Epidemiological Research with Special Reference to Nuclear Worker Studies: Commentary

Keywords: Cancer risk; Low-level radiation exposure; Nuclear workers; Hormesis

Abstract

Limitations of some epidemiological studies on low-dose low-rate exposures to ionizing radiation include dose comparisons disregarding natural radiation background, unfounded classification of sporadic diseases as radiogenic and conclusions about causality of dose-effect relationships. Other bias, confounders and inter-study heterogeneity have been pointed out. Some dose-effect correlations can be explained by a dose-dependent selection, self-selection and recall bias. It can be reasonably assumed that individuals knowing their higher doses would be more motivated to undergo medical examinations being at the same time given more attention. Reported dose-effect relationships between low-dose low-rate exposures and non-neoplastic diseases call in question the causality of such relationships for cancer detected by the same researchers. Reliable evidence in regard to biological effects of low radiation doses can be obtained in large-scale animal experiments with registration of life duration. The monitoring of human populations exposed to low-dose radiation is important but conclusions should be made with caution considering potential bias and economical motives to stratangulate nuclear energy production in accordance with the interests of fossil fuel producers. Of note, health burdens are the greatest for power stations based on coal and oil; the burdens are smaller for natural gas and still lower for the nuclear power. The same ranking applies for the greenhouse gas emissions.

Introduction

According to the linear no-threshold hypothesis (LNT), the risk of cancer is proportional to the radiation dose; a dose-response correlation can be extrapolated down to low doses, where the relationship is unproven and can become inverse in accordance with hormesis. Among hormetric agents are numerous physical and chemical factors, light, ultraviolet as well as products of water radiolysis [1-3]. By analogy with other environmental factors, an evolutionary adaptation to the natural radiation background (NRB) can be reasonably assumed. Cells may have retained some capability to repair damage from higher radiation levels than today’s NRB [4]. The experimental evidence in favor of hormesis and adaptive responses to ionizing radiation is considerable [5-9] i.e. experimental data are partly at variance with the epidemiological research. The evidence supporting radiation hormesis has been obtained also in human studies [10-12]. In animal experiments, doses associated with carcinogenicity have been generally higher than averages in the Chernobyl, East Urals Radioactive Trace cohorts and contemporary professional settings [13-18].

Some assessments of the data about survivors of atomic explosions in Hiroshima and Nagasaki (A-bomb survivors) do not support the LNT and are consistent with hormesis [19]. For solid cancers and leukemia, significant dose-response relationships were found among A-bomb survivors exposed to ≤500 mSv but not ≤ 200 mSv [20-22]. Artificial neural networks applied to the data on A-bomb survivors indicated a presence of thresholds ~200 mSv varying with organs [23,24]. The value 200 mSv has been referred to in reviews as a level, below which the cancer risk elevation is unproven [22,25]. According to the UNSCEAR, a significant risk increase was observed at doses ≥100-200 mGy [26]. This value may have been underestimated as a result of biased epidemiological research. Among limitations of some epidemiological studies on low-dose low-rate exposures have been unfounded classification of sporadic diseases as radiogenic, dose comparisons disregarding NRB, conclusions about incidence increase without valid comparison with control [27,28], inexact citation [29]. Other bias, confounders and inter-study heterogeneity have been pointed out [11,23,30-32]. Some dose-effect correlations may be explained by a dose-dependent selection, self-selection and recall bias noticed in different exposed cohorts [33-35]. It can be reasonably assumed that individuals knowing their higher doses would be more motivated to undergo medical examinations at the same time given more attention. Therefore, diagnostics would be a priori more efficient in people with higher doses. For example, the dose-dependent incidence increase of cardio- and cerebro-vascular diseases among Mayak Production Association (MPA) workers was not accompanied by an increase in mortality [36-39], which can be explained by recording of mild cases in people with higher doses. Moreover, the excess relative risk per unit dose (ERR/Gy) for leukemia (excluding chronic lymphatic leukemia) among MPA workers using incidence data has been considerably higher than that using mortality data [40]. A more efficient detection of latent leukemia with occasional registration of unverified cases can provide an explanation. The author agrees with Dr. Little [41] that the research of questionable reliability “should therefore probably not be used for epidemiologic analysis, in particular for the Russian worker studies considered here [42-45]” and some others. The inter-study heterogeneity [32], mixture of more and less reliable data assessed together remains a problem of some systematic reviews and meta-analyses. As discussed previously [9,46], reported dose-effect relationships between low-dose low-rate exposures and non-neoplastic diseases call in question the causality of such relationships for cancer revealed by the same and other scientists. Certain data on enhanced cancer risk after low-rate exposures appear doubtful. For example, a significantly increased
risk of non-melanoma skin cancer was reported by Azizova and co-workers among MPA workers [47]. An observation bias was not excluded. The workers and probably some medics knew individual work histories, wherefrom accumulated doses could be inferred, potentially influencing the diagnostic thoroughness. Skin doses were unknown [47]. Among A-bomb survivors, non-melanoma skin cancer incidence dataset was consistent with a threshold at ~1 Sv [48]. The MPA workers were exposed mainly to γ-rays that have a relatively long penetration distance in tissues, so that the absorbed doses in the skin must have been correspondingly low. Not surprisingly, premalignant skin lesions and/or actinic keratoses were “very rare” [47]. Considering the above, a cause-effect relationship between radiation and skin tumors in the study [47] appears improbable. Risk estimates by Azizova et al. [49] were found to be significantly higher than those by other experts [50]. Reliability of some other studies has been questioned previously [29,51,52].

