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Health Impacts of Low-Dose Ionizing Radiation: Current Scientific Debates and Regulatory Issues

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Abstract

Health impacts of low-dose ionizing radiation are significant in important fields such as X-ray imaging, radiation therapy, nuclear power, and others. However, all existing and potential applications are currently challenged by public concerns and regulatory restrictions. We aimed to assess the validity of the linear no-threshold (LNT) model of radiation damage, which is the basis of current regulation, and to assess the justification for this regulation. We have conducted an extensive search in PubMed. Special attention has been given to papers cited in comprehensive reviews of the United States (2006) and French (2005) Academies of Sciences and in the United Nations Scientific Committee on Atomic Radiation 2016 report. Epidemiological data provide essentially no evidence for detrimental health effects below 100 mSv, and several studies suggest beneficial (hormetic) effects. Equally significant, many studies with in vitro and in animal models demonstrate that several mechanisms initiated by low-dose radiation have beneficial effects. Overall, although probably not yet proven to be untrue, LNT has certainly not been proven to be true. At this point, taking into account the high price tag (in both economic and human terms) borne by the LNT-inspired regulation, there is little doubt that the present regulatory burden should be reduced.

Keywords

disease risk, hormesis, linear no-threshold model, low-dose radiation, longevity, mortality

Background

Ionizing radiation plays an important role in the modern world. The use of X-rays brought about a revolution in diagnostics. It is difficult to imagine modern medical care without X-ray imaging, including computed tomography (CT) scans, and nuclear medicine. Every medium-sized hospital in the developed countries has a radiation therapy unit that provides remedies to many patients with cancer. Over 10% of the world's electricity is provided by nuclear power plants. On the other hand, high dose of ionizing radiation can kill human and any other living organism. In addition, it is certainly carcinogenic for those who survive the acute radiation syndrome (ARS).[1] Therefore, ionizing radiation (as any other potentially dangerous agent) should be used with due caution. The principal question is, What are (are there?) the detrimental health effects of low-dose radiation exposure, such as those used in medical diagnostics or experienced by radiation workers and the general public? Usually, radiation with cumulative dose up to 100 mSv is referred to as low-dose radiation, though sometimes relevant doses are higher.

Acute adverse effects of high-dose ionizing radiation were discovered back in the 19th century. However, it was only after World War I that medical practitioners—people most exposed to ionizing radiation at that time—began to regularly monitor and limit their exposures. For example, the British X-ray and Radium Protection Committee was formed in 1921. In 1924, 0.2 R/d was proposed as the permissible dose rate for radiation workers.[2] The above rate of 0.2 R/d (corresponding to at least 500 mSv/y), then considered to be a *tolerance level* (ie, causing no harm at all), was derived by dividing the commonly accepted erythema dose of 600 R (not by chance, such dose

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is lethal in a case of acute whole-body irradiation) by 30 days and by then further dividing by a safety factor of 100. The International X-ray and Radium Protection Committee (presently—International Commission on Radiological Protection [ICRP]) accepted this dose rate as a universal recommendation in 1931. As described in the section "Occupational Exposure," there is no solid evidence that such exposure for practitioners (0.2 R/d) caused harm of any type. The current exposure limits are much lower. For example, ICRP sets the occupational exposure limit at 20 mSv/y (25 times lower than the ICRP-1931 limit) and the limit for the general public at 1 mSv/y (500 times lower).

High-dose radiation carcinogenesis is currently considered to be a generally accepted long-term radiation health effect. Radiation carcinogenicity, however, is *weak* (although most of the general public imagines otherwise) in the sense that excess cancer risk is *low* for the highest survivable doses. To illustrate this claim, we mention that the amount of *excess* solid cancer deaths among the Japanese atomic bombing survivors was probably about 900 during the period 1950 to 2009. In comparison, more than 20 000 survivors died of cancer due to causes unrelated to the irradiation by atomic bombs.[1] Actually, the fact that radiation carcinogenicity is *weak* caused the decades-long ambiguity regarding the low-dose radiation effects.

The linear no-threshold (LNT) model of radiation-induced cancers evolved in the end of the 1950s[3]; it substituted the *tolerance dose* concept that governed the radiation protection policies for nearly 4 decades (since about 1920). According to the LNT, every fraction of ionizing radiation, no matter how small, constitutes increased cancer risk (linear with the dose). This model is the basis for current radiation regulation. Since the end of the 1950s, LNT has been assumed to be a *null hypothesis*, a presumption considered true until proven false. However, since radiation carcinogenicity is *weak*, neither large-scale nuclear accidents[4] nor even the atomic bombings of Japan[5] provide statistically significant epidemiological evidence in support of LNT.

The atomic bombings of Japan require special attention here since the survivors of those attacks are probably the largest and most intensely studied radiation-exposed cohort to date. Indeed, most of the present population-based estimates of cancer risks following radiation exposure are based primarily on the data from the Life-Span Study (LSS) of this cohort.[6] However, even this cohort of about 100 000 survivors is not big enough to provide statistically significant results for low-dose irradiation. This result of a Monte Carlo simulation[5] is confirmed by the latest LSS assessment of solid cancer incidence in the survivors[1]: The best estimate of dose threshold for radiation carcinogenesis in males (ie, half of the statistical sample) is as high as 0.75 Gy, but this value is *not* statistically significantly different from 0. The dose of 0.75 Gy is far from being low: It is just below the onset of ARS at about 1 Gy.[7] If this high value is not different from 0 within statistical uncertainties, one surely cannot claim that LSS results confirm LNT, though they (as well as many other epidemiological studies) do not prove the falsity of LNT. However, "not proven false" is far from being "proven true." So while LNT has been accepted and put as a basis of radiation regulation all over the world, the ambiguity regarding its accuracy has always been acknowledged. For example, the US National Council on Radiation Protection and Measurements formulated in 1995[8]: "... essentially no human data can be said to prove or even to provide direct support for the [LNT] concept with its implicit uncertainties of nonthreshold, linearity and dose rate independence with respect to risk. The best that can be said is that most studies do not provide quantitative data that, with statistical significance, contradict [LNT]" (p. 61).

It is quite common that while a high dose/amount/rate of some medication or procedure is detrimental, a low dose is beneficial. Classical widely known examples include physical exercise (as opposed to forced labor), immunization (as opposed to virulent infection), and—directly related to biologically active radiation—controlled sun tanning (as opposed to sunburns and skin cancer caused by overexposure). Therefore, low-dose radiation effects may well be different from the effects of high doses. Actually, people have been using ionizing radiation for centuries: Already Herodotus and Hippocrates described healing properties of what we know now as radon springs. Radon treatment is considered to be a legitimate tool by mainstream medicine in Europe, especially for treating arthritis and other inflammatory diseases.[9] During the past few decades, there has been a growing body of biological evidence regarding low-dose radiation effects. This evidence is concurrent with the shift in radiobiology from a DNA-centric view on radiation damage to a more systemic view that incorporates multilevel protection and nonlinear systems.[10] Many studies demonstrated that radiation effects are far from linear.[11] Moreover, experimental, epidemiological, and ecological studies have shown that low doses of ionizing radiation can be beneficial to health.[12,13] Beneficial low-dose effects of an agent that is harmful in high doses are called *hormesis*. There is an increasing interest in the question of radiation hormesis. In 2005, the French Academies of Science and Medicine prepared probably the most comprehensive up-to-date report disputing the LNT hypothesis and summarizing scientific evidence for the existence of radiation hormesis.[14] However, nearly simultaneously, the US National Academies of Sciences published the Biological Effects of Ionizing Radiation (BEIR) VII report,[6] which concluded that the existing scientific evidence is consistent with LNT. Since then, no summary report on LNT of similar extent has been published. In the recent 512-page United Nations Scientific Committee on the Effects of Atomic Radiation (2016) report,[15] the term "LNT" is not mentioned at all.

The rest of this article is organized as follows: First, we review the available evidence for different mechanisms by which ionizing radiation might have an impact. Then, we review the epidemiological evidence of 3 cohorts: (1) occupationally exposed radiation workers, (2) patients irradiated for diagnostic or therapeutic purposes, and (3) populations residing in areas with above-average levels of natural background radiation. Lastly, we discuss regulatory issues taking into account ethical and economic aspects and make conclusions.

Search Strategy

In this review, we searched the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) to find all published epidemiological studies estimating long-term health impacts of low-dose ionizing radiation. The main topics reviewed were health outcomes of medical occupational exposures and radiation-based medical procedures such as diagnostic irradiation and low-dose radiotherapy and data from nuclear worker cohorts and nuclear test participants such as findings from environmental radiation studies, in particular, health effects related to residential radon exposures, as well as long-term health consequences of accidents in nuclear power plants. In addition, we reviewed ethical, economic, and regulatory considerations related to health effects of low-dose ionizing radiation in human populations. Only studies describing effects of low-to-moderate doses (cumulative mean <500 mSv) were included in this literature search. The outcomes involved in our analysis included both incidence and mortality data. We used various combinations of search terms such as "low-dose," "low dose rate," ionizing radiation," "occupational radiation exposure," "environmental radiation exposure," "medical radiation exposure," "linear no-threshold model," "hormesis model," "health outcome," "disease risk," "incidence," "mortality," "cancer incidence," "cancer mortality," and "longevity." The time period of the searched articles ranged from January 1976 to October 2017 with no language restrictions. There was no restriction on the type of study design; therefore, all ecological, cohort, and case–control studies satisfying search criteria were included. In parallel, we examined selected papers cited in the 2 most comprehensive up-to-date reports: the joint report of the French Academy of Sciences and of the French Academy of Medicine published in 2005 and the BEIR VII—Phase 2 Report of the American National Academy of Sciences published (final version) in 2006, as well as all recent papers citing any of the 2 above articles. The 2 authors of the present article (A.V. and Y.S.) reviewed each paper and independently decided whether potentially eligible papers met inclusion criteria, assessed them for methodological quality, and extracted data. For the few studies that were not written in English, if the information in the abstract was insufficient to include/exclude the article, the full text of the article was translated by the current authors (AV: Russian; YS: Hebrew). Experimental studies were also analyzed to determine whether they were informative regarding health effects associated with low-dose ionizing radiation exposure and to what extent. We used these papers to determine whether there is a coherence of effects across human and nonhuman species and to examine the biological plausibility of low-dose and low dose rate irradiation as a risk factor for health and longevity.

Differences in Biological Effects of Low- and High-Dose Radiation

The abovementioned LNT model assumes de facto that an organism's ability to repair damage caused by ionizing irradiation (including genome integrity and cellular viability) is affected only slightly by radiation dose and dose rate and that complete repair is impossible. As already mentioned, the LNT concept is the subject of active debate (see, eg, recent discussion by Beyea[16] and Calabrese[17] in the *Environmental Research Journal*). This debate was triggered during the past decades following the accumulation of biological findings that contradict the aforementioned hypothesis, showing that damage repair ability actually does depend on the irradiation dose and dose rate. For example, immune responses have been repeatedly demonstrated to be stimulated by low-dose exposures,[18] though definitely suppressed by high-dose exposures. DNA repair has also been found to be stimulated by low-dose exposures[19] and inhibited by high-dose exposures. Biological responses to low-dose irradiations largely depend on various physical factors. The first and foremost factor is, clearly, total absorbed dose and dose rate (and in general, temporal patterns of radiation exposure). Other factors include distribution of the radiation sources and structure and dimensions of the biological targets.[20] Generally, the low-dose radiation-induced DNA damage has been shown to be much less than the damage caused by the oxidative processes of normal metabolism.[21-23]

Furthermore, it has been demonstrated that low-dose radiation induces hormetic responses that can compensate, or even overcompensate, for genotoxic effects of reactive oxygen species, which are by-products of normal metabolism.[24] Such responses might likely help prevent various environmentally induced detrimental health effects. In particular, with regard to the process of DNA repair, the resulting effect of low-dose irradiation can be determined by the balance between the rate of DNA damage (increasing linearly with the dose) and the rate of DNA repair. The DNA repair mechanisms are effective at low-dose irradiations and, as expected, become less efficient with increasing dose.[25] At single doses below 100 mGy, the beneficial effects tend to outweigh the detrimental effects.[26] Irradiations at this dose range can stimulate protection mechanisms that not only compensate for the initial DNA damage but also mitigate the effects of subsequent high-dose radiation, as well as of other potentially damaging exposures that might otherwise lead to progression of cancer.[27]

All these processes are interrelated and accompanied by a highly coordinated adaptive modulation of epigenetic regulators.[28-31] Coordinated epigenetic reprogramming in large numbers of cells has been hypothesized to be a crucial component of the adaptive response induced by irradiation.[32] It is supposed that such epigenetic reprogramming may provide protection of the cells against further radiation exposures. Epigenetic effectors may also play an important role in *nontargeted (bystander)* effects of ionizing radiation occurring in the cells that were not directly hit by radiation but received signals from the hit cells.[33,34] These bystander effects can be detrimental (chromosomal aberrations, point mutations, genome instability, and neoplastic transformation) or beneficial (radioadaptive response, apoptosis, and induction of terminal differentiation)

depending on the dose, dose rate, and other conditions during and after the irradiation.[35]

Since radiation-induced protective pathways are more efficient in the low-dose range, it is really not surprising that most dose–effect relationships are not linear but rather either have a finite threshold (tolerance dose) or may even be hormetic, that is, biphasic with beneficial effects at low doses and detrimental at high doses.[36-38] These dose–response relationships can be apparently affected by various integrative end points such as tissue repair, compensatory cell proliferation,[21,26,39,40] growth patterns, adaptive and preconditioning responses, aging processes, and also by different complex behaviors that can be induced or modulated by radiation among other environmental stimuli.[41] Additional important pathways potentially involved in hormetic responses include synthesis of heat shock proteins, free radical scavenging, activation of cell membrane receptors, and secretion of various growth factors and cytokines. In addition, many senescent or damaged cells (eg, preneoplastic cells) can be eliminated by apoptosis, cellular competition, and immunological surveillance.[42] Furthermore, these relationships are likely to become complicated by several phenomena: radioadaptive responses where preexposure to small doses of ionizing radiation reduces detrimental effects of subsequent high-dose exposures,[43] by bystander effects,[44] and also by abscopal effects—sporadic events of tumor regression in nonirradiated fields occasionally observed in radiotherapy.[45] All the above effects can be beneficial or detrimental depending on the dose and dose rate,[46] the type of radiation exposure (ie, acute, chronic, or fractionated), genetic background, age, sex, and any combination of radiation with other toxic factors such as pesticides or other chemical contaminates.[47] Schematic representation of molecular and cellular mechanisms operating at low- and high-dose radiation exposures and also time schedule of pathways involved in radiation-induced hormetic response is provided in Figure 1.

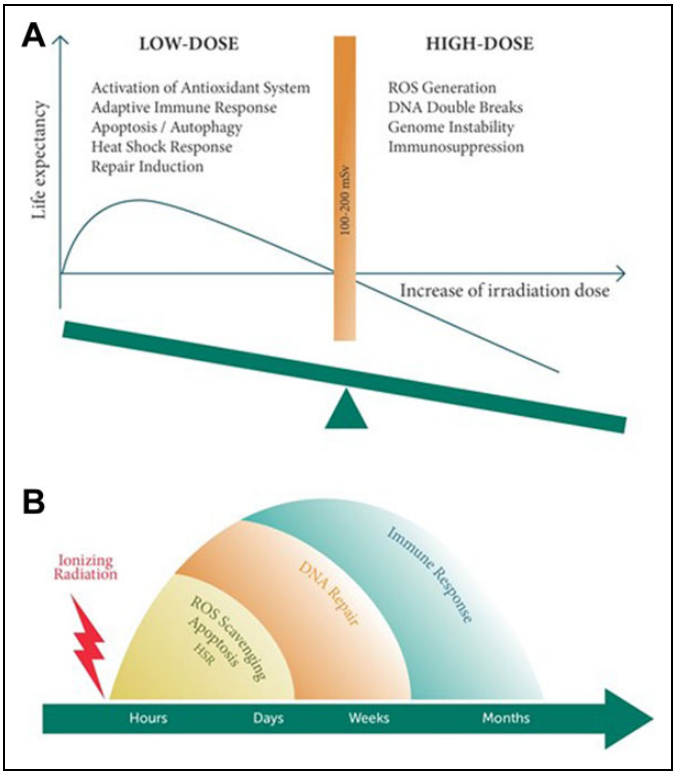

Figure 1. A, Schematic representation of molecular and cellular mechanisms operating at low- and high-dose radiation exposures. B, Time schedule of pathways involved in radiation-induced adaptive response. HSR indicates heat shock response.

Evaluation of Low-Dose Radiation Effects: Methodological Issues

Effects of radiation exposure have been repeatedly identified in various experimental models as well as in epidemiological studies. However, while dose-dependent adverse effects have been easily monitored in the high-dose region, the evaluation of effects from low-dose exposures has presented a considerable investigative challenge so far. Most of the epidemiological studies in which external radiation dose estimates were available had insufficient statistical power, involved many confounding factors, and used inadequate methodological approaches.[48,49] One faulty approach was discarding particular ranges of radiation doses, when such discarding led to pro-LNT conclusions, including the entire data might have provide evidence for threshold dose. Another kind of problematic approach was including low-dose individuals in the nonirradiated group; this approach could potentially mask hormetic (adaptive) responses. Moreover, many researches in this field have been devoted to investigating populations exposed to relatively high doses of radiation for a relatively short time period. This tendency is significant since the effects of radiation exposure are well known to be proportionately greater at high doses and high dose rates. However, the effects of low doses and low dose rates are generally more commonly a characteristic of environmental and occupational exposure.[50] Since biological mechanisms operating in the moderate- to high-dose range are likely to differ from those operating at low-dose exposures, it seems appropriate to consider the high-dose, moderate-dose, and low-dose (and low dose rate) investigations separately.[51] In addition, an important methodological issue in epidemiological studies is the use of the so-called "geographical" or "ecological" methodology. This methodology is based on the comparison of health indices averaged over areas with similar social, economic, and environmental conditions, but with differing levels of ionizing radiation exposure or radioactive contamination. This approach may obviously lead to biased conclusions through "ecological fallacy" that occur when data averaged for a group are used to make conclusions about an individual.[52] The meta-analyses of various pathologies from exposure to low-dose ionizing radiation and estimates of potential mortality risks in exposed populations are commonly limited by heterogeneity between studies. There is high probability that uncontrolled confounding factors in several populations

and occupational groups by particular lifestyle factors and higher dose groups (>500 mSv) drive the revealed trends.[51,53]

Finally, the most important methodological issue in occupational studies is the healthy worker effect (HWE). The HWE should be considered when a general population is selected as a reference to a population dealing with ionizing radiation in a workplace.[54] For example, employed people are generally healthier than the general population. Indeed, while the general population consists of either healthy individuals or unhealthy individuals, those persons from the general population who are not healthy are less likely to be employed. As a result, comparisons of mortality rates between employed groups and general populations can be biased. Although HWE is an important factor, it has led to the discarding of any potential hormetic observations. One common method to take HWE into account correctly is to compare professional subgroups that differ in occupational radiation exposure. For example, if more exposed workers are compared with those with low or no exposure, HWE should be equal for both. More particular methodological limitations in the evaluation of health outcomes of exposure to low-dose radiation in human populations are given in the subsequent sections of this review.

Most well-designed and methodologically rigorous studies of the health effects of ionizing radiation have used the following cohorts: occupationally exposed radiation workers, patients irradiated for diagnostic or therapeutic purposes, and populations residing in areas with above-average levels of natural background radiation.[55] An overview of these studies is provided in the subsequent sections. Since the readers may not be familiar with radiobiological terminology used in these sections, the main radiobiology terms and units are presented in Box 1. Basic epidemiological indicators used in radiation epidemiology are given in Box 2.

Box 1. Basic Terms and Units in Radiobiology.

Becquerel (Bq): a unit of radioactivity or the strength of radioactive source; 1 Bq = 1 event of radiation emission per second.

Gray (Gy): a measure of the absorbed dose, that is, energy deposited per unit mass. 1 Gy = 1000 mGy.

Absorbed dose: an amount of radiation absorbed by an organ or a tissue.

Cumulative dose: a total dose resulting from repeated or continuous exposures to ionizing radiation.

Sievert (Sv): an equivalent or effective dose (for X-ray or γ rays, 1 Sv is equivalent to 1 Gy). Sievert, effective dose and equivalent dose are used in the framework of linear no-threshold (LNT) model to estimate carcinogenic effect.

Effective dose: a dose parameter used to normalize partial-body radiation exposures, that is, a dose to the whole body that carries the same risk as a higher dose to only a part of the body.

Equivalent dose: a measure of the biological effect of radiation depending on the type of radiation, absorbed dose, and body organs or tissues exposed.

Box 2. Basic Epidemiological Indicators in Radiation Epidemiology.

Relative risk (RR): in cohort-based studies, a ratio of disease incidence between exposed and nonexposed cohorts.

Standardized mortality ratio (SMR): the same as RR but the "risk" is not disease but death.

Hazard ratio (HR): the ratio of hazard of occurrence of an event at a particular point in time in the 2 groups under comparison.

Excess relative risk (ERR): ERR = RR − 1.

Odds ratio (OR): an analog of RR in case–control studies.

Occupational Radiation Exposure

Evaluation of health outcomes associated with exposure to ionizing radiation in different occupational groups has become a subject of extensive study since the second half of the 20th century. The main research activities have been focused on cancer incidence and mortality among those persons who are professionally exposed to ionizing radiation in their workplaces, such as radiologists, radiotherapists, nuclear industry workers, and military personnel participating in nuclear weapons testing. These studies are of particular relevance to radiation protection since most individuals from these professional groups are typically exposed to protracted low-dose and low dose rate radiation exposure, that is, a type of exposure that is especially important in the context of public radiation protection. This point was particularly emphasized in the BEIR[6] report by the US National Research Council where it was noted that these occupational groups are well suited for direct evaluation of health effects of low-dose and low dose rate ionizing radiation because "a large numbers of workers have been employed in this industry since its beginning in the early to mid-1940s (more than 1 million workers worldwide); these populations are relatively stable, and by law, individual real-time monitoring of potentially exposed personnel has been carried out in most countries with the use of personal dosimeters (at least for external higher-energy exposures) and the measurements have been kept."

The research of health outcomes of occupational exposures to ionizing radiation, however, faces many obstacles with respect to proper assessment of dose–response relationships in the low-dose region. In order to provide sufficient statistical power to detect detrimental low-dose health effects typically encountered in occupational settings, large numbers of exposed persons and long-term follow-ups (which take into consideration very long latency periods) are required. The statistical power of most follow-ups conducted in occupational cohorts is, unfortunately, insufficient for a reliable assessment of these associations.[6] Moreover, problems with the choice of suitable comparison groups is additional limitation of many such studies. An ambitious epidemiologic study of 1 million US radiation workers has been proposed in 2009 by collaboration led by John Boice.[56] Although the pilot study was reported to be

successful by 2015, no publications appeared since then. The official web site of the project (http://www.OneMillionWorkerStudy.org/) was last modified in 2013 (as accessed July 30, 2018).

The subsections highlight key research areas in which most reliable and robust data were obtained on the effects of low-level radiation exposure in occupational exposure groups.

Medical Occupational Exposure

Currently, most accurate and thorough studies giving information on the health effects of low-dose radiation exposure are conducted in cohorts of physicians and technical personnel occupationally exposed to radiation. Cause-specific and age-specific mortality rates were determined among radiologists and radiologic technologists in a series of studies to evaluate the effects of long-term radiation exposure. Several serious health problems such as increased risk of skin cancer and leukemia along with enhanced cancer and all-cause mortality rates have been reported in radiologic technologists and radiologists in the first half of the past century.[57] For example, increased mortality rates due to leukemia were demonstrated in 8 historical cohorts of over 270 000 radiologists and radiologic technologists employed before 1950, when the levels of radiation exposure in these professional groups were high (eg, 30 000 mSv/y in 1902).[58] However, after the first radiation protection recommendations were implemented in early 1920s (dose limit of 0.2 R/d, equivalent to at least 500 mSv/y), excess mortality disappeared.[58,59] The pattern of cancer mortality has changed significantly for those radiologists who started to work after 1940.[60] While among the early entrants the mortality rates were higher in young radiologists than those of other specialists, among the later entrants, young radiologists exhibited lower mortality rates. However, as the later entrant radiologists grew older, their mortality rates exceeded those of other specialists. Using their analyzed data, Matanoski et al[60] suggested that low-level radiation exposure might produce protective effects among radiologists. In the Berrington et al's[61] study, all-cause mortality in British radiologists, who were first registered in a radiological society in 1920 or later, was significantly lower than that of the general population (standardized mortality ratio [SMR] = 0.72; for more details, see also Table 1). In this cohort, the number of cancer deaths was similar to that of all the medical practitioners combined (SMR = 1.04). Mortality rates in British radiologists who were registered after 1954 were significantly lower relative to those in other medical professional groups; this was true for both cancer mortality and all death causes combined. On the basis of these findings, Cameron[62] concluded that "British radiology data show that moderate doses of radiation are beneficial rather than a risk to health."

The findings of British radiologists were largely consistent with those reported by Mohan et al[63] in their analysis of a nationwide cohort of US radiologic technologists (total n = 146 022). In this cohort, SMRs were found to be 24% lower for all-cause mortality and 18% lower for cancer mortality compared to those in the general US population. The relative risks (RRs) were higher for both breast cancer (RR = 2.92) and all cancers (RR = 1.28) among those radiologic technologists who were employed before 1940 compared to those who were first employed after 1960. In fact, later employment corresponded to reduced mortality risk.[63,64] Similarly, the risks of acute lymphocytic leukemia and acute and chronic myeloid leukemia were also found to be elevated among those employed before 1950 relative to those first employed after 1950. The adjusted breast cancer risks for female radiologic technologists who started working before 1935, from 1935 to 1939, in the 1940s, 1950s, and 1960s were 2.9, 1.8, 1.0, 1.2, and 1.0, respectively, relative to those who began employment in 1970 or later.[65] The RRs increased with the total number of years employed before 1940 and were significantly greater among those who started to work before 17 years of age (RR = 2.6) but were not associated with the number of years employed beyond 1940. Occupational radiation exposure in low- to moderate-dose range in the US cohort of radiologic technologists was also demonstrated to be associated with increased breast cancer risk.[66] However, the most pronounced risk for breast cancer was found in women born before 1930 who started working before 1950 when cumulative annual doses (37 mGy) were substantially higher than those in later years (1.3 mGy). No association between protracted, low-to-moderate doses of radiation (cumulative mean absorbed brain dose, 12 mGy; range, 0-290 mGy), and malignant intracranial tumor mortality in the US nationwide cohort of radiologic technologists was found in the very recent study by Kitahara et al.[67] In another study by the same authors,[68] both total and cause-specific mortality rates were compared in nationwide cohorts of physicians who performed fluoroscopy-guided interventional procedures (n = 45 634) and psychiatrists (n = 64 401). Radiation-exposed physicians (both male and female) had 20% lower total mortality and cancer mortality (men: RR = 0.92; women: RR = 0.83) compared to mortality rates in psychiatrists. In addition, mortality from specific types of cancer and circulatory diseases was not elevated in physicians in comparison with those of psychiatrists. In another study by the same cohorts,[69] male radiologists showed decreased all-cause death rates (RR = 0.94) and similar cancer death rates (RR = 1.00) but elevated acute myeloid leukemia and/or myelodysplastic syndrome death rates (RR = 1.62) compared to psychiatrists; importantly, these rates were driven by those radiologists who have completed their education up to 1940 (RR = 4.68). An increased risk of brain cancer mortality (hazard ratio [HR] = 2.55) and an increased incidence of melanoma (HR = 1.30), breast cancer (HR = 1.16),[70] and stroke (HR = 1.34)[71] were found in a nationwide prospective cohort of 90 957 US radiologic technologists who worked with fluoroscopically guided interventional procedures in 1994 to 2008. These results were compared to those who never performed these procedures. The authors noted that although low-dose irradiation is one possible explanation for these elevated risks, these results could also be confounded by some unaccounted nonradiation risk factors.[70] An increased mortality rate from circulatory diseases in

Table 1. Mortality Rates in Cohorts Occupationally Exposed to Radiation.

References	Country	Exposed Cohort, n	Reference Population, n	Outcome	SMR (95% CI)
Matanoski et al[61]	United Kingdom	Radiologists, 2698	General population, NA	Overall mortality	0.72 (0.67-0.77)[a]
				Cancer mortality	0.63 (0.54-0.74)[a]
			All physicians combined, NA	Cancer mortality	1.04 (0.89-1.21)[a]
Cameron[63]	United States	Radiologic technologists, 146 022	General population, NA	Overall mortality	0.76 (0.70-0.80)[a]
					0.76 (0.70-0.80)[b]
				Cancer mortality	0.73 (0.70-0.80)[a]
					0.86 (0.80-0.90)[b]
Linet et al[69]	United States	Radiologists, 43 763	Psychiatrists, 64 990	Overall mortality	0.94 (0.90-0.97)[a,d]
				Cancer mortality	1.00 (0.93-1.07)[a,d]
Kitahara et al[68]	United States	Radiologic technologists, 45 634	Psychiatrists, 64 401	Overall mortality	0.80 (0.77-0.83)[a,d]
					0.80 (0.63-1.00)[b,d]
				Cancer mortality	0.92 (0.85-0.99)[a,d]
					0.83 (0.58-1.18)[b,d]
Tubiana[76]	United States	Radiation workers, 46 970	Nonradiation workers, 41 169	Overall mortality	0.81 (0.78-0.85)[c]
				Cancer Mortality	0.88 (0.81-0.94)[c]
				Leukemia mortality	1.11 (0.76-1.56)[c]
Boice et al[77]	United Kingdom	Radiation workers, 124 743	General population, NA	Overall mortality	0.82 (0.81-0.84)[c]
				Cancer mortality	0.82 (0.79-0.85)[c]
Muirhead et al[78]	United Kingdom	Radiation workers, 174 541	General population, NA	Overall mortality	0.81 (0.80-0.82)[c]
				Cancer mortality	0.84 (0.82-0.86)[c]
Muirhead et al[79]	Japan	Nuclear workers, 120 000	General population, NA	Overall mortality	0.94 (0.90-0.97)[a]
				Cancer mortality	0.98 (0.93-1.04)[a]
				Noncancer mortality	0.86 (0.82-0.91)[a]
Iwasaki et al[80]	Russia	Nuclear workers, NA	Unexposed residents, NA	Overall mortality	0.77 (0.73-0.81)[a]
					0.74 (0.66-0.83)[b]
				Cancer mortality	0.89 (0.78-1.01)[a]
					0.96 (0.78-1.17)[b]
			General population, NA	Overall mortality	0.86 (0.83-0.89)[a]
					0.82 (0.79-0.85)[b]
				Cancer mortality	0.97 (0.89-1.05)[a]
					1.05 (0.97-1.13)[b]

Abbreviations: CI, confidence interval; NA, not available.
[a]Male.
[b]Female.
[c]Male + female.
[d]Relative risk for death.

American radiologic technologists has been also reported, but only for those who have been first employed prior to 1950 when doses of occupational radiation exposure were high.[72] Since it has been suggested by several authors that parental preconceptional irradiation can cause childhood cancer, the risk of childhood cancer among 105 950 offspring born to US radiologic technologists in 1921 to 1984 was evaluated.[73] However, no statistically significant association between parental preconceptional radiation exposure and elevated risk of childhood cancer in offspring was discovered in this study. Brenner and Hall[74] discussed the data on cancer incidence and mortality among radiologists and other exposed-to-radiation medical professional groups. They noted that in the first half of the 20th century, the radiation risks to radiologists were easily identifiable. However, after introducing more rigorous standards of radiation safety, radiation effects often became below the limit of detectability by current epidemiological methods. In his summary of research findings accumulated in this research field, Tubiana[75] concluded that the lowest potentially carcinogenic cumulative dose of radiation is about 500 mSv. Considering the totality of evidence available (Table 1), it can be suggested that lower doses have no effect whatsoever or may even be beneficial.

Nuclear Worker Cohorts

Large-scale observational studies have been conducted in cohorts of personnel employed in the nuclear industry. A comprehensive Nuclear Shipyard Worker Study was conducted in the United States in the 1980s. The radiation staff involved in this research had been exposed to the external cobalt-60. Three cohorts were compared: a high-dose cohort (n = 7872, cumulative doses $\geq$5 mGy), a low-dose cohort (n = 10 348, cumulative doses <5 mGy), and an unexposed cohort (n = 32 510) of shipyard workers of the same ages and jobs.[81] Although the authors pointed out that this study was designed to search for

unfavorable outcomes of occupational low-dose and low dose rate gamma radiation, no risks were reported. High-dose-exposed workers, on the contrary, demonstrated evident health benefits, including 24% lower all-cause mortality and substantially lower respiratory, circulatory, and cancer mortality than did the unexposed workers. Unfortunately, the report has not been published in its entirety, and only a rather short summary[81] is available in easy-to-access form. Similar data were obtained from a pooled cohort of nuclear and nonnuclear workers at 4 department of energy nuclear weapons facilities in the United States (n = 119 195; mean cumulative dose = 20 mSv).[82] Nonsignificant dose responses were reported.

In most of the conducted studies, the mortality rate in the exposed cohort was below that of the general US population, but pleura and mesothelioma cancer rates were significantly elevated. No statistically significant evidence of an association between radiation exposure and mortality from all forms of cancers or from leukemia was found in the analyses of nuclear facility employees who were continuously exposed to low-dose radiation (mean cumulative dose <50 mSv) at the Hanford Site, Rocky Flats Nuclear Weapons Plant, and Oak Ridge National Laboratory (United States).[83,84] The multiple myeloma was the only cancer type with a significantly increased risk in an exposed cohort. Low mortality rate for all causes of death (SMR = 0.82) was demonstrated in 46 970 workers employed in 1948 to 1999 at Rocketdyne/Atomics International in California.[76] A decreased cancer mortality rate compared to those in the general population was observed by studying a large cohort (n = 45 468) of Canadian nuclear power industry workers.[85] A substantial reduction in the risk of all solid cancers combined (RR = 0.70) was found in the 1 to 49 mSv category compared with the lowest dose category (<1 mSv). Above 100 mSv, the risks tended to increase. For most causes of death researched, a lower mortality rate was found in a Canadian cohort of about 200 000 workers first exposed to radiation before 1984 than that in the general population.[86] The same has been demonstrated for cancer incidence, except for increased incidence of thyroid cancer and melanoma, which was not significantly associated with radiation exposure. A Canadian Nuclear Safety Commission[87] also reported lower rates of all-cause and cancer mortality among the Canadian nuclear power plant workers first employed after 1965 in comparison with the general Canadian population. In the study conducted by the National Registry for Radiation Workers, the largest epidemiological research of the United Kingdom radiation workers (n = 95 217), it was found that mortality rates from various forms of cancer, in particular multiple myeloma and leukemia (excluding chronic lymphatic leukemia), were lower in radiation workers employed at major sites of the United Kingdom nuclear industry than those found in the general population.[88] As a continuation of this study, subsequent analyses were performed in 1999 and 2009. In the 1999 study having been conducted on an enlarged cohort (n = 124 743), overall mortality rate was shown to be lower than those expected by comparison to the national mortality rate (SMR = 0.82).[77] In the 2009 study (n = 174 541), SMRs for all-cause and all malignant neoplasm mortality were 0.81 and 0.84, respectively.[78] Within this cohort, both incidence and mortality from all malignant neoplasms excluding leukemia increased significantly with increasing dose. In the French combined cohort of nuclear workers (n = 59 021), a positive significant excess relative risk (ERR)/Sv was found only for myeloid leukemia. The ERRs/Sv for solid cancers, leukemia (excluding chronic lymphocytic leukemia), cerebrovascular disorders, and ischemic heart diseases were all positive but nonsignificant.[89] All the findings of the decreased mortality and morbidity were attributed by corresponding researchers to HWE. Although HWE is an important factor as discussed above, no attempt was done by either research group to estimate HWE quantitatively and to discuss possibility of radiation hormesis.

A 4.5-year follow-up of health outcomes in a cohort of 120 000 nuclear industry workers in Japan showed that SMR was 0.94 for all causes combined and 0.86 for nonmalignant diseases combined.[79] In addition, no significant correlation between radiation dose and all-cause cancer mortality was found. In a subsequent analysis of cancer mortality in the cohort of male Japanese nuclear workers (n = 200 583; average individual cumulative dose = 12.2 mSv), ERR/Sv was negative for leukemia (−1.93; 95% confidence interval [CI], −6.12 to 8.57) and positive (1.26; 95% CI, −0.27 to 3.00) for all cancers excluding leukemia.[90] Remarkably, ERR/Sv for alcohol-related cancers was 4.64 (95% CI, 1.13-8.91) and ERR/Sv estimate of all cancers excluding leukemia and alcohol-related cancers was 0.20 (95% CI, −1.42 to 2.09). These results demonstrate that confounding by important lifestyle factors potentially associated with cancer risk can have a substantial effect on risk estimates.

Most large-scale studies in this field were conducted in multinational cohorts. In the large international cohort (n = 410 000) of nuclear plant workers in 15 countries (Australia, Belgium, Canada, Finland, France, Hungary, Japan, Korea, Lithuania, Slovakia, Spain, Sweden, Switzerland, the United Kingdom, and the United States), no excess risk of cancer was found for cumulative doses below 150 mSv.[91,92] In studies of chronic lymphocytic leukemia mortality conducted in 7 countries belonging to this cohort (n = 295 963), RR at a dose of 100 mSv was 0.84 compared to the unexposed control group.[93] Another multinational retrospective cohort study, in which 308 297 nuclear industry workers in France, the United Kingdom, and the United States participated, utilized detailed individual monitoring data for external exposure to ionizing radiation. This project—International Epidemiological Study on Workers in the Nuclear Sector—is usually referred to as INWORKS. This study demonstrated an association between protracted low-dose ionizing radiation exposure (average cumulative colon dose = 0.9 mGy, median dose = 4.1 mGy) and mortality from solid cancers.[94] The estimated rate of all-cause cancer mortality (excluding leukemia) increased with cumulative dose by 48% per Gy (90% CI, 20%-79%; lagged 10 years). In another study conducted in the same cohort, a positive association between protracted low-dose radiation exposure (mean cumulative dose = 1.1 mGy/y) and leukemia

mortality was found.[95] The ERR of leukemia mortality (excluding chronic lymphocytic leukemia) was 2.96 per Gy (90% CI, 1.17-5.21; lagged 2 years). The external radiation exposure was also significantly associated in this cohort with noncancer mortality (ERR/Sv = 0.19; 90% CI, 0.07-0.30), especially with mortality due to circulatory diseases (ERR/Sv = 0.22; 90% CI, 0.08-0.37).[96] In summarizing these findings, the authors claimed that INWORKS provided some of the strongest evidence that links low-dose and low dose rate exposure to ionizing radiation to health risks in occupational cohorts to date.[95] The authors, however, noted that influence of potential confounders such as occupational asbestos exposure and smoking cannot be excluded.[94] Moreover, significant risk of heterogeneity was evident in this study. In particular, increased ERR/Gy for chronic myeloid leukemia was observed shortly after exposure (2-10 years) and again substantially later (20-30 years); ERR/Gy for solid cancers was restricted to exposure at age over 35 and diminished for exposure 30 years prior to the attained age. The authors therefore note that caution is needed in interpretation of the INWORKS data due to apparent analytical limitations and a lack of consistent findings from other studies.[96,97]

In Russia, long-term health outcomes were analyzed in the residents of the city of Ozyorsk (Southern Urals) employed in a nuclear facility and exposed to radiation in the early years of operation and possibly further exposed from inhalation of plutonium aerosols.[80] Average annual doses were about 200 mGy or higher until 1953, with a gradual decrease of up to 5 mGy or less during the following 20 years. Although the accumulated doses were high, all-cause SMRs were lower among workers, with ratios of 0.77 for men and 0.74 for women, compared to the unexposed Ozyorsk residents, and of 0.66 for men and 0.60 (95% CI, 0.54-0.67) for women compared to national figures. For overall cancer mortality, SMR between workers and national figures was 0.86 in men; there was no difference in women (SMR = 1.01). Here also, the authors concluded without quantitative estimation that the HWE should be explanation for their results.

A dose–response relationship between α-radiation exposure and incidence of various cancerous and noncancerous disorders was observed in nuclear workers chronically exposed by inhalation to plutonium (^{239}Pu) in the Mayak Nuclear Enterprise (Chelyabinsk region, Russia).[98-120] For instance, the incidence of lung cancer corrected for smoking was 0.56, 0.59, and 0.83 at body burdens of 343, 1180, and 4200 Bq, respectively, in 500 nuclear workers relative to internal controls. Of note, the lung cancer incidence was linearly associated with cigarette smoking, with 2-fold risk of lung cancer in those workers who smoked 1 pack of cigarettes per day for at least 5 years. No clear associations were observed in workers employed at the Mayak Nuclear Facility between chronic external γ irradiation and incidence of lung cancer.[98] More recently, a linear association between cumulative internal plutonium lung dose and risk of both lung cancer mortality and incidence was obtained in the pooled cohort of the Mayak and Sellafield (United Kingdom) worker cohorts.[99] In analyses by Azizova et al, statistically significant trends to increase in ischemic heart disease incidence with both total external γ-ray dose and internal liver dose were found.[101,102] A significant decrease in ischemic heart disease incidence was, however, observed among the Mayak workers exposed to external γ-rays at a dose range of 200 to 500 mGy (n = 18 763) who were first employed in 1948 to 1972 and followed up to the end of 2005. Recent proteome profiling showed a dose-dependent increase in the number of downregulated mitochondrial and structural cardiac proteins in this cohort, suggesting that chronic external radiation can enhance the risk of ischemic heart disease by altering the expression of mitochondrial, structural, and antioxidant components of the heart.[103] Incidence of cerebrovascular diseases was positively associated with total absorbed dose from external γ rays and total absorbed dose to the liver from internal α-particle radiation in 22 377 workers who were first employed at Mayak in 1948 to 1982 and followed up to the end of 2008.[104] Cerebrovascular disease incidence was substantially increased in workers with total absorbed external γ-ray doses greater than 100 mGy, in comparison with those exposed to lower doses. This incidence was significantly enhanced in workers with total absorbed internal α-particle doses to the liver from incorporated plutonium greater than 10 mGy, in comparison with those exposed to lower doses. Incidence of lower extremity arterial disease was positively associated in this cohort with total dose from external γ-rays and not associated with doses from internal α-radiation.[105] It should be noted, however, that these workers were exposed not in a low-dose but in a moderate-dose range (on average, 540 mGy for men and 440 mGy for women). Relative risk of cataract incidence was found to be the highest in workers exposed at doses above 2.0 Gy.[106] No evidence, however, was revealed for the influence of low-dose and low dose rate radiation on cataract incidence.[107] Data on the effects of radiation exposure on the mortality rates in the cohort of Mayak workers appear somewhat inconsistent and dose dependent.[109-111] There was no evidence that exposure to plutonium aerosols significantly affected the risks of mortality from solid cancers other than the lung, liver, and bone.[109] No associations were observed between chronic external γ irradiation and mortality from cardiovascular disorders in a cohort of 12 210 Mayak workers first employed in 1948 to 1958 and followed up until the year 2000.[101] Similar patterns of associations were also found in the pooled cohort of the Mayak and Sellafield (United Kingdom) worker cohorts.[110]

It is well established that the human organism is most sensitive to radiation exposure during developmental stages characterized by an increased proliferative activity.[111,112] Therefore, it is generally assumed that prenatal irradiation influences the risk of cancer development as well as the development of other chronic diseases. The long-term cancer risks following radiation exposure in utero were evaluated in offspring born of female workers of the Mayak Production Association. In these studies, every mother's cumulative radiation dose during pregnancy served as a surrogate for fetal dose. No evidence was found that prenatal low-dose γ radiation exposure increased the risk of solid cancers or leukemia mortality in the

8000 offspring born of the Mayak female workers in 1948 to 1988.[113] The solid cancer incidence in the same offspring cohort (n = 8466) also did not differ from that in the general population[114]; there was also no consistent association demonstrated between the risk of hematologic malignancies and plutonium exposure.[115] In a more recent study aimed to analyze cancer risk in a cohort of patients exposed in utero due to releases of nuclear waste into the Techa River in the Southern Urals (n = 10 482 for solid cancers, and n = 11 070 for hematological cancers), no association between in utero exposure and risk for both solid and hematological cancer was found.[116] In the pooled analyses of 2 offspring cohorts of Mayak female workers and female residents of contaminated areas near Techa River, a tendency toward both decreased solid cancer incidence and mortality was observed in this large pooled cohort (mortality analysis, n = 16 821; incidence analysis, n = 15 813).[117] A positive association between in utero exposure to ionizing radiation and risk of hematological malignancies was revealed in the same pooled cohort (n = 19 536); the risk was increased in patients who received in utero doses of $\geq$80 mGy. No association was found in mortality-based analyses.[118] Consistent with findings from the Mayak Nuclear Facility studies, Draper et al[119] also demonstrated that paternal preconception irradiation did not cause childhood leukemia and non-Hodgkin lymphoma in the offspring of radiation workers in United Kingdom.

Several studies were conducted in hard-rock miners, including uranium miners. In a cohort of former German miners (n = 58 972) exposed to a low linear energy transfer (LET; mainly external ionizing radiation) and high LET (mainly radon and its decay products) radiation (red bone marrow doses, 48 and 9 mGy, respectively), an increased risk of death for chronic myeloid leukemia in relation to low-LET radiation was found (ERR/Gy = 7.20; 95% CI, 0.48-24.54). No such relation for chronic lymphocytic leukemia was demonstrated.[120] In the Ontario uranium miner's cohort consisted of 28 546 male miners with a mean cumulative radon exposure of 21.0 working-level months (WLMs), an increased risk of lung cancer was observed in miners exposed to >100 WLM.[121] These miners exhibited significant increase in the risk of lung cancer incidence (RR = 1.89) compared to the nonexposed group, with similar trends for mortality. No association was observed for cancer sites other than the lung or for noncancer mortality. A positive association between low-dose irradiation from α emitters and lung cancer risk was found in the case–control study with Belgian, French, and United Kingdom cohorts of uranium and plutonium workers.[122] The cases were 553 workers who died of lung cancer. Excess odd ratios (ORs)/Gy adjusted for external radiation, socioeconomic status, and smoking were 11 (90% CI, 2.6-24) for total α dose, 50 (90% CI, 17-106) for plutonium, and 5.3 (90% CI, −1.9 to 18) for uranium.

In uranium miners, causal link between radon exposure and lung cancer risk was repeatedly demonstrated. For example, 34% higher risk of lung cancer death (SMR = 1.34) was found in the French cohort of uranium miners employed between 1946 and 2007; this risk was increased significantly with cumulative radon exposure.[123] A similar correlation between lung cancer incidence/mortality and radon exposure levels was observed in cohorts of uranium miners in other countries, such as German,[124] Canada,[123] and the United States.[125]

Summarizing research findings from across the world, it is now generally accepted that radiation exposures in doses of less than 100 mSv are too low to detect any statistically significant cancer excess in the presence of naturally occurring malignancies.[126,127] The doses received by workers employed in the nuclear industry obviously fall into this category since the resulting dose is typically accumulated through many years with a mean annual dose of about 2 orders of magnitude smaller than 100 mSv. Indeed, annual monitoring of more than 100 000 radiation workers carried out in the United States since the year 1983 showed that no workers in the US nuclear industry were exposed to more than 50 mSv in a year.[126] The data on the Chernobyl emergency workers (*liquidators*) will be reviewed later in the section "Accidents at Nuclear Power Plants."

Nuclear Test Participants

Additional information on the health effects of low-dose radiation exposure was provided from follow-up studies investigating the health status in servicemen and civilians who took part in nuclear weapon tests. In the cohort of participants who participated in atmospheric nuclear weapon tests in the 1950s to 1960s in the United Kingdom (n = 22 347), no significant effects were revealed regarding mortality or subsequent risk of cancer and other fatal diseases.[128,129] The SMRs in the participants compared to that in unexposed control populations were 1.01 for all causes and 0.96 for all neoplasms.[128] Significant differences in mortality were observed for several kinds of cancer: Leukemia and multiple myeloma rates were higher in the participants, whereas prostate and kidney cancers were more frequent in the controls. The differences found were mainly interpreted by the authors as due to chance, but some were assumed to be caused by differences in smoking habits. During further 7-year follow-up, the death numbers detected in participants were lower than was to be expected from national rates for all causes, all neoplasms, leukemia, and multiple myeloma (SMRs: 0.86, 0.85, 0.57, and 0.46, respectively), and these death rates were also lower than in controls (RRs: 0.99, 0.96, 0.57, and 0.57, respectively).[129] When periods above 10 years after the initial participation in the tests were examined, mortality risk in participants was found to be comparable with controls for all causes (RR = 0.99) and all neoplasms (RR = 0.95). These results were again confirmed in further follow-up of mortality and cancer incidence in the same cohort.[130,131] Similarly, no evidence for raised all-cause mortality was found in a cohort of Australians (n = 10 983) who participated in the British nuclear tests in Australia.[132] No association was also observed between radiation exposure and all-cause cancer incidence or mortality, as well as with any cancer or excess cancer deaths. A retrospective cohort study of 12 219 military veterans at the Nevada test site (Operation Plumbbob nuclear test series)

showed that veterans remained sufficiently healthy 53 years after irradiation and had a lower mortality rate than those in the general population.[133]

High rates of all-cause mortality and cancer mortality were found in the Semipalatinsk (Union of Soviet Socialist Republics) historical cohort (n = 19 545) exposed to radioactive fallout during nuclear testing in the vicinity of the Semipalatinsk Nuclear Test Site, Kazakhstan, with a cumulative effective dose ranging from 20 to 4 Sv.[134] The ERR/Sv for all solid cancers combined was 1.77 (95% CI, 1.35-2.27) based on the total cohort data. High cardiovascular mortality rate was also found in this cohort.[135] However, when taking into account differences between the baseline rates in exposed and unexposed groups, no significant dose–response relationship for all cardiovascular disease, heart disease, or stroke could be demonstrated.

Radiation-Based Medical Procedures

Patients treated with radiation therapy are usually irradiated at high doses (~40-60 Gy) targeted to particular tumors; nonneighboring tissues typically receive low doses of radiation up to 0.1 Gy.[6] Investigating the effects of such exposures raises, however, a number of issues because partial-body exposures can obviously lead to a different risk than equivalent whole-body exposures.

In contrast, target organs receive small doses during diagnostic X-ray examinations and fluoroscopy-guided interventional procedures that are increasingly used in clinical practice. In general, the additional radiation load from these procedures is not large. For example, in the year 2000, of the about 3 mSv annual global per caput effective dose, 2.4 mSv was from natural background and only 0.4 mSv from diagnostic medical examinations.[136] Since radiation doses from diagnostic examinations are typically low, they are difficult to investigate using conventional epidemiologic approaches. Several such procedures, such as CT, can, however, deliver sizable cumulative doses in the order of 100 mSv to target tissues, thereby representing a useful model for investigating the health effects of low-dose radiation.[137]

Diagnostic Irradiation

Advanced imaging technologies currently play a central role in the screening of asymptomatic patients. Since 2000, however, a lot of scientific and public articles on the potential risks from CT screenings were published, provoking widespread public concern on this matter.[138] As a consequence, imaging examinations were delayed or canceled in several cases, causing a much greater risk to patients than that associated with diagnostic radiation exposures.[139] Indeed, doses used in CT generally range from 1 to 20 mSv, while no cancer excess has been detected for doses below 100 mSv.

At least 2 widely cited recent papers challenge the above statement and claim linear relationship between radiation dose and cancer even below 100 mSv. We shall discuss them now in brief. Pearce et al[140] reported, probably for the first time, evidence for direct association of the radiation from CT scans with cancer. Their interpretation of the data was criticized; there is the possibility of reverse causation due to confounding factors.[141] However, not only the interpretation of data is problematic but the data itself. Data points on cancer RR versus CT dose in the paper fit straight lines corresponding to the LNT model suspiciously well. As shown by Socol and Welsh by applying rigorous statistical analysis,[142] the probability of the fit truly being that good or better is only 2%. The results of Pearce et al are therefore "too good to be true" and it could very well be that some kind of parameter adjustment that yielded the LNT model results was, perhaps unknowingly, performed by the researchers.

Another paper reported increased RR of thyroid cancers for both less than 10 mGy, without significant departure from linearity.[143] But it should be stressed that, unfortunately, due to the recently acknowledged problem of thyroid cancer overdiagnosis,[144] the entire field of thyroid cancer epidemiology should be deemed irrelevant. For example, after the Fukushima nuclear accident, subsequent massive screening of children for thyroid cancers yielded 30- to 60-fold increase in thyroid cancer incidence for both exposed and unexposed prefectures of Japan.[145] It can be therefore said that the incidence of thyroid cancer is related to a function of the screening extent. Lubin et al[143] overviewed 2 cohorts of childhood cancer survivors, 6 cohorts of children treated for benign diseases, and 1 cohort of atomic bombings' survivors. It can hardly be doubted that children in all those cohorts were subjected to increased screening, leading to large number of overdiagnosed thyroid cancers.

An excess of breast cancer was detected in women after repeated chest fluoroscopic procedures for chronic tuberculosis or scoliosis. An increased breast cancer mortality was found in a cohort of 31 710 Canadian women who had been treated for tuberculosis between 1930 and 1952 (SMR = 1.36).[146] An increased breast cancer mortality rate (SMR = 1.69) was also found in a US cohort of 5 466 female patients with scoliosis who were repeatedly examined with diagnostic radiography (a mean cumulative dose to the breast: 108 mGy; range: 0-1700).[147] Breast cancer risk was increased significantly concomitant with the increase in the total number of radiograph exposures and, accordingly, with the increase in the cumulative radiation dose. In a more recent analysis of a cohort of 5573 women with scoliosis and other spine disorders who were exposed to repeated diagnostic X-ray procedures, breast cancer mortality was also significantly increased (SMR = 1.68).[148] Remarkably, death rates from some other cancers were significantly less than expected, in particular, from lung (SMR = 0.77), cervical (SMR = 0.31), and liver cancers (SMR = 0.17). It should be taken into account, however, that although doses from single treatments are typically low, many patients can be subjected to repeated treatments over time, which can eventually lead to relatively large cumulative doses. This consideration is especially important for studies like these because diagnostic examinations can be very frequent in these cases. For example, in the Boice et al's[149] study, women who were

repeatedly examined by X-ray fluoroscopy (observed/expected ratio = 1.29; 95% CI, 1.1-1.5) and in whom increased breast cancer incidence was observed, underwent such diagnostic procedures an average of 88 times. In this study, increased breast cancer incidence definitely resulted only from large cumulative doses that ranged from 10 to 6400 mGy, 790 mGy on the average. In discussing these observations, Tubiana[75] emphasized that cancer excess has been consistently demonstrated only for cumulative doses greater than 500 mGy.

Scott et al[150] speculated that the risk of cancer induced by diagnostic X-rays exposures (eg, CT scans) could possibly was rather reduced than increased. This assumption has been confirmed by findings from animal studies which demonstrated that development of experimental tumors may be suppressed by low-dose radiation exposure by stimulation of the removal of preneoplastic cells and/or through prevention of metastasis of already existing cancer.[151-154] From these data, it is assumed that doses currently associated with routine diagnostic X-ray procedures (range from 1 to 100 mGy) fall in the "hormetic" zone for high-energy γ-ray photons[155,139] and therefore can likely be protective against cancer and several noncancer diseases.

Having said this, caution should be exercised in recommending radiation-based procedures for diagnostic purposes. This is especially true for pregnant women since fetuses may be exceedingly sensitive. Therefore, severe developmental abnormalities such as pregnancy loss, growth retardation, congenital malformations, and neurobehavioral defects may result in some cases from fetal radiation exposures that exceed 100 mGy.[156,157] All these adverse effects, however, have threshold doses above 100 to 200 mGy, and the risk is considered to be negligible at 50 mGy. Potentially hazardous doses can be achieved only very rarely (for reference, 100 mGy is equivalent to about 1000 conventional chest X-rays).[156] Therefore, when deciding whether to conduct such procedures, the sum of all maternal and fetal risks and benefits should be taken into account.[158]

Low-Dose Radiotherapy

As a part of their treatment, more than half of all patients with cancer today undergo radiotherapy in which high doses of ionizing radiation are aimed to kill cancer cells.[159] However, the efficiency of radiation therapy is substantially limited since moderate (0.1-2.0 Gy) or high (>2 Gy) radiation doses which are commonly used in present day radiotherapy may damage normal tissues, inhibit immune functions, and enhance the risk of secondary neoplasms.[160] In contrast, these complications do not occur when low-dose radiation exposures ($\leq$100 mGy for acute exposure or $\leq$0.1 mGy/min dose rate for chronic exposures) are applied. Low-dose radiation exposure has thereby been suggested by some authors to be more effective than conventional radiotherapy protocols because it provides tumor control with negligible toxic side effects.[161-163] This assumption is based on data that show that low-dose radiation may stimulate DNA repair, antioxidant capacity, apoptosis, and immune responses, thereby potentially providing effective tumor control. In particular, low-dose irradiation was shown to lead to activation of many anticancer pathways, such as antibody formation, secretion of interferon and other cytokines, and induction of natural killer activity.[164] These processes, collectively, can retard tumor growth, decrease metastasis, and inhibit carcinogenesis triggered by high-dose radiation, as can be seen in many animal models.

Some preclinical studies demonstrated that low-dose radioimmunotherapy can likely be more effective than chemotherapy in treatment of lymphosarcoma (non-Hodgkin lymphoma).[162] Consistent findings were obtained in several clinical trials. In clinical studies conducted by Harvard University, low-level total-body and half-body irradiation was used for treatment of non-Hodgkin lymphoma. Four years after the beginning of the trial, 70% of the low-dose irradiated patients were still alive, while only 40% survived in the control group treated with chemotherapy.[165] In the subsequent study, similar 4-year survival rates were observed: 74% and 52% for the low-dose irradiated patients and patients with cancer treated with chemotherapy, respectively.[166] These findings were later confirmed in similar preclinical and clinical studies conducted in Tohoku University, Japan.[167] Typical irradiation doses in both Harvard and Tohoku clinical trials were about 15 rad (150 mSv) given twice weekly, calculated to midpelvis, to a total dose of about 150 rad (15 Sv). More recently, it was shown that low-dose radiotherapy can be utilized as an efficient palliative treatment mode for different types of lymphoma, such as indolent non-Hodgkin lymphoma,[168,169] cutaneous B-cell and T-cell lymphomas,[170-172] and marginal zone lymphoma.[173-175] Low-dose pretreatment has also been proposed as a promising therapeutic approach in radiation therapy. Such pretreatment may trigger an adaptive response which could provide improved protection when large therapeutic doses are subsequently applied, thereby reducing the resultant damage and the probability of secondary cancer.[176] There is also some preclinical experimental evidence that low-dose radiation can be used in the treatment of several noncancer diseases, such as autoimmune diseases,[177,178] neurodegenerative diseases,[179,180] as well as diabetes and diabetic cardiovascular complications.[181-184]

Environmental Radiation

Natural environmental radiation may be derived from various sources. About three quarters of the background radiation originate from a natural γ radiation emitted by rocks, soil, and terrestrial radon. Approximately one quarter of the background radiation originates from cosmic radiation and from radionuclides incorporated in the human body.[185] In recent decades, the levels of environmental radiation are substantially affected by man-made sources of radiation around the globe, such as accidents in nuclear power plants, nuclear tests, and atomic bomb explosions, which are reviewed and discussed in detail in the subsections subsequently.

Environmental Background Radiation

The levels of natural background radiation vary substantially, sometimes by even 2 orders of magnitude, in different geographical regions around the globe. In most areas, the average values of the effective dose rate are about 2 to 4 mSv/y. Regions with effective dose rate above 10 mSv/y are generally referred to as high natural background radiation areas. In some regions such as Guarapari (Brazil), Kerala (India), Ramsar (Iran), and Yangjiang (China), natural background radiation can reach several hundred mSv/y. For example, in the Ramsar province, Iran, the total annual effective dose reaches 260 mSv/y.[186] Some studies were conducted to investigate the potential relationship between high levels of background radiation and health outcomes in the exposed populations, primarily cancer incidence and mortality. An advantage of this kind of study is that they are relatively easy to conduct because they usually utilize already existing data. A shortcoming of this sort of study is that the units of analysis are not individual,[6] that is, such investigations are usually descriptive and ecological in design. Nonetheless, although the value of such studies is substantially limited by their ecological design, they could yet be informative in assessing associated risks.[187]

Most epidemiological studies evaluating health outcomes in areas with high natural background radiation levels explored the risks for cancer and noncancer diseases based on incidence or mortality data. Even though, initially, a positive relationship between background radiation levels and risk for disease was expected, in fact, in most of these studies, when comparing populations residing in areas of high-level background radiation to those residing on low-level background radiation locales, no health hazard was found. Indeed, neither cancers nor early childhood deaths were positively correlated with radiation dose in the high-level background radiation areas.[186,188] Furthermore, several studies demonstrated some evidence that the levels of natural background radiation are inversely correlated with cancer mortality.

In a study conducted in the United States, not only was no increase in both malignant mortality and mortality from congenital malformations with increasing background levels found. On the contrary, a consistent and continuous decrease in these phenomena was observed.[189] In a more recent study, cancer mortality rates were also found to be inversely related to natural background radiation levels in the United States ($r = -0.656$, $P < .0001$).[190] Among 8 predictors thought to be linked to cancer mortality, background radiation ranked second in predictive strength concerning cancer mortality, after smoking. In an analysis study conducted in those states in the United States where nuclear testing was carried out, more background radiation exposure was associated with less lung cancer incidence.[191] Since the levels of background radiation tend to increase with increasing land elevation, cancer mortality rates were also compared in 6 low versus s6 high elevation US jurisdictions.[192] Statistically significant decrease in mortality in high land elevation was found for 3 of the 4 health outcomes studied, including cancer. Since mortality rates tend to vary by race, only data for people belonging to the Caucasian race were subsequently analyzed by Hart.[193] In this study, US counties with higher elevation also exhibited significantly decreased cancer mortality rates compared to lower elevation counties (53.90 ± 13.76 and 73.47 ± 18.35, respectively; $P < .0001$). In higher land elevation counties, significantly lower death rates from heart disease were also observed compared to those in lower land elevation counties ($P < .0001$ for both black and white persons).[194] On the basis of these analyses, the author suggested that radiation hormesis is one possible explanation for the decreased mortality in high elevation regions. Admittedly, other explanations, such as adaptive physiological responses to lowered oxygen levels (at least for heart disease mortality), cannot be excluded. No association between cancer mortality rates and natural background radiation levels was observed in Ireland.[195] In China, similar cancer mortality rates were found in regions with high average background radiation levels (2.31 mSv/y average) and with low levels (0.96 mSv/y average).[196] Similarly, no increase in cancer incidence or mortality associated with a high background radiation was observed in Yangjiang, China,[197] and in Kerala, India.[198] Moreover, both cancer incidence and mortality rates were found to be substantially lower in areas with high background radiation levels when compared to low-level areas in several regions in India[199] and China.[200] Thus, epidemiological studies carried out so far have failed to demonstrate any unfavorable health effects in the populations living in areas with high background radiation levels. Based on the analysis of available literature data, Dobrzyński et al[188] concluded that the LNT hypothesis can hardly explain these results. They can be better explained by the model of threshold or hormesis. By generalizing these findings, Cameron[201] provocatively stated that "we need increased background radiation to improve our health."

There is one study conducted in Bavaria, Germany, which provides evidence that an increase in the dose rate from natural background radiation, and thus an increase in the lifetime accumulated dose, can have adverse impacts on human health.[202] Dobrzyński et al[188] later questioned the plausibility of the model used to explain the dose–risk relationships analyzed in the study. Based on their reanalysis, the authors concluded that health risks from low-dose and low dose rate exposures, such as those from elevated natural background radiation, do not exist or are substantially lower than the risks expected based on LNT extrapolation.

Residential Radon Exposure

Radon gas is the leading source of natural background radiation exposure worldwide (Figure 2).[203] (In the United States, the distribution of relative radiation exposure is different. Due to extensive health care, including medical imaging, medical exposure contributes about 48% of the total exposure.) Radon is also considered to be the second (after tobacco smoking) most common cause of lung cancer.[204] However, recent meta-analysis of 32 case–control and 2 ecological radon studies of lung cancer concluded that for radon concentrations below

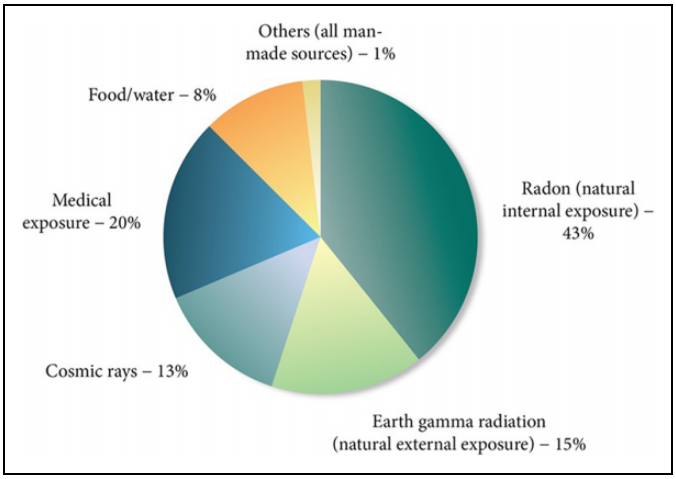

Figure 2. Sources and distribution of average radiation exposure to the world population. Source: World Health Organization.[203]

$\sim$1000 Bq/m^3 ($\sim$20 mSv/y of effective dose to the whole body), no statistically significant increase in lung cancer incidence was observed.[205,221-225]

The informative value of studies from high natural background radiation regions is rather doubtful since such studies are ecological in design and ensure only very rough effective dose categorization. More reliable information on the health effects of low-dose radiation can be obtained from research on residential radon exposure. This kind of study is more reliable because it includes dose reconstruction (especially lung doses), large study samples, and availability of information on potentially confounding factors.[186]

However, it should be noted that dose rates and, consequently, accumulated doses are typically much larger for miners than for residential exposures. Therefore, extrapolating the risk of residential exposure from that of miners can generate considerable uncertainty, and extrapolation of data from miners is commonly not applicable for a correct estimation of the situation of people living in above-ground buildings.[206] Furthermore, extrapolation of risks for lung cancer from the miner data is problematic since miners are known to be cigarette smokers far in excess of the general population. For example, the smoking rate of miners in the Schneeberg area (Germany) during an early uranium mining period (from 1946 until 1954) was estimated to be above 90%.[207] This statistic is significant because the effects of smoking on the risk of lung cancer are typically much higher than those from only radon exposure.[208] Indeed, as reported by BEIR,[209] smoking can increase the risk of lung cancer by a factor of 10 to 20, while radon can increase this risk by 0.2 to 0.3 at most. In other words, the risk of lung cancer from smoking is about 50 times higher than the risk associated with radon exposure.

In cohort (ecological) studies performed in the United States, a significant negative association between residential radon exposure and a risk for lung cancer was unexpectedly discovered (for illustration, see Figure 3). In particular, after correction for smoking, a significant negative correlation was found between the average residential radon levels and lung cancer mortality rates in nearly 2000 counties housing more than 90% of the general US population.[19,210-212]

A negative correlation was also demonstrated between natural radon levels and mortality from lung cancer in 3 Rocky Mountain states (Idaho, Colorado, and New Mexico) and 3 Gulf states (Louisiana, Mississippi, and Alabama).[215] An U-shaped dose–response relationship was revealed between 1950 and 1954 lung cancer mortality county rates and residential radon levels in women who have never smoked.[216] A lower cancer mortality rate relative to that of the general population was also reported in residents of the Misasa spa area (Japan), an area with a particularly high level of background radon.[217]

Epidemiological evidence on the causative role of indoor radon exposure in the pathogenesis of lung cancer has been obtained in case–control studies. Most comprehensive and methodically sound case–control studies were, until now, performed in the United States. An overview of such research is provided in Table 2. Findings from these studies are, however, quite inconsistent. For example, in a recent systematic review of 24 case–control studies around the world by Sheen et al,[218] a statistically significant positive association was reported in 7 studies, while 13 papers reported no association and a negative association was revealed in 4 studies. Notably, positive association was quite pronounced in the radon-prone areas, while studies conducted in areas with relatively low radon exposure levels usually failed to demonstrate such a link. In addition, both positive and negative effects were reported in several studies depending on the dose. For instance, an U-shaped (hormetic) dose–response relationship between levels of residential radon exposure and lung cancer incidence rates was also identified in the study by Thompson et al[219]: The adjusted ORs for lung cancer were 1.00, 0.53, 0.31, 0.47, 0.22, and 2.50 for the radon exposures of <25, 25 to 49, 50 to 74, 75 to 149, 150 to 249, and $\geq$250 Bq/m^3, respectively. These findings have been confirmed in a subsequent study where a significant decrease in cancer risk with increased radon exposure was observed for values $\leq$157 Bq/m^3.[220] Overall, as mentioned at the very beginning of this section, it can be concluded that data on the dose–response relationship between radon exposure and lung cancer risk are rather inconsistent.[205,221-225]

Accidents at Nuclear Power Plants

Since the beginning of the atomic era, the expansion of nuclear technologies has generated public concern over the health risks posed by the potential of nuclear power plant breakdowns. During this time, several serious nuclear accidents occurred throughout the world. The Three-Mile Island nuclear power plant accident in 1979 was probably the first resulting in mass media coverage. More accidents occurred at the Chernobyl nuclear power plant in the Soviet Union in 1986 and at the Japanese Fukushima Daiichi nuclear power plant in 2011. Long-term health risks related to these accidents are the subject of comprehensive investigations.

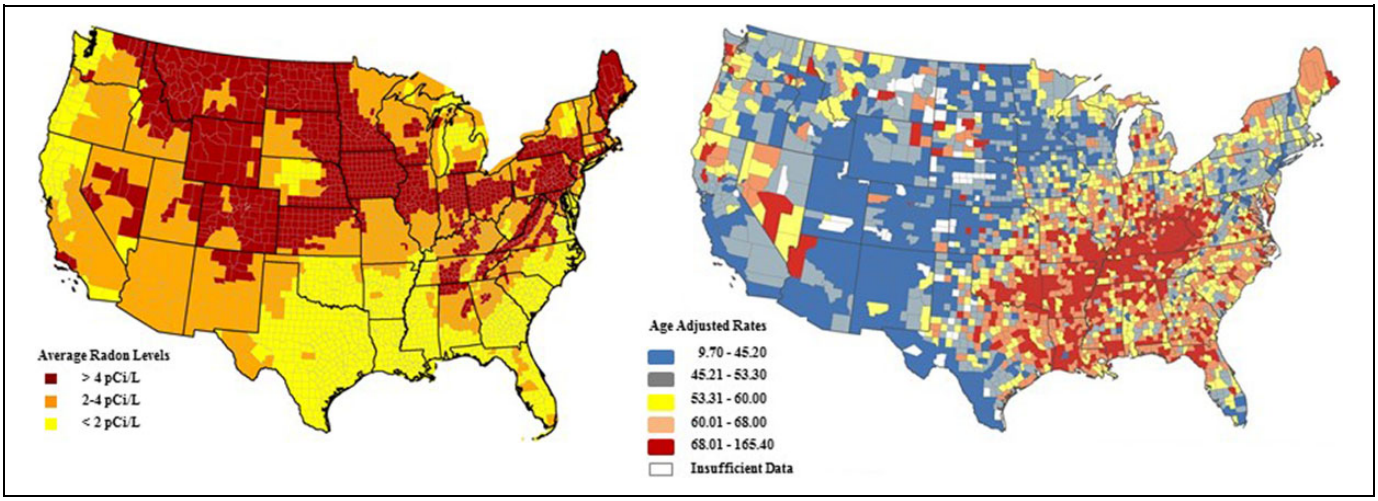

Figure 3. A comparison of the radon concentrations and lung cancer mortality rates in the United States. Left panel: Predicted average indoor radon levels (source: EPA Map of Radon Zones;[213] the version available currently on EPA's web page is provided with permission of the Radiation Protection Division at the EPA). Right panel: Lung cancer mortality rates by county 2000 to 2009, per 100 000 age adjusted to the 2000 US census (source: Static Maps. National Community Mapping Institute).[214] Available currently on the web page of the National Community Mapping Institute). EPA indicates Environmental Protection Agency.

Although the Three-Mile Island nuclear accident was serious and led to the loss of the plant, the average radiation dose received by exposed individuals (total up to 2 000 000) was rather low (about 1.7 mrem).[226] Not unexpectedly, no evidence for adverse health effects was revealed. In particular, there was no increased risk of cancer incidence neither in men nor in women (RRs = 1.00 and 0.99, respectively).[227] In the long-term follow-up of the residents of this area (n = 32 135), overall cancer mortality was also similar to that of the local population (SMRs = 103.7, male; 99.8, female).[228]

To date, it was the long-term health outcomes of the Chernobyl disaster that has been most comprehensively studied. Due to this nuclear accident, many regions of Ukraine, Belarus, and South Russia were vastly contaminated by radionuclides iodine-131 (^{131}I) and cesium-137 (^{137}Cs). A total of 116 000 people were relocated from the area surrounding Chernobyl to noncontaminated regions during the spring and summer of 1986; another 220 000 persons were relocated in subsequent years. The most frequently reported adverse health outcome of this accident is the post-Chernobyl radiogenic childhood thyroid cancer.[229] ^{131}I is a radionuclide with a very short half-life (8 days only), but it may quickly get into the human body through consumption of contaminated vegetables and milk and from the air. Most ^{131}I is localized in the thyroid gland. Due to the small size of thyroid glands in children and features of their metabolism, the radiation doses are usually much higher for children than for adults. The radiation doses to the thyroid gland were high in the affected areas owing to high contamination levels (no shielding, no food restriction, and late evacuation of contaminated populations) and high radioiodine intake of the thyroid gland (due to both iodine deficiency and no iodine prophylaxis).[230] A unique feature of the Chernobyl accident was that radiation doses to the thyroid gland were 3 to 4 orders of magnitude higher than the doses to other organs.[231] As a result, the accumulated doses reached several grays or even several tens of grays; thus, they were much higher than the doses discussed in other subsections of this review.

After the accident, the incidence of infant thyroid cancer increased rapidly in children, especially those aged 0 to 5 years.[232] By 2005, more than 6000 thyroid cancer cases (15 of them with lethal outcomes) were diagnosed among the about 2 million highly contaminated patients who were children and adolescents during the accident. It has been assumed that a large fraction of these thyroid cancers can be attributable to ^{131}I exposure. A positive relationship between childhood thyroid cancer and thyroidal ^{131}I exposure was observed in ecological research, and it was confirmed in several case–control studies.[233] The dose threshold of radiation-associated childhood thyroid cancer has, however, not been scientifically clarified till now, and no consensus exists in modern literature on the applicability of the LNT model in evaluating this association.[234] Moreover, as already mentioned, the recently acknowledged problem of thyroid cancer overdiagnosis may make the abovementioned evidence irrelevant. Even 15 lethal cases can be explained by surgeries' complications.

Except for the substantial increase in thyroid cancer incidence in children and young people, there was no increase in the incidence of other radiation-associated solid cancers or leukemia as well as nonmalignant disorders in the exposed populations.[235]

When discussing the long-term health outcomes related to the Chernobyl accident, it should be taken into account that a trend of increased cancer incidence was observed even *before* the Chernobyl accident in the affected areas.[229] Moreover, a strong upward trend in the incidence rate of thyroid cancer has been evident worldwide since the 1970s.[236] Therefore