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Overestimation Of Harm from Low Dose Ionizing Radiation with Special Reference to Cardiovascular Conditions

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ABSTRACT

Informative value of systematic reviews may be limited if more and less reliable studies are analyzed together. A narrative review based on observations, qualitative analysis of the literature and plausibility of supposed mechanisms might provide some additional information. Populations exposed to elevated radiation background in the former Soviet Union are analyzed here in some detail: the areas of Chernobyl, the Urals and Semipalatinsk Nuclear Test Site. After the Chernobyl accident appeared numerous publications overestimating its medical consequences. Various limitations can be found in such studies: interpretation of spontaneous diseases as radiation-induced, indication of radioactivity or dose levels without comparison with the natural radiation background, conclusions about incidence increase without statistically correct comparison with growth tendencies for larger regions. Dose levels associated with cardiovascular derangements in experimental animals and humans undergoing radiotherapy are generally higher than averages in above-mentioned cohorts. Unrealistic cardiovascular risks at low-dose exposures call in question cancer risks reported by the same and other researchers. Pathogenetic mechanisms at low-doses are not well understood. Undoubtedly, high-dose exposure to ionizing radiation causes cardiovascular damage. It is uncertain whether low-dose chronic exposure causes measurable cardiovascular risk; further research is needed. Reliable data can be obtained in large-scale animal experiments with registration of the life duration. Current radiation protection follows the reasonable precautionary principle. Strictly observed realistic safety regulations would bring more benefit for the public health than excessive restrictions that might be violated in some countries disregarding international law, bringing economic and strategic advantages to the trespassers.

Keywords: Ionizing Radiation; Chernobyl Accident; East Urals Radioactive Trace; Semipalatinsk Nuclear Test Site; Cardiovascular Diseases

INTRODUCTION

Since many years we have tried to demonstrate that certain environmentalists and scientific writers act in accordance with the interests of fossil fuel producers [1,2]. According to insider observations, the unofficial directive to exaggerate Chernobyl consequences was issued in the former Soviet Union (SU) in the late 1980s, when studies of that kind were started or planned e.g. [3-9]. After the Chernobyl accident, numerous poorly substantiated publications appeared, where spontaneous diseases in clean-up workers or residents of radio contaminated areas, sometimes quite distant from Chernobyl, were claimed to be radiogenic [3-7]. Apparently, motives for the overestimation of Chernobyl consequences included scientific careers, financing, international help, etc. Later on, the Chernobyl accident has been exploited to strangle the worldwide development of atomic energy [10].

METHODS

This article is a narrative review. The informative value of systematic reviews may be limited if more and less reliable data are intermingled due to selection, ideological or other bias. A narrative review based on observations, qualitative analysis of the literature and of plausibility of supposed pathogenetic mechanisms might be more informative. 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 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.

Overestimation of Chernobyl Consequences

After the Chernobyl accident appeared numerous publications overestimating its medical consequences. The following flaws can be found in such studies: interpretation of spontaneous diseases as radiation-induced, indication of radioactivity or dose levels without comparison with the natural radiation background, conclusions about incidence increase without statistically correct comparison with growth tendencies for larger regions or the whole country. Abundance of poorly substantiated publications created the Chernobyl Myth, which has hindered development of nuclear energy production in many countries [10,11]. In some studies, high morbidity figures were caused by non-random selection or inaccurate morphological assessment of tissue specimens. Some studies were based on small samples or singular observations, do not provide any statistically significant information, but create an exaggerated impression about consequences of the accident. For example, severe urothelial dysplasia and carcinoma in situ (CIS) were found as frequently as in 76 % and 92 %, respectively, among randomly selected patients with benign prostatic hyperplasia, residing in the contaminated areas [12]. In another paper, even higher percentages for severe urothelial dysplasia and CIS (86 % and more) were reported in random patients from the contaminated areas [13].

It should be commented that interpretation of a moderate elevation of the background radiation as low doses would have been applicable if the radioactivity were counted from zero. In fact, the radioactivity level for the majority of residents of the contaminated areas was just a moderate increase in the overall exposure that also included the natural radiation background and medical exposures. In terms of the cesium-137 deposition, the population exposure in contaminated areas was estimated as follows: around 6,800,000 inhabitants resided in territories with a contamination level of 37-555 kBq/m2, and 270,600 inhabitants lived on territories with a contamination level ≥555 kBq/m2. To the latter group belonged 115,000 evacuees, who, according to the official classification of contaminated zones, must have been resettled from the areas with the contamination levels above 1480 kBq/m2. External doses received by evacuees from the 30 km exclusion zone were predominantly less than 250 mSv, but a few residents in the most contaminated areas might have received doses around 300-400 mSv [14]. Annual average effective doses received by residents of the strictly controlled zones, which surround the 30 km exclusion zone, were around 40 mSv in the first year after the accident, but decreased to less than 10 mSv in the following years, thus remaining below the recommended upper limit for occupational exposure, which is 20 mSv/year (averagely over a period of 5 years, not exceeding 50 mSv in any single year). For comparison, 3414 Uranium miners with lung cancer who worked in Eastern Germany during the years 1946-1990 received the average cumulative doses over 800 Working Level Months (WLM), which is approximately equivalent to more than 4000 mSv [15]. WLM is a unit used to determine cumulative exposure from radon and its progeny: 1 WLM = 1 WL for 170 h corresponding approximately to 5.1 mSv. For about 13,000 miners with archived occupational data, an average exposure level of 725 WLM (3700 mSv) was determined, including about 800 workers with the levels above 1800 WLM, roughly equivalent to 9200 mSv [16-18].