Concluding his recent review, Dr. Wakeford writes: “Ultimately, it will be powerful epidemiological studies examining exposure conditions of direct relevance to radiological protection against low-level radiation exposure that will provide the most reliable evidence” [40]. Neither eXperimental studies nor the NRB are mentioned in this review. As discussed below, reliable data on the biological effects of low radiation doses can be obtained in extensive animal experiments rather than in epidemiological studies. Annual average doses from NRB should be indicated if cohorts from different regions are compared; otherwise exposures in a control group may turn out to be not significantly different from those in “exposed” cohorts e.g. from Colombia and Spain vs. Ukraine [53,54], discussed in [52]. In the International Nuclear Workers Study (INWORKS), many workers received 2-4 mSv/year [40]. Annual doses from the NRB are generally expected to be in the range of 1-10 mSv, 2.4 mSv being the estimated global average. The mean cumulative doses in the INWORKS (red bone marrow - 17.6 mGy, colon - 19.2 mGy) protracted over years (follow-up 1950-2005) [55] are comparable with the NRB. These and other considerations about INWORKS have been expressed previously: “Failure to account for natural background radiation exposure, the differences in which potentially dwarf the occupational exposures of the study cohort” [1].

Another example is a study of Bushehr nuclear plant workers in Iran [56]. The average individual total dose received by workers who developed cancer was 45.1 mSv; the median duration of follow-up was 34.8 months. No doses from NRB are given. The data on the NRB are of particular importance for Iran, where in some areas the natural radiation background is relatively high. The mean individual annual dose to the residents of high background radiation areas at Ramsar (Mazandaran Province) is ~10 times higher than the public dose limit recommended by the International Commission on Radiological Protection (1 mSv/year); a part of the residents receive annual doses ~260 mSv [57] i.e. much higher than nuclear workers at Bushehr. There have been no consistent reports on any detrimental health effects in the residents of the Ramsar area [57]. It can be reasonably assumed that the screening effect and increased attention of exposed people to their own health would result one day in an increase of the registered cancer incidence in areas with enhanced natural or anthropogenic radiation background, which would prove no causal relationship. Another comparison: around 13,000 German uranium miners with archived occupational data, who worked during 1946-1990 for the Soviet nuclear industry, underwent average individual exposures of 725 WLM (3.7 Sv), including about 800 workers with levels >1800 WLM (>9.2 Sv). Annual exposures of some miners were >200 WLM (>1 Sv) combined with silica dust that may act synergistically [58]. The working-level month is a dose unit used for cumulative exposures from radon and its progeny; 1 WLM is equivalent to ~5.1 mSv [59].

