause-effect relationships between radiation exposures from CA and the incidence increase of cancers in residents of contaminated territories other than TC in people exposed at a young age [18]. TC and probably also other cancers were under-reported before CA. Mechanisms of the registered TC incidence increase included the screening and improved medical surveillance after CA [18]. According to the UNSCEAR, "the background rate of thyroid cancer among children under the age 10 was approximately two to four cases per million per year" [26]. The UNSCEAR 2008 Report compared 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 [18]. The period 1986-1990 was chosen for comparison because "since 1986 and not earlier, specific data on thyroid cancer incidence have been specifically collected by local oncologists" (UNSCEAR Secretariat, e-mail communication 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 [27]; more details are in [28]. 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 parts of the world [29]. This indicates that there were undiagnosed cases in the population. The underreporting tendency is known also for renal malignancies [30]. Some neglected 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]. Many people wanted to be recognized as Chernobyl victims to gain access to health care provisions and compensations [31]. Cases from non-contaminated areas must have been averagely more advanced as there was no extensive screening there.

Renal cell carcinoma (RCC)

By analogy with TC, the registered incidence rise of RCC in Ukraine following CA [4,7,9,10] was probably caused by improved diagnostics [12]. 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 from 236 (26.3 %) of Ukrainian vs. 11 from 112 (9.8 %) of Spanish cases ($p<0.001$) [1]; the significant difference was confirmed by the subsequent study [7]. Apparently, the difference was caused by the more efficient and early cancer diagnostics in Spain. In this connection, the following citations should be commented: "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" [4]. These differences can be attributed to a more efficient and early cancer diagnostics in Western Europe and, conversely, detection by the screening of advanced cases in Ukraine. The misinterpretation of such cases as aggressive radiogenic cancers has been conductive to an overtreatment (discussed below).

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 [8]. 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 [10]. The statement that "in RCC the level of serum VEGF has been shown to be closely related to tumor stage and grade of RCC, and the expression of VEGF to be significantly associated with tumor stage" [10] was confirmed by the reference [11]. Other studies also reported associations between VEGF expression and microvascular density, nuclear grade, tumor size, stage, and prognosis of RCC [32-35]. The study under discussion also "demonstrated a close relationship between VEGF expression and the stage of clear-cell RCC" [10]. 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 [7]. 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 ($p<0.05$) [7]. NF-kappa-B activation is discussed in the literature as a potential biomarker and promoter of the cancer progression [36-41].

Papillary thyroid carcinoma (PTC)

For interpretation of the above data, the analogy with RET/PTC3 chromosomal rearrangements in PTC is helpful. The RET/PTC3 fusions apparently correlate with the progression of PTC and hence with the disease duration [42]. An association was found between the RET/PTC3 expression and aggressive phenotype, advanced stage and larger size of PTC [43]. With the time passing after CA, the prevalence of RET/PTC3 declined [44,45] while advanced neglected TCs were sorted out by the screening. The cohort of post-Chernobyl pediatric PTC, with RET/PTC3 being the most prevalent RET rearrangement

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type, was supposed to be worldwide exceptional [46]. In fact, the cohort has been unique not globally but for industrialized high-income countries where cancer is diagnosed relatively early. Similarly to Chernobyl, RET/PTC3 was the most prevalent RET rearrangement in the studies from India [47,48]. Asian populations generally demonstrated a higher positive rate for RET/PTC3 compared to Western populations (26.50% vs. 17.05%) [49]. Of note, in Japan the frequency of RET/PTC3 is relatively low [49,50]. Pediatric TC in Japan has been different from that after CA, showing less frequently the poorly differentiated solid and solid-trabecular patterns [51,52]. International comparisons of TC size and stage may be less meaningful than those of differentiation grade because large nodules with uncertain malignant potential can be classified as high-stage cancers if there is a propensity to histological over-diagnosis, while screening activities may be a confounding factor. Unlike Chernobyl, most TCs after the Fukushima accident were of the classical papillary i.e. higher differentiated type [53,54], which suggests the averagely earlier tumor detection in such developed country as Japan. Along the same lines, RET/PTC3 are rare in France [55]. Mutations were found in TC from Russia more frequently compared to the United States [56,57], which indicates earlier diagnostics in the latter country.

Another recent example is the study making a comparison between 359 PTCs from patients who underwent radiation exposure from CA and the control group - TCs from 81 patients born >9 months after CA [58]. The "study population included a substantial number of PTCs occurring after <100 mGy," where development of radiogenic cancer would be improbable as per dose comparisons presented above. 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" [58]. These findings are not surprising: DNA damage tends to accumulate along with the tumor progression. Double-strand breaks with error-prone repair contribute to the genome diversity in cancer cells [59]. The NHEJ repair pathway is potentially mutagenic [60]. Some aberrant gene fusions drive the tumor progression [61]. At the same time, no association of the radiation exposure with transcriptomic and epigenomic features was found [58]. This indicates that the latter markers are to a lesser extent associated with the neoplastic progression than the DNA lesions. As for individuals born after CA (the control group in [58]), 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 among the controls in [58]. The causative role of low-dose radiation e.g. "a dose-dependent carcinogenic effect of radiation derived primarily from DNA double-strand breaks" in the studied population [58] is unproven. Finally, the "…increased detection of pre-existing PTCs 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" [58] should be commented. This concept has been formulated in several publications since 2011 [1,2,62-66] that have not been cited in [58]. The study [58] is well-designed; but the authors should think about a re-interpretation of their results. Other studies of molecular-genetic features of Chernobyl-related cancers have been commented previously [65,66].