Previously we commented on some works by Drs. Alfred Körblein, Hagen Scherb and associates [8]. Using mathematical calculations, Körblein has alleged a cause-effect relationship between the Chernobyl fallout and perinatal mortality increase in the former Soviet Union (SU) and even in Western Europe [19-22]. The following arguments should be recollected in this connection: correlations (especially weak ones) do not prove causality; there have been social confounding factors in action since 1986; vested interests: first time after the Chernobyl accident prevailed the aspiration after international aid and cooperation; later on, the interests of fossil fuel producers have come to the fore; data from the former SU may have been biased in accordance with the above-mentioned interests; worldwide variations of natural background radiation are larger than average surplus from Chernobyl on contaminated territories.

An example: "It is hypothesized that the observed increase in perinatal mortality in the 1990s may be a late effect of incorporated strontium-90 on the immune system of pregnant women. The analysis is based on a theoretical model, as no data on strontium concentrations were available" [23]. Moreover: "Acceptance of the strontium hypothesis means that atmospheric weapons testing could be responsible for the deaths of millions of infants in the Northern Hemisphere" [23]. Of note, significant deposition of 90Sr after the Chernobyl accident was limited to the zone adjacent to the NPP; virtually no areas outside the 30 km zone were contaminated at a level ≥100 kBq/m2. Contaminations exceeding 37 kBq/m2 were almost all within a distance less than 100 km from the NPP. An individual lifetime dose as a function of contamination 185-555 kBq/m2 was estimated in the range 5-20 mSv [11], which is a small addition to the average dose from NBR. According to a study conducted in the first half of the 1990s, the intake of 90Sr with residents' food in the most contaminated Gomel province was in the range 1-1.7 kBq/year. Individual doses estimated based on measurements of 90Sr in the body did not exceed 10% of internal radiation from natural radionuclides. The annual effective dose from 90Sr in Gomel province in 1994 was negligible: <0.002 mSv or <5% of the dose from 137Cs [14]. Analogous data ("Internal doses from 90Sr in Gomel oblast during 1986-2001 are estimated 10-30 times smaller than from Cs ingestion for the same time period") were cited by Körblein [21] with reference to a report of the Belarusian Ministry of Health [24]. Further dose comparisons are presented here below. Another questionable statement: "A highly significant peak [of perinatal mortality] was also found in Ukraine in 1991, in addition to the effect of gross domestic product. These peaks occurred too early to be attributed to the socioeconomic crisis (sic)" [19]. For inside observers it is obvious that after the anti-alcohol campaign (1985-1989) followed a deep "socioeconomic crisis" i.e. deterioration of the healthcare and mass consumption of poor-quality toxic beverages sold through legally operating shops. According to observations, the quality and availability of some medicaments, foodstuff, and infant food decreased at that time.

Expectant mothers having anxiety and post-traumatic stress are at a higher risk of preterm birth [25]. Exaggeration of increased risk especially for pregnant women "repeatedly created a situation of panic, like a posttraumatic stress disorder" [26]. After the Chernobyl accident, "conflicting information and false rumors spread considerable alarm among the public in general and among pregnant women in particular" [27]. Radiation phobia with psychosomatic manifestations must be more prevalent in most contaminated areas thus contributing to dose-effect correlations. It can be reasonably assumed that radiophobia contributed to illegal abortions during the last trimester of pregnancy influencing perinatal mortality statistics. There was an increase in the induced abortion rate in different countries after the Chernobyl accident. Certain professional publications may prevent physicians from giving adequate advice to pregnant women inquiring about a possible abortion. Presumably, "the public debate and anxiety among the pregnant women and their husbands 'caused' more fetal deaths… than the accident" [28].

Undoubtedly, ionizing radiation can cause damage to the embryo and elevate prenatal mortality. According to the ICRP and UNSCEAR, there may be a threshold for teratogenic effects at ~100 mGy [29-31], which is much higher than average doses related to accidents. Diagnostic imaging can expose a fetus to 50 mGy, which poses no known risk of anomalies or pregnancy loss [32]. Of note, epidemiological studies tend to overestimate radiation-related risks due to selection and self-selection bias (higher probability of exposed people to be medically examined), social and psychological factors sometimes accompanying exposures. Threshold doses in animal experiments are generally higher than those calculated on the basis of epidemiological studies in humans [33-35].

The author agrees with Mark P. Little [36], who stated that data of equivocal reliability "should therefore probably not be used for epidemiologic analysis, in particular for the Russian worker studies considered here [37-40]." Similar concerns may apply to certain studies discussed in this review. Given the current abundance of literature, it is essential that future reviews and meta-analyses incorporate rigorous evaluation of research quality, selection criteria, self-selection effects, and potential ideological bias in determining which studies merit inclusion.