The following citations should be commented: the “puzzling finding from INWORKS is that the primary ER/R Gy estimate for photon doses and all cancers except leukemia, which was adjusted for neutron monitoring status, 0.48 (95% CI: 0.15, 0.85), reduced by ~60% to 0.20 (95% CI: 0.07, 0.51) when no such adjustment was made… A further perplexing result from INWORKS is that when the analysis was confined to the 83% of workers who were not monitored for intakes of radionuclides, the ER/R Gy for all cancers except leukemia increased by 50% to 0.72 (95% CI: 0.21, 1.28); similar increases in external exposure risk estimates for workers not monitored for potential exposure to internal emitters when compared with those for workers who were monitored for internal exposures has been noted in other studies” [40]. The answer to the “puzzle” seems to be as follows. The workers monitored for intakes of radionuclides and those under the “neutron monitoring” probably received averagely more attention from medics and were better supervised. Consequently, there must have been fewer undiagnosed diseases among them. As a result, the mechanism of dose-dependent diagnostic/observation quality would be less efficient as fewer neglected cases are left to be preferentially found in persons with higher doses. Of note, 6% of workers with doses >100 mGy, received predominantly at an early date (years 1960-1979), were influential in a downwards [emphasis added] leverage of the dose-response. In the range of low doses, ER/R Gy for cancer in the INWORKS was even higher than in the Life Span Study (LSS) of A-bomb survivors [40,55]. The LSS data originated from earlier times. Apparently, the non-radiation-related dose-dependent mechanisms were less efficient in the remote past, when diagnostic possibilities were limited. It can be speculated that modern methods, diversification, more differences between the superior and inferior diagnostic quality at a later time provided more opportunities for the dose-dependent selection and self-selection. Fitted (under a simple linear excess relative rate model) excess deaths from solid cancer were higher in the INWORKS than in the LSS among individuals with average colon doses in the range 1-78.3 mGy, while in those with mean doses ≥143.1 mGy the aforesaid index was higher in the LSS [55]. This indicates that some cancers were radiogenic in the LSS but not in the INWORKS as the doses ~100 mGy have never been satisfactorily proven to be carcinogenic. Logically, the dose-response relationship must be stronger at >200 mGy than at <200 mGy. In the INWORKS, the tendency was vice versa [55]. By analogy, in the epidemiologic study [35] a curve of the linear-exponential dose-response model, providing an improved fit to the data, is most steep at low doses, becomes more gently sloping with increasing doses and nearly horizontal at the level of 5-7 Gy. Similar proportions were reported also earlier, but the leveling of the dose-response curve occurred at >10 Gy [60]. The decrease in the risk increment per dose unit at higher doses was explained by the cell killing [61,62], which seems to be the only thinkable radiation-related mechanism. However, no leveling of thyroid cancer risk was noticed at doses...
≥10 Gy [63]. In children after radiotherapy, exposures to 60 Gy were associated with a high risk of thyroid cancer [64]. In a series of studies in rats, the carcinogenic effect of 11 Gy from acute x-ray exposure was comparable to that of 1.1 MBq of iodine-131, which would produce a thyroid dose of ~100 Gy, when a significant cell killing effect might be expected [65]. The cell killing concept is obviously inapplicable to low doses, when tissues remain morphologically intact. Apparently, both the dose-effect relationships at low doses and their reduction at higher doses in [35,55] were caused by non-radiation factors.

The monitoring of populations exposed to low-dose radiation is important but conclusions should be made with caution considering known and unknown bias. For example, “the very high rates of circulatory disease” [66] in some nuclear worker cohorts from the former Soviet Union are probably caused by habitual overdiagnosis of cardiovascular diseases in unclear cases, which is a known confounder [67]. Reliable evidence in regard to biological effects of low radiation doses can be obtained in extensive animal experiments rather than in epidemiological studies. It is unnecessary to examine each mouse or rat; it would suffice to maintain large groups of animals to record the average life duration. Such experiments would objectively characterize the net harm or potential benefit (as per hormesis model) at various doses and dose rates [1,13,68]. Among other things, the Dose and Dose Rate Effectiveness Factor (DDREF) can be evaluated in such experiments. The argumentation about DDREF based on the epidemiological research [40] is questionable because radiogenic nature of discussed conditions is unproven. Certain models suggested that protracted exposures are between 2.0 and infinitely times safer than acute ones [69]. The latter would correspond to a threshold or hormesis concept. DDREF assessments should be based primarily on direct comparisons of acute and protracted exposures [69]. Further research in this direction would better quantify the radiosensitivity of different animal species enabling more precise extrapolations to humans [70].

Conclusion

Evidently, some epidemiological research has been influenced by economical motives to boost gas and oil prices [46,71]. The Chernobyl accident has been exploited to stranglepile “the cleanest, safest and practically inexhaustible” nuclear energy [31]. Hidden conflicts of interest, ideological bias and research quality should be taken into account deciding about inclusion of studies into systematic reviews and metaanalysis. Not constricted e.g. [72, 73] (commented [28,71]) (commented [28,71]) but obvious Chernobyl consequences are coming - the increasing prices for gas and oil [28,46]. Probably not all writers exaggerating consequences of mild elevations of the radiation background and/or of low-dose exposures do realize that they serve the interests of fossil fuel producers. Some of them have good intentions; others may have conflicts of interest, serve certain governments or companies [46]. Of note, health burdens are the greatest for power stations based on lignite, coal and oil. The health burdens are smaller for natural gas and still lower for the nuclear power. This ranking also applies for the greenhouse gas emissions [74]. 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. The worldwide use of nuclear energy must be managed by a powerful international executive based in most developed parts of the world.

References

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