OVERESTIMATION OF CARDIOVASCULAR CONSEQUENCES OF LOW DOSE LOW RATE IONIZING RADIATION

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ABSTRACT

This commentary is focused on radioactive contaminations in the Urals, where the consequences have been more severe in the long term than those after the Chernobyl accident. The difference is that the latter was a technogenic catastrophe, but the former - a radioactive contamination tolerated since 70 years with several accidents in between. In earlier publications of Russian researchers no cancer frequency elevation was reported in cohorts with average exposures below 0.5 Sv or generally in the populations exposed to low doses. Later on, the same scientists started to claim similar relative risks for cancer and other diseases among exposed people in the Urals and in atomic bomb survivors of Hiroshima and Nagasaki. Recent publications claiming cardiovascular risks after low-dose low-rate exposures and recommending more stringent standards of radiological protection are discussed here in some detail. Such recommendations for dose rates compatible with the natural radiation background are obviously nonsensical.

KEYWORDS

cerebrovascular diseases, cardiovascular diseases, ionizing radiation, low doses, hormesis

1. INTRODUCTION

It is important in the time of international tensions that researchers preserve objectivity. Potential conflicts of interests should be discussed. Since decades we have tried to demonstrate that certain environmentalists and grassroots act in accordance with the interests of companies and governments selling petroleum and natural gas [1-3]. Most evident is this tendency in regard to ionizing radiation, while the overestimation of medical and environmental side effects of nuclear energy contributes to its strangulation [4], supporting appeals to dismantle all nuclear power plants. The nuclear power is on the agenda today due to increasing energy needs of the growing humankind. Of note, health risks and environmental damage are maximal for coal and oil, lower for gas and much lower for the atomic energy - the cleanest, safest and practically inexhaustible energy resource [4,5].

Potential biases of epidemiological studies of low dose low rate ionizing radiation are known: arbitrary classification of spontaneous conditions as radiation-induced, conclusions about incidence increase of certain diseases without adequate control and trimming of data [2,3, 6]. Some studies with negative results were neither included in databases nor cited in reviews [7]. Other bias and confounders were noticed [4,8-10]. Of particular importance are the dose-dependent selection and self-selection. It can be reasonably assumed that people knowing their higher doses would be more motivated to undergo medical examinations being at the same time given more attention. Therefore, diagnostics would be more efficient in cohorts with higher average doses. Some epidemiological studies disregarded the radiation background. Individual doses from the natural background are generally expected to be within limits 1-10 mSv/year, some national averages being above 10 mSv/year [11,12]. For comparison, the average individual whole body dose to 6 million residents of the territories recognized as contaminated due to the Chernobyl accident was ~9 mSv [13].

2. Mechanisms of Radiation-Related Cardiovascular Disease

The pathogenesis of atherosclerosis, which underlies the development of many cardio- and cerebrovascular diseases, has been studied extensively. Atherosclerotic plaques develop after an endothelial injury by hemodynamic factors (hypertension), hyper- and dyslipidemia, hypoxia, infection, free radicals and endotoxins. Cytokines and growth factors secreted by macrophages and T-cells play their roles in the process. Capillaries are the radiosensitive component of the vasculature. Radiation-induced microvascular injury may lead to damage of other tissues including the myo- and pericardium. The extent, to which these models can explain cardiac damage by low-dose irradiation, is not clear [14]. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) could not reach a final conclusion concerning causality between exposures below 1-2 Gy and cardiovascular diseases [14]. Apparently, the level 1-2 Gy is an underestimation as a result of the screening effect, selection, self-selection, other bias and confounding factors in epidemiological studies delineated in the Introduction. In humans after radiotherapy, myocardial fibrosis developed at doses ≥30 Gy. An increased risk of coronary disease after radiotherapy has been registered after exposures to 7.6-18.4 Gy [15], which is much higher than mean doses in the cohorts discussed in this review. Furthermore, the quality of dose estimation is essential for studies of radiation risks [16]. Recall bias should be mentioned in this connection: cancer patients tend to recollect the circumstances related to radiation better than controls [17]. Dose levels associated with cardiac derangements in animal experiments [15,18-20] have been much higher than average doses in the cohorts discussed below. Results of animal experiments are generally compatible with hormesis, i.e. favorable effect in a certain low-dose range, with possible exception of genetically modified e.g. cancer-prone animals. In certain experimental and epidemiological studies, low doses turned out to be protective against cardiovascular disease [18,20]. The experimental evidence in favor of radiation hormesis is considerable [9,21-24].