Misunderstanding can arise from the paper by Mikhail Balonov [41], containing the following phrase in the abstract: "Apart from the dramatic increase in TC incidence among those exposed at a young age and some increase of leukemia and solid cancer in most exposed workers, there is no clearly demonstrated increase in the somatic diseases due to radiation." However, in the Chernobyl Forum publication [42] cited by Balonov [41], leukemia and solid cancers (except thyroid carcinoma) are not discussed. In another Chernobyl Forum publication [43] it is stated that "apart from the dramatic increase in TC incidence among those exposed at a young age, there is no clearly demonstrated increase in the incidence of solid cancers or leukemia due to radiation in the most affected populations" and further "there have been many post-Chernobyl studies of leukemia and cancer morbidity in the populations of contaminated areas in the three countries. Most studies, however, had methodological limitations and lacked statistical power. There is therefore no convincing evidence at present that the incidence of leukemia or cancer (other than thyroid cancer) has increased in children, those exposed in utero, or adult residents of the contaminated areas" [43]. In the Report of the UN Chernobyl Forum Expert Group "Health", it was commented that "there is currently no evidence to evaluate whether a measurable risk of leukemia exists among the exposed as adults in the general population. With regard to liquidators, there is clearly a need to clarify the existing observations" and further "there is no evidence of increased risk of non-thyroid solid cancers resulting from Chernobyl" [44]. The same, in principle, is said in the text of the article by Balonov [41]. So, the above-cited statement from the open access abstract is substantiated neither in the article text nor in the Chernobyl Forum publications directly or indirectly referred to in this article named "The Chernobyl Forum: major findings and recommendations" [41], which is in fact misquoting. Furthermore, the counterpart of the "the most exposed workers or liquidators" [41] in the general population, middle-aged men from the working class, are incompletely covered by medical services, so that regular medical checkups of the exposed workers have predictably resulted in an increase of the registered incidence of various diseases. These considerations, as well as bias due to the dose dependent self-reporting of patients [45], pertain also to another study [46], where national statistics for leukemia were used as external control for a cohort of clean-up workers (liquidators). Oncological aspects of the problem have been discussed previously [47]. This article is focused on cardiovascular conditions.

Radioactive Contamination in the Urals

Consequences of the radio contamination in the Urals were summarily more significant than those after the Chernobyl disaster. The difference is that the latter was an accident, but the former - a radio contamination lasting over 70 years with several accidents in between. Apart from professional exposures, the disposal of radioactive substances into the river Techa, the 1957 Kyshtym accident and dispersion by winds from the lake Karachai in 1967, led to exposures of residents. The East Urals Radioactive Trace (EURT) cohort included people exposed after the Kyshtym accident. Large discharges of radioactive materials into the Techa River in the Southern Urals occurred between the years 1949 and 1956. The most exposed individuals were residents of villages along the river.

At earlier times (until 2005-2010), researchers found no cancer increase in exposed populations of the Urals with average exposures below 0.5 Sv or among employees of the Mayak Production Association (MPA) [48-50]. The absolute risk of leukemia per 1 Gy and 10000 man-years was found to be 3.5-fold smaller in the Techa river cohort than in the Life Span Study (LSS) of atomic bomb survivors in Japan. This was reasonably explained by a higher efficiency of the acute exposure compared to chronic and fractionated ones. Later on, the same experts reported comparable or even higher risks of cancer and other diseases in the cohorts from the Urals and in LSS [51-53].

Increased risks of non-malignant diseases - cardiovascular, respiratory, digestive - have been reported by the same and other scientists in the Urals and Chernobyl cohorts. For example, the incidence of cerebrovascular disease was significantly elevated among MPA workers with a total external dose ≥0.1 Gy protracted over years [54]. This is indicative of bias, in particular, of dose-dependent self-selection, noticed also by other researchers in radiation-exposed cohorts [55,56]. It can be reasonably assumed that individuals with higher dose estimates were on average more interested in medical examinations. In the health care system of the former SU, thoroughness of medical examination has often depended on a patient's initiative. According to a personal communication with Techa River expert Ludmila Krestinina (year 2014), exposed residents were preoccupied with monetary compensations. Most probably, individuals with higher dose estimates or those residing in more contaminated areas were more insistent at examinations, visited medical institutions more frequently, being given more attention. As a result of the screening effect, observation bias, dose-dependent selection and self-selection, diagnostics was a priori more efficient in patients with higher doses, especially of diseases without local symptoms such as leukemia. Therefore, epidemiological studies alone do not prove causality for low doses.