Overtreatment of Chernobyl-Related Lesions

Renal cell carcinoma (RCC)

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" [5]. Based on this premise, some surgeons might decide to perform nephrectomy more often than clinically indicated instead of a kidney-preserving procedure.

Thyroid cancer (TC)

The misclassification of neglected advanced cases as aggressive radiogenic cancers has given rise to the concept that supposedly radiogenic TCs, at least those from the "first wave" after CA, were more aggressive than sporadic ones [14,67-69]. This had consequences for the practice: the surgical treatment of radiogenic TC was recommended to be "more radical" [70]. After 1998-1999, the thyroid surgery in some institutions of the former SU, Belarus in particular, adopted more radical approaches. The following was recommended for Chernobyl-related pediatric TC: "Radical thyroid surgery including total thyroidectomy combined with neck dissection followed by radioiodine ablation" [29] and/or high-dose external radiotherapy (40 Gy) [72]. Some experts regarded subtotal thyroidectomy to be "oncologically not justified" and advocated total thyroidectomy with prophylactic neck dissection [70,73-75]. More limited 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" [71]. It was stipulated in a recent instructive publication that a bilateral neck dissection must be performed in all TC cases independently of the tumor size, histology and lymph node status [76]. This approach is at variance with a more conservative treatment of TC applied internationally. The articles [77,78] were misquoted in the paper [73] advocating total thyroidectomy with bilateral neck dissection for all types of pediatric TC. The articles [79-81] were cited in support of the statement: "The most prevailing opinion calls for total thyroidectomy regardless of tumor size and histopathology" [71]. In fact, subtotal thyroidectomy was used or recommended in these studies, in some of them in parallel with total thyroidectomy [79-81]. The total thyroidectomy with neck dissection is known to be associated with complications e.g. hypoparathyroidism and recurrent laryngeal nerve palsy. Moreover, a large part of post-Chernobyl thyroid patients were young females potentially concerned about cosmetic aspects. The overall survival rate was very high in adolescents and young adults with differentiated TCs regardless of the extent of the surgery [82], which indicates that the radicalism had sometimes been superfluous. Similar surgical tactics were applied to TC patients from the East Urals Radioactive Trace [83]. The relatively high suicide rate noticed among patients with Chernobyl-related TC [84,85] can be explained by a decreased quality of life after the excessively radical surgery. Epidemiologists warned against the over-diagnosis and overtreatment of patients with indolent thyroid tumors. It is essential to exclude adenoma and borderline/precursor tumors because they can be treated with simple excision or less extensive resections [86]. Relevant considerations about TC over-diagnosis and overtreatment

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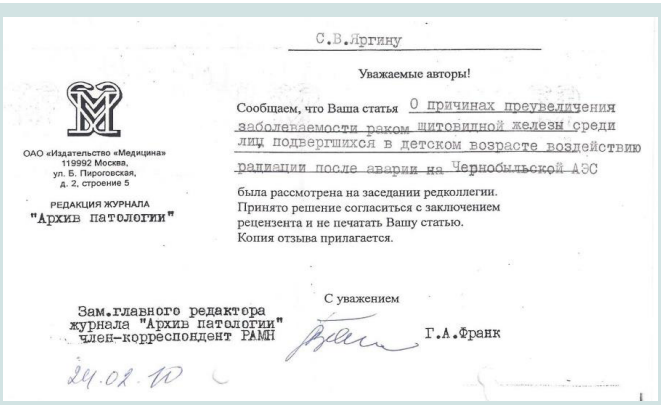
have been phrased in the recent review: "After the Chernobyl and Fukushima nuclear accidents, thyroid cancer screening was implemented mainly for children, leading to case over-diagnosis;" "The existence of a natural reservoir of latent thyroid carcinomas, together with advancements in diagnostic practices leading to case over-diagnosis 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" [87] without citing preceding publications expressing the same ideas [1,2,62-66,88,89].

Potential mechanisms of TC false-positivity after CA have been discussed in detail previously; among others, the misinterpretation of nuclear pleomorphism as a malignancy criterion of thyroid nodules [89]. Potentially misleading histological images from Russian-language handbooks were reproduced and commented [64,90,91]. The post-Chernobyl radiophobia contributed to the over-diagnosis of cancer, which can be illustrated by the following citation (from Russian): "Practically all nodular thyroid lesions, independently of their size, were regarded at that time in children as potentially malignant tumors, requiring an urgent surgical operation" [92]. Ultrasound devices were introduced into practice earlier than fine-needle biopsy [92], which probably contributed to the false-positivity in the 1990s. The iodine deficiency on the contaminated territories and goiter associated with it was a contributing factor because more thyroid abnormalities were found by the screening, providing more opportunities for the over-diagnosis of malignancy. The articles describing mechanisms of the false-positivity, possibly operative until today, have been rejected by the main journal of Russian pathologists Arkhiv Patologii (Archives of Pathology) despite personal communications with the editor-in-chief Georgii Frank (Figure 1). As a result, the articles about the over-diagnosis and overtreatment of Chernobyl-related lesions have been published abroad and later also in Russian journals that are rarely read by pathologists [93].

Urinary bladder lesions

The over-diagnosis and potential overtreatment of post-Chernobyl urinary bladder lesions was discussed previously [94]. The same researchers, who participated in the RCC research discussed above [4-10], found by means of cystoscopy and bladder biopsy in different groups of patients with benign prostatic hyperplasia and females with chronic cystitis, from contaminated areas and Kiev, severe urothelial dysplasia or carcinoma in situ in 56-96 % of all randomly selected (consecutive) cases [95-100]. These percentages are unrealistic and indicative of the false-positivity. The microphotographs from [95,96] were reproduced in [94]: the sections are visibly thick, many nuclei are poorly stained. Neither cancer nor severe dysplasia is recognizable in the illustrations. The poor quality of specimens could have been additionally caused by inadequate fixation, processing-related factors and/or electrocoagulation. The over-diagnosis must have entailed over-manipulation and overtreatment. Apparently, "Chernobyl cystitis" or "irradiation cystitis" reiterated in [96,100], reportedly characterized by the "reactive epithelial proliferation associated with hemorrhage, fibrin deposits, fibrinoid vascular changes, and multinuclear stromal cells" [100], was at least in part caused or maintained by repeated cystoscopies with "mapping" biopsies, electrocoagulation etc. Accordingly, some of the immunohistochemical and molecular-genetic markers, especially those associated with the tissue alteration, inflammation and cell proliferation (mitogen-activated protein kinases, growth factors, TGF-β1, NF-κB, p38) as well as the "marked activation of angiogenesis in urinary bladder lamina propria" [96], discussed within the scope of the radiation-related carcinogenesis [96], reflected chronic inflammation and increased cellular proliferation unrelated to ionizing radiation and partly iatrogenic. Scrutinizing the figures from [101,102] (reproduced in [94]), it seems that the over-diagnosis of malignant and premalignant bladder lesions by the same experts occurred also earlier in the 1980s potentially leading to an overtreatment. It is known that excessive screening for cancer and precancerous lesions can lead to an over-diagnosis [87], especially if diagnostic facilities are not perfect.



С.В.Яргину

Уважаемые авторы!

Сообщаем, что Ваша статья О причинах преувеличения заболеваемости раком щитовидной железы среди лиц подвергшихся в детском возрасте воздействию радиации после аварии на Чернобыльской АЭС

была рассмотрена на заседании редколлегии.
Принято решение согласиться с заключением рецензента и не печатать Вашу статью.
Копия отзыва прилагается.

С уважением

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Figure 1: The rejection letter signed by G.A. Frank, dated 2010.

Conclusions and Future Research

By analogy with RET/PTC3, there may be a correlation 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 [10] can be explained by averagely earlier cancer diagnostics and hence better functioning health services in both latter countries compared to the former SU. 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. Some markers may characterize efficiency of healthcare services.

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. Well-conducted epidemiological studies can account for some bias, which has not always been the case in the Chernobyl-related research [62,63]. 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 registration of unexposed individuals as exposed. As mentioned above, some people wanted to be recognized as Chernobyl victims to gain access to health care

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provisions and compensations [31]. "Uncertainties in radiation dose estimates" were acknowledged e.g. in the article discussed above [58]. Indeed, "doses were estimated using detailed information derived from individual direct thyroid radioactivity measurements taken within 8 weeks of the accident" [58], whereas the half-life of [131] I is ~8 days. Furthermore, dose-effect correlations can be explained by a recall bias: it is known that cancer patients tend to recollect circumstances related to radiation better than healthy people [103]. 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 screening. Therefore, even in the absence of the causative role of radiation, certain features associated with post-Chernobyl cancer would be 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 [1,63,64]. The following citation is insightful: "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" [104]. The explanation is not far to seek: the more efficient and early diagnostics in Valencia. Considering the above argumentation and the data from the study [10], the same is probably true for Barranquilla (Colombia).

It can be reasonably assumed that the screening effect and increased attention of exposed people to their own health will result in new reports on the elevated cancer and other health risks in the areas with enhanced natural or anthropogenic radiation background. A promising approach to the study of dose-response relationships are lifelong animal experiments. The life duration is known to be a sensitive endpoint attributable to radiation exposures [105], which can reveal the net harm or potential benefit (within a certain range according to the concept of hormesis [106]) from low-dose exposures.

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