3. Low-Dose Radiation and Cardiovascular Disease: Epidemiological Studies

The radiation safety regulations are partly based on the linear no-threshold theory (LNT): extrapolations of dose-response relationships down to low doses, where such relationships have not been proven experimentally. The LNT is based on the concept that cells are altered by ionizing radiation: the more tracks pass through cell nuclei, the higher would be damage. This concept does not take into account the natural radiation background and the fact that DNA damage and repair are normally in a dynamic balance. Presumably, there is a harmless exposure level, as it is for many other environmental agents potentially toxic at higher doses. Details and references are in the preceding review [3].

This commentary is focused on the radioactive contamination in the Urals, where the consequences have been more severe in the long run than those after the Chernobyl accident. The Chernobyl disaster has been discussed previously [1-3]. Mayak Production Association (MPA) has been the first plutonium production site in the Soviet Union (SU) built in 1948. The dumping of radioactive materials into Techa river, 1957 Kyshtym accident and dispersion by winds from the open repository lake Karachai in 1967, led to exposures of residents. The East Urals

Radioactive Trace (EURT) cohort includes people exposed after the Kyshtym accident. The difference between contaminations in the Urals and Chernobyl is that the latter was a technogenic catastrophe, but the former - a radioactive contamination continued since 70 years with known and unknown accidents in between.

In earlier publications by Russian researchers no cancer frequency elevation was reported in cohorts with average exposures below 0.5 Sv or among MPA employees in general [25-30]. For example, 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 compared to atomic bomb survivors of Hiroshima and Nagasaki. This was reasonably explained by a higher efficiency of the acute exposure compared to chronic ones [29,30]. Later on, the same scientists started to claim similar risks for cancer and other diseases in the Techa river, MPA and EURT cohorts, on one hand, and atomic bomb survivors on the other hand [31-33]. Analogously, an earlier study found a reduction of cancer mortality in the EURT cohort compared with the general population [26]. A review confirmed the same level of both cancer and all-cause mortality in the EURT cohort vs. control [30]. In a later report on the same cohort, the authors avoided direct comparisons but fitted the data into a linear model. The configuration of dose-response curves shown in this paper is inconclusive but nonetheless the authors claimed an elevated cancer risk in the EURT population [34]. An unofficial directive was apparently behind this ideological shift noticed around the year 2005. Trimming of statistics has been not unusual in the former SU [6]. Potential motives have been discussed previously: fostering radiophobia, stirring anti-nuclear protests in other countries and strangulation of nuclear energy aimed at the boosting of fossil fuel prices [1-3]. Some papers about radioactive contaminations in the former SU have common features: large volume, plentiful details and mathematical computations, but no clear insight into medical consequences. Oncological aspects of the problem have been reviewed previously [1-3]. Cardiovascular diseases and their supposed associations with low-dose low-rate radiation exposure are discussed below.

In earlier reports, an incidence increase in cardiovascular diseases, if even found in MPA, Techa river and EURT populations, was not accompanied by a mortality increase [35-37]. This can be reasonably explained by a higher diagnostic effectiveness in people having higher doses with registration of mild and questionable cases. However, in the recent paper based on the MPA cohort, an increased excess relative risk (ERR/Gy) of mortality from ischemic heart disease was claimed for the range of 5-50 mGy/year [38]. It might be that our preceding comments [39], though not cited, have been taken into account by the authors. Moreover, the recent review [40] has apparently been influenced by our comments cited by the same first author [41] (commented in [42]), trying however to shift responsibility for biased information onto foreign experts, which can be illustrated by the following citation from the English abstract: "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" [40]. Note that relevant papers co-authored by Prof. Little e.g. [43,44] used statistics provided by co-workers from the former SU. In this connection, the author agrees that the "Russian national mortality data is likely to be particularly unreliable, with major variations in disease coding practices across the country [references], and should therefore probably not be used for epidemiologic analysis, in particular for the Russian worker studies considered here [references]" [45].