Along the same lines, an earlier study found a reduction of cancer mortality in the EURT populace [57]. A review confirmed approximately the same level of both cancer-related and all-cause mortality in the EURT vs. control [49]. In a later report on the same cohort, the authors avoided direct comparisons but fitted the figures into a linear model. The configurations of dose-response curves depicted in this paper seem to be inconclusive but nevertheless an elevated cancer risk in the EURT population was claimed [58]. In earlier reports, an incidence elevation of cardio- and cerebrovascular diseases in MPA, Techa River and EURT cohorts was not accompanied by a mortality increase. This can be reasonably explained by a greater diagnostic effectiveness in people receiving higher doses, leading to a diagnosis of mild and questionable cases. A similar tendency for cancer was noticed among Chernobyl emergency workers [59]. Chernobyl cleanup workers underwent repeated medical checkups. As a result, lesions were efficiently detected including small, dormant cancers and nodules with uncertain malignant potential. The early detection and treatment of diseases contributed to the diminution of mortality. Besides, some differentiated and borderline tumors, statistically filed as cancers, did not lead to death. However, in a recent paper based on the MPA cohort, an increased mortality risk from myocardial ischemia was claimed for the range of 5-50 mGy/year [60]. Presumably, some our comments, though not cited, have been taken into account. The review by Koterov et al. [61] has apparently been influenced by the comments cited by the same first author [62], discussed previously [63], yet trying to shift responsibility for misleading information onto foreign scientists: "In most sources, 2005-2021 (publications by M.P. Little with co-workers, and others) reveals an ideological bias towards the effects of low doses of radiation ... In selected M.P. Little and co-authors sources for reviews and meta-analyses observed both absurd ERR values per 1 Gy and incorrect recalculations of the risk estimated in the originals at 0.1 Gy" [61]. Note that relevant papers co-authored by M.P. Little used the data provided by co-workers from the former SU.

Cardio- And Cerebro-Vascular Conditions

Most of current understanding on the effects of ionizing radiation comes from in vitro and in vivo models. Results suggest that acute doses may induce cardiovascular damage by several mechanisms, including DNA damage, mitochondrial dysfunction, perturbations of myocyte calcium handling and ion channel regulation, increased production of reactive oxygen species or pro-inflammatory mediators. These mechanisms can lead to aberrant endothelial and cardiac gene expression, cell dysfunction, and inflammation [64,65]. However, it is not well understood whether these or other mechanisms are operative at low-dose exposures [66].

Excess cardiovascular risks have been observed in a number of occupationally exposed groups, reviewed in [67]. In particular, increased risks of cardiovascular diseases were claimed for the cohorts from Chernobyl and the Urals, whereas average doses have been compatible with those from the natural background. There are many populated areas on the Earth where annual dose rates from the background are 10-100-fold greater than the worldwide average (2.4 mSv) with no health risks reliably proven [68]. The doses have been protracted over many years: studied MPA workers were employed since 1948-1982. Average doses of gamma radiation were around 0.54 Gy in males and 0.44 Gy in females in the research, where the incidence of atherosclerosis in lower limbs reportedly correlated with the dose [69]. Average doses in the Techa River cohort were 34-35 mGy while the follow-up was since the 1950s [70], so that the dose rates were comparable with those from the natural background. The same research team acknowledged that the risk for doses <0.1 Gy can be lower than that calculated using a linear model [71].

Doses mentioned above are hardly suitable for computations of the dose and dose rate effectiveness factor (DDREF). Earlier Russian publications pointed out a higher biological efficiency of acute exposures compared to chronic ones; later on the same researchers claimed that the International Commission on Radiological Protection (ICRP) underestimates health risks from chronic exposures, and recommended the use of DDREF = 1.0 [72], thus implying the same effect for acute and protracted exposure to the same dose. This recommendation is obviously unsuitable for the dose rates compatible with those from the natural background.

The average total dose to male MPA workers studied by Moseeva was 0.91 Gy. Over 90% of the Techa river cohort received ≤0.1 Gy protracted over years [73,74]. For comparison, some studies found no evidence for excess morbidity and mortality from coronary artery disease in women treated with radiotherapy for the left breast cancer compared to those with right-side tumors [75]. An increased risk of heart disease has been related to breast tumor doses of 40-50 Gy and mediastinal doses in excess of 40 Gy [76]. The 7th Report of the Committee on the Biological Effects of Ionizing Radiation BEIR VII summarized that "there may be some risk of cardiovascular morbidity and mortality for very high doses and high-dose-rate exposures" [77]. According to the judgment by the UNSCEAR, given the inconsistent epidemiological data and the lack of biologically plausible mechanisms, the present evidence is not sufficient to establish a causal relationship between ionizing radiation and cardiovascular disease at doses ≤1-2 Gy [76]. The latter figure may be an underestimation as some epidemiological data are biased due to the dose-dependent self-selection, while doses associated with functional or morphological cardiovascular changes in experiments were considerably higher [78-80].

Prof. Little have rightly noted that the "diagnosis (by a physician knowing the patient's history) could vary with dose" [81]. Mild and borderline conditions are probably more often diagnosed in people with higher doses due to more thorough examinations and the patients' attention to their own health. The high frequency of cardiovascular diseases in studied populations from Russia have been explained by unfounded conclusions in unclear cases both post- and ante-mortem [82]. There is a tendency in the former SU: the lower the diagnostic quality, the higher the fraction of cardiovascular diseases among all recorded causes of death. The same is true also for deceased people not undergoing autopsy: cardiovascular diseases are often recorded as causes of death in unclear cases [83].

Another study based on the MPA cohort analyzed 9469 cases of cerebrovascular diseases including 2078 strokes [84]. The following statements are contradictory: "Cerebrovascular diseases incidence was found to be significantly associated with cumulative radiation dose" and "No significant associations of either stroke or its types with cumulative gamma-ray dose of external exposure or alpha-particle dose of internal exposure were found" [84]. It can be reasonably expected that with more arterial occlusions and stenoses there would be more strokes. A possible explanation for the discrepancy is the dose-dependent diagnostic quality and a larger screening effect in populations with higher average doses. At that, mild and questionable conditions would be diagnosed more often. On the contrary to cerebrovascular diseases in general, strokes are diagnosed based on distinct morphological or clinical criteria, overdiagnosis thus being less probable. Moreover: "The estimates of the cerebrovascular diseases incidence risk significantly decreased with the increasing duration of employment for the entire cohort ($p < 0.001$)" and "In addition, a significant decrease in cerebrovascular diseases incidence risk with increasing attained age was observed in both males and females" [84]. The incidence of cerebrovascular diseases is known to increase with age; so that the above quotes are compatible with a protective (hormetic) effect of low radiation doses. In the author's opinion, Azizova should have discussed serious cerebrovascular diseases (strokes) and concluded that there was no increase of strokes after low-dose low-rate exposures [84]. By including mild and unreliably diagnosed conditions, they were able to make a conclusion that low doses elevate the frequency of cerebrovascular diseases.

Greater risks of cerebrovascular diseases at higher doses in females than in males agree with the known tendency that women in Russia care more than men about their health and are generally given more attention by medical personnel. Some men, especially those supposed to be alcohol consumers, are not given sufficient attention [94]. Hence the worldwide greatest gender gaps in the life expectancy: countries of the former SU crown the list [85]. Accordingly, the diagnostics in women must be on average more efficient and reliable than in men. This notion doesn't contradict to the higher relative risk in some low-dose male groups: Tables 1 and 1S in [84]. Cerebrovascular diseases are more frequent in men, among others, thanks to alcohol, smoking and untreated hypertension. Some overdiagnosis of mild conditions may occur just because these conditions are expected. The author encountered descriptions of age- and hypertension-related changes of retinal vessels in a medical record of a middle-aged man after a dispensarization (yearly workplace examination) whereas his eye grounds had not been inspected. As for post mortems, supposedly age-related changes (aortal, coronary, cerebral or basilar atherosclerosis) have been habitually written without sufficient evidence in autopsy reports and death certificates [83]. In higher-dose groups the diagnostics would be more reliable resulting in a more pronounced screening effect especially in women but less frequent unsubstantiated recordings especially in men.

Among members of the MPA cohort who received gamma-ray doses more than 0.1 Gy, the incidence of circulatory diseases was found to be higher than in people exposed to lower doses [54,86]. The excess relative risk (ERR/Gy) of cerebrovascular conditions in MPA employees was claimed to be even higher than among A-bomb survivors in Japan [86], where dose-dependent selection could have taken place like in other epidemiological studies. Some data assessments of life span study (LSS) of A-bomb survivors are compatible with hormesis [87-90].

Considering the above, the following statements by the same scientists may create biased impression. The statements cited below, not specifying dose levels, are inapplicable to the cohorts from the Urals and to low radiation doses in general, being suggestive of bias. Here follow the examples:

"It is concluded that this study provides evidence for an association of lower extremity arterial disease incidence with dose from external gamma-rays" [91].

"This study provides strong evidence of ischemic heart disease incidence and mortality association with external gamma-ray exposure and some evidence of ischemic heart disease incidence and mortality association with internal alpha-radiation exposure" [37].

"A significant increasing trend in circulatory diseases mortality with increasing dose from internal alpha-radiation to the liver was observed" [92].

"Significant associations were observed between doses from external gamma-rays and ischemic heart disease and cerebrovascular disease incidence and also between internal doses from alpha-radiation and ischemic heart disease mortality and cerebrovascular disease incidence" [40].

"Findings are that aortal atherosclerosis prevalence was higher in males and females underwent external gamma-irradiation of total dose over 0.5 Gy, in males and females underwent internal alpha-irradiation from incorporated plutonium of total absorbed radiation dose in liver over 0.025 Gy" [93].

"There was a significantly increasing trend (ERR/Gy) of ischemic heart disease mortality with the total absorbed dose to liver from internal alpha-radiation due to incorporated plutonium" [94].

"The incidence data point to higher risk estimates (in MPA workers) compared to those from the Japanese A-bomb survivors" [73].

"The categorical analyses showed that cerebrovascular disease incidence was significantly higher among workers with total absorbed external gamma-ray doses greater than 0.1 Gy compared to those exposed to lower doses and that cerebrovascular disease incidence was also significantly higher among workers with total absorbed internal alpha-particle doses to the liver from incorporated plutonium greater than 0.01 Gy compared to those exposed to lower doses" [86].

The risk estimates by Azizova et al. [93] were found to be significantly higher than those in other studies [95]. Nonetheless, Azizova and co-workers have been cited in reviews in support of questionable statements like "Emerging evidence indicates that late-onset cardiovascular disease... occur after protracted low-dose ionizing radiation exposure at doses >0.5 Gy" [96] or "Increasing evidence indicates that low-dose IR - typically defined as less than 100 mSv - can contribute to the long-term risk of cancer and cardiovascular disease" [97]. As mentioned above, among members of the MPA cohort who received total gamma-ray doses ≥0.1 Gy, the incidence of circulatory diseases was found to be greater than in people exposed to lower doses [54,86]. The dose 0.1 Gy protracted over years is comparable to that from natural background in some regions. Cause-effect relationships are improbable at such a low dose and dose rate. In humans after radiotherapy, myocardial fibrosis developed at the doses above 30 Gy. An increased risk of coronary heart disease after radiotherapy was noted after exposures to 7.6-18.4 Gy [98], which is much higher than mean doses in the cohorts from Chernobyl and the Urals.

Dose levels associated with cardiac derangements in experimental animals and in humans after radiotherapy have been higher than average values in Chernobyl and Urals cohorts [64,80,98-101]. Results of some animal experiments are compatible with hormesis, i.e. favorable effect within a certain low-dose range [100]. There is considerable evidence in favor of hormesis although not all studies confirm this phenomenon [102-106]. Finally, the recall bias should be mentioned: cancer (and possibly some other) patients remember facts related to radiation more often than healthy controls [107], which may lead to overestimation of doses and dose-effect correlations. It should be stressed in conclusion of this section that unrealistic cardiovascular risks at low-dose exposures call in questions cancer risks reported by the same and other researchers.

Semipalatinsk Nuclear Test Site (STS)

The STS in today's Kazakhstan was the place where 456 nuclear explosions were carried out between 1949 and 1989, including 111 atmospheric tests in the period 1949-1962 [108]. STS was shut down in early 1990s. The villages most affected by the atmospheric tests were located northeast of STS. Yuri Dubrova stated 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" [109] with reference to the review [110]. However, in the abstract of the latter review it is 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" [110]. Earlier publications estimated maximum external doses for adult residents of Dolon at 1.3 Sv [111] or 0.63 Gy with a remark that integral exposures at Dolon may have been factually less than estimated [112]. Other authors reported lower doses [113]. Apparently, the single historical measurement was performed at the axis of the radioactive trace 1.5-1.6 km northwest of Dolon, while the width of the cloud was narrow [114,115]. The dose estimate based on this measurement is believed to be a maximum rather than average for Dolon residents [114], while in other villages the doses were much lower. The average individual dose estimates for townships near STS, received in the period 1949-1953, have been estimated as follows: Dolon 1600 mGy, Abai 370, Kainar 240, Sarzhal 200, and Semipalatinsk city ≤ 5.6 mGy. In the period 1971-1990 annual individual doses in the area were ≤5 mGy [116]. In 2008 the annual individual dose in the STS compound was 0.073-0.749 mSv and outside STS - 0.036-0.37 mSv [117], which is a negligible addition to the natural radiation background. The worldwide annual exposures to the radiation background are generally expected to be in the range 1-10 mSv but can be higher. There are populated areas in the world where dose rates from the background are 10-100-fold higher than the global average (2.4 mSv/year) with no health risks reliably proven [30].

The tendency to overestimate medical consequences of elevated background radiation in the Semipalatinsk area can be exemplified by the international study [118]. The following was stated in the abstract: "17 patients (group 1) lived close to the testing area from the childhood to 1993 and were exposed to the radiation at the year dose 0.1 ber." A radiation dose unit "ber" (Biological Equivalent of Rad), used in the former SU, is designated internationally as rem. The annual individual dose of 0.1 rem (1 mSv) is below the global average for annual doses from natural background, which is 2.4 mSv. The term "radiogenic carcinoma" was used for cancers of unknown etiology. Unfounded suppositions about their rapid growth and "poor prognosis" were made [118]. The study was based on two sets of tissue specimens from patients with lung carcinoma: the "exposed" group - 17 cases from the area of Semipalatinsk, and the control (40 specimens). Cumulative doses were unknown. The following data are remarkable (from Russian): "The specific cytogenetical feature of the lung carcinoma in patients from the area of Semipalatinsk was the neuroendocrine differentiation of cancer cells in all tumors independently of their histological structure. We have established it by means of immunohistochemical and ultrastructural investigations." At the same time, "no neuroendocrine differentiation was shown in the control group." It means that the marker was found by two methods in 100 % (17/17) of the cases and in 0 % (0/40) of controls. The extremely high level of significance ($P<0.0001$) agrees with the supposition that the "lung cancer in persons exposed for a long time to radionuclide radiation pollution" [118] is a distinct entity, different from spontaneous lung carcinoma. Significant differences between the two groups were found also for other markers, which additionally enhanced statistical significance of the difference. It was concluded that "lung carcinoma in patients, who resided in the area of Semipalatinsk and underwent elevated radioactivity, can be classified as neuroendocrine carcinoma" [118]. In the general population, tumors from neuroendocrine cells (small cell carcinoma and carcinoids) were reported at that time at 20-30 % of lung malignancies [119]. The age and sex data in the "exposed" group were typical for spontaneous cancer possibly caused by cigarette smoking or industrial air pollution: 15 from 17 patients were 51-70 years old. Patients with radiation-induced cancer could be younger. In particular, spontaneous lung cancer is characterized by male predominance due to cigarette smoking and professional carcinogens. Radiation would exert a similar effect on both genders. In the "exposed" group there were 16 males and one female [120]. The designation "radiogenic carcinoma" and discussion of its supposedly rapid growth and poor prognosis [118] contributed to exaggeration of medical consequences of low-dose exposures and could lead to overtreatment. Other studies on STS and Chernobyl by the same authors [121-124] are characterized by similar limitations. For example, a discussion of molecular markers of "radiogenic cancer" is led on the basis of 15 random autopsy and surgical cases of lung cancer from the areas quite distant from Chernobyl: eight cases were from the Tula province in Russia [121].

Studies discussed above illustrate the approach persisting until today. Despite the low average doses, long-since within limits of the natural background, residents of the Semipalatinsk area are designated as "exposed to radiation" [125-127]. Admittedly, some nuclear tests, conducted from 1949 to 1956, resulted in non-negligible external doses [128]. However, the last atmospheric test at STS was performed in 1962, and underground test in 1989 [129]. After the 1963 Partial Test Ban Treaty, the nuclear testing was restricted to underground so that, with a few exceptions, little or no off-site environmental contamination was caused. The exceptions included cratering events in the period 1965-1968 [129].

The medical and ecological research about STS is associated with limitations and confounding factors. Studies are not well connected with each other. Biological specimens were not always properly stored and labeled, individual migration and residence histories being often unknown [113]. In regard to cancer, the morbidity and mortality in exposed people were reported to exceed those in control groups [130]. The same problem has been discussed with regard to radioactive contaminations in Chernobyl and the Urals. An explanation for higher detection rates from various diseases in the exposed populations is the better coverage by medical examinations (including post mortems) and increased attention of exposed individuals to their own health: the selection and self-selection bias. Besides, people knew about the Kazakhstani law "Social protection of citizens who suffered as a result of nuclear tests conducted at the STS" [127]. Some patients from non-contaminated areas have been falsely registered as radiation-exposed. The circumstantial evidence thereof is a marked increase in the incidence of diseases, prima facie unrelated to radiation, in contaminated compared to "clean" territories. For example, the incidence of tuberculosis in children in the Semipalatinsk province was 1.5 times higher than in the whole Kazakhstan with a threefold higher frequency of severe and complicated cases [131]. Remarkably, the incidence of neoplasia in children of exposed parents was found to be nearly fourfold higher than among controls: 92.6 vs. 24.7 per 1000 children [132].

Several publications discussed the elevated morbidity and mortality from cardio- and cerebro-vascular diseases in people residing near STS [133]. Admittedly, no direct conclusions on cause-effect relationships have been made in recent papers [125-127]. When account was taken of the difference in baseline rates between the exposed and unexposed groups, no statistically significant dose-response relationship was observed either for cardiovascular diseases or for stroke [133,134]. This is in agreement with the fact that dose-response associations among A-bomb survivors in Japan became significant at exposures >2 Gy for cerebrovascular and >0.5 Gy for heart disease [96,135,136].

DISCUSSION

There are confounding factors preventing reasonable interpretation of medical statistics from some countries of the former SU. Like in Russia, cardiovascular mortality in Kazakhstan is higher compared to West Europe [137]. The causes thereof are known by anatomic pathologists. Since the Soviet time, the autopsy remained obligatory for patients dying in hospitals but the quality deteriorated. Post mortem examinations were often made perfunctorily. The quality decrease in anatomic pathology during the 1990s coincided with the elevation of the registered cardiovascular mortality. If a cause of death is not entirely clear, it has been usual to write on a death certificate: "Ischemic heart disease with cardiac insufficiency" or a similar formulation. It is known that ill-defined cardiovascular codes from the International Statistical Classification of Diseases (ICD) are used in cases with insufficient clinical information. The frequent cause of cardiovascular death in some countries of the former SU has been "coronary atherosclerosis". The nonstandard disease classifications used in Russia complicated the evaluation of medical statistics [138]. The tendency that radiation-exposed people are on average more thoroughly examined is known. Finally, manipulation with statistics following official or unofficial directives has been known to occur in the former SU [139]. Human factors have remained largely unchanged.

A tendency to over-diagnose cardiovascular diseases is generally known also for people dying at home and not undergoing post mortem examination. It can be confirmed by the following: "Increases and decreases in mortality related to cardiovascular diseases … but not to myocardial infarction, the proportion of which in Russian cardiovascular mortality is extremely low" [140]. The diagnosis of myocardial infarction is usually based on clinical or morphological criteria, while the diagnoses of ischemic heart disease and coronary atherosclerosis are often used post mortem without strong evidence. Furthermore, contrary to myocardial infarction, gross features of ischemic brain infarction were sometimes mimicked destroying brain tissue using autopsy knife by a pathologist or postgraduate student not inclined or unable (for a lack of toxicological tests) to search for the true cause of death even at university mortuaries let alone peripheral institutions. The post-mortem diagnosis of stroke has been overused for poisonings, especially with alcohol surrogates [141]. Along with inadequate treatment of arterial hypertension, this was probably the cause of higher reported stroke mortality in Russia compared to other developed countries [142,143].

Dose levels associated with cancer or cardiovascular diseases in animal experiments and in humans after radiotherapy have been higher than averages in the cohorts from contaminated areas of the former SU. Results of experiments are generally not supportive of detrimental effects of low doses, with possible exception of genetically modified cancer-prone animals. According to the latest review, low- to moderate-doses are defined as 2-20 Gy [64], which is much higher than averages in the cohorts discussed in this review. Other experts opine that the dose-risk relationship below 0.5 Gy for cardiovascular disease is inconclusive [144]. While there are ongoing discussions about the definition of low-dose radiation, it is typically considered as doses under 0.5 Gy, while potential pathogenetic mechanisms at low-dose radiation exposures are not well understood [66].

In humans after radiotherapy, myocardial fibrosis developed after exposures ≥30 Gy. An increased risk of coronary disease has been reported after radiotherapy with doses 7.6-18.4 Gy [98], which is still much higher than averages in the exposed cohorts discussed above. In certain experimental and epidemiological studies, low doses turned out to be protective against cardiovascular diseases and other adverse effects. As mentioned above, the evidence in favor of hormesis is considerable [102-106]. Unrealistic cardiovascular risks at low-dose exposures call in question cancer risks reported by the same and other researchers. A major part of the literature about STS is characterized by large volume, abundant details and mathematical computations, but no clear insight into medical consequences of contamination. Papers on dosimetry or retrospective dose estimation contain discourses e.g. about diets of different ethnic communities, living in or relocated to the Semipalatinsk area; but provide no clear information on radiation doses, morbidity and mortality. Along with other ethnic groups, more than 440,000 Germans were deported to Kazakhstan during during and after the World War II [145], including the subsequently contaminated areas near STS [133,146].

Several publications are discussed here because of inadequate use of the term “long-term low-dose exposure to ionizing radiation”, which was, in fact, a slight elevation of the radiation background. It is difficult to determine with certainty the level of exposure, below which there is no appreciable risk for humans; it appears to be 200 mSv or more; this latter figure is mentioned in the reviews [147,148]. For solid cancers and leukemia, a significant dose-response relationship was found in survivors of atomic explosions who had received doses less than 500 mSv but not for the doses below 200 mSv [33,90,149]. According to the UNSCEAR, statistically significant elevations of cancer risk are observed in epidemiological research at the doses 100-200 mGy and above [30]. As discussed in this review and elsewhere [2,8,47], some epidemiological studies overestimated biological effects of low doses. The practical thresholds are probably higher in view of bias in the epidemiological research [76,150]. Thresholds for cardiovascular damage are higher than those for cancer. Unrealistic cardiovascular risks at low-dose exposures call in question cancer risks reported by the same and other researchers.

In small animals, minimal doses associated with carcinogenesis are in the range of thousands or hundreds of mGy [33,151-153]. Studies of human populations exposed to low-dose low-rate ionizing radiation, though important, will hardly add reliable information on dose-effect relationships. Screening effect, selection, self-selection and ideological bias will contribute to appearance of new reports on elevated risks associated with a slight increase of the radiation background, which would not prove causality. Finally, manipulations with statistics have been not unusual in the former SU [139], which should be taken into account by authors of systematic reviews and meta-analyses.

CONCLUSION

High-dose exposure to ionizing radiation causes cardiovascular damage. Radiation-induced heart disease is known to occur after radiotherapy. It is uncertain whether low-dose chronic exposure causes measurable cardiovascular risk. Hormesis remains controversial; international radiation protection organizations do not consider it proven. Evidence suggests that increased risk may exist at moderate doses. The magnitude of risk at low doses remains debated; further research is needed. Reliable data can be obtained in large-scale animal experiments with registration of the life duration. With regard to the clinical practice, patients should not develop fear of diagnostic imaging. Medical radiation exposure must follow the principles of justification, optimization and ALARA (As Low As Reasonably Achievable). The latter is important because radiation effects can accumulate, while exposures may occur unpredictably. Patients receiving high-dose radiotherapy require cardiovascular risk assessment and long-term follow-up.

The worldwide use of nuclear energy must be managed by a powerful international executive based in the most developed parts of the world. It would permit construction of nuclear power plants in optimally suitable places, notwithstanding national borders, considering all socio-political, geophysical and other conditions. In this way, nuclear accident like the Fukushima Daiichi, caused by the earthquake and tsunami, or in Chernobyl, favored by negligence and disregard for written instructions [154,155], would be avoided. Considering vulnerability of large NPPs, attention should be directed to smaller reactors, which have some economic advantages. Small reactors can be used by the military [156].

Current radiation protection follows the reasonable precautionary principle. The adequate approach is to determine the threshold dose for the carcinogenic effect and establish regulations to ensure that doses are kept well below the threshold, as low as reasonably achievable taking into account economical, societal and military considerations [157]. Strictly observed realistic safety regulations would bring more benefit for the public health than excessive restrictions that would be violated in some countries disregarding international law, bringing economic and strategic advantages to the trespassers.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this case report. No financial or personal relationships influenced the work reported in this manuscript.

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