Enhanced risks of cardiovascular diseases were claimed for Chernobyl, MPA, Techa and EURT populations, where average doses have been comparable with those from the natural radiation background. There are many densely populated areas in the world where dose rates from the natural background are 10-100-fold higher than the global average (2.4 mSv/year) with no health risks reliably proven [8]. The doses have been protracted over decades: studied MPA workers were first employed in the years 1948-1982. For example, the mean dose of gamma-radiation was 0.54 Gy in men and 0.44 Gy among women in the MPA cohort study, where the incidence of arteriosclerosis in lower limbs correlated with the radiation dose [46]. Average doses in the Techa river cohort were 34-35 mGy whereas the follow-up was since the 1950s [47], so that the dose rates were compatible with those from the natural background in some populated areas. Apparently, the Techa river cohort data do not possess sufficient statistical power to determine the dose response shape. The authors acknowledged that the risks for doses ≤0.1 Gy may be smaller than those calculated on the basis of the linear model [48]. In particular, the uncertain and biased data are unsuitable for computations of the Dose and Dose Rate Effectiveness Factor (DDREF). Earlier Russian publications stressed the higher biological efficiency of acute exposures compared to chronic and fractionated ones [29]; later on the same scientists reiterated that the International Commission on Radiological Protection (ICRP) underestimates cancer risks from chronic exposures, and recommended the use of DDREF = 1.0 [49]. This recommendation is obviously unreasonable for dose rates compatible with those from the natural radiation background. The topic of DDREF has been comprehensively discussed elsewhere [50,51].

It has been rightly noted in the recent review that “diagnosis (by a physician knowing the patient’s history) could vary with dose”; and the “interstudy variation in unmeasured confounders or effect modifiers” [44]. We have pointed out these considerations previously [2,3,39]. Mild and borderline conditions are probably more often diagnosed in people with higher doses due to averagely more thorough examinations and patients’ attention to their own health. The high frequency of cardiovascular diseases in studied populations from Russia [43] have been explained by unsubstantiated conclusions in unclear cases both post- and ante-mortem. At least in the former SU, there has been a tendency: the lower the diagnostic quality, the higher the fraction of cardiovascular diseases among all causes of death. The same is true to some extent also for lifetime diagnostics and for deceased patients not undergoing autopsy, where cardiovascular diseases are often recorded as causes of death in questionable cases [52].

Another recent study based on the MPA cohort analyzed 9469 cases of cerebrovascular diseases including 2078 strokes. The following statements seem to be 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” [53]. It can be reasonably expected that with more arterial occlusions and stenoses there would be more strokes. An apparent explanation for the discrepancy is the dose-dependent diagnostic quality and a larger screening effect in subjects with higher doses. At that, mild and borderline conditions would be recorded more frequently. On the contrary, strokes are usually diagnosed based on distinct morphological and/or clinical criteria, false-positivity being thus 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” [53]. The incidence of cerebrovascular diseases increases with age; so that the above citations are compatible with a protective effect of radiation i.e. hormesis. Radiation hormesis is mentioned neither in [53] nor in other above-cited papers. In our opinion, the authors should have discussed harmful cerebrovascular diseases (strokes) and concluded that there was no increase of strokes after the low dose low rate exposures. In fact, this is common knowledge. By including relatively harmless and less reliably diagnosed conditions, they were able to generate a sensational headline that low-dose radiation elevates the frequency of cerebrovascular diseases.

The higher risks of cerebrovascular diseases at higher doses in females than in males [53] agrees with the known tendency that women in Russia care more than men about their health and are generally given more attention by medical personnel. Hence the worldwide highest gender gaps in the life expectancy: countries of the former SU crown the list [54]. 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 [53]). Cerebrovascular diseases are more frequent in men, among others, thanks to alcohol and smoking. Some overdiagnosis of mild conditions may occur just because these conditions are expected. For example, 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 eyegrounds 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 [52]. 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 [55,56]. The excess relative risk (ERR/Gy) of cerebrovascular conditions in MPA employees was claimed to be even higher than among atomic bomb survivors in Japan [55,57], where dose-dependent selection could have taken place like in other epidemiological studies. Some data assessments of life span studies (LSS) of atomic bomb survivors are compatible with hormesis [58-61]. For cancers, a dose-response association was detected among the survivors who received doses ≤0.5 Sv but not below 0.2 Sv [61-63]. For example, the data about renal cancer in men indicated hormesis: U-shaped dose-response with negative ERR estimates at low-to-moderate doses, while those in women did not. The authors noted that these findings could have been observed by chance [59]. A preceding article by the same researchers also showed different shapes of dose response curves for males and females [64]. When studies based on the same cohort report different dose responses, reliability should be doubted. Other studies found no significant risks for kidney cancer from low doses [65-67]. Apparently, epidemiological data have too many uncertainties to reliably evaluate hormesis; large-scale animal experiments would be more informative. Unrealistic cardiovascular risks at low-dose exposures call in question cancer risks reported by the same researchers.

4. Significance and Limitations

This article is a narrative mini-review. The inter-study heterogeneity [68], a mixture of more and less reliable data assessed together is a limitation of systematic reviews and metaanalyses. The systematic approach is hardly applicable to the topic, where bias, economical and political interests are mingled. Objective evaluation by an inside observer has advantages in this regard. On the other hand, a focused review cannot encompass all relevant data, evaluating reliability and significance of different studies. More research and expert opinions are needed, in particular, self-criticism by scientists involved in biased research in accordance with directives. For an inside observer it is evident that behind numerous publications with participation of Russian authors, overestimating consequences of exposures to low dose low rate ionizing radiation (partly referenced in [69] and commented in [70]), was a directive, which has been not unusual for the Soviet science. Research themes were often assigned to researchers, while expected results were suggested in advance, which has been favored by the authoritative management style [2,6].

The significance of this paper is that it continued the discussion of motives and conflicts of interest [2]. If an ideological bias is suspected, a question cui bono (to whose benefit?) should be posed. In the former SU, among the motives to exaggerate medical consequences of the Chernobyl accident were financing, international help, publication pressure, writing of dissertations and articles for scientific careers [6]. Moreover, the Chernobyl disaster has been exploited to strangle nuclear energy [4] thus boosting fossil fuel prices. In more developed countries, antinuclear resentments have been supported by certain writers, well in agreement with the interests of fossil fuel producers. Today, there are no alternatives to nuclear energy: in the long run, non-renewable fossil fuels will become more expensive, contributing to an excessive population growth in oil-producing regions and poverty elsewhere.

5. Discussion and Conclusion

Summarizing the above and previously published arguments [1-3], the harm caused by anthropogenic radiation would probably tend to zero with a dose rate decreasing down to a wide range level of natural background. The dose-effect relationship may become inverse in a certain range according to the concept of hormesis. Obviously, hormesis cannot be used in radiation safety regulations without consistent experimental evidence obtained in large-scale animal experiments using different species. Even thereafter, precautions would be necessary as hormetic stimuli may act without threshold on pre-damaged or atrophic tissues, or synergistically with known or unknown noxious agents. The DNA damage and repair are normally in a dynamic equilibrium. Accordingly, there must be an optimal exposure level, as it is for many other environmental agents: visible and ultraviolet light, various chemical elements and compounds, as well as products of water radiolysis [71]. Moreover, evolutionary adaptation to a changing environmental factor would lag behind its current value and correspond to some average from the past. Apparently, natural background radiation has been decreasing during the time of life existence on the Earth [72].

In conclusion, studies of human populations exposed to low-dose low-rate ionizing radiation, though important, will hardly add much reliable information on dose-effect relationships, hormesis and DDREF. Screening effect, selection, self-selection and ideological biases will contribute to appearance of new reports on enhanced risks, which would not prove causality. Reliable results can be obtained in lifelong animal experiments [73]. Exaggeration of effects of low dose low rate radiation facilitates the strangulation of atomic energy in accordance with the interests of fossil fuel vendors.

6. Conflicts of Interest

The author declares that he has no conflicts of interest.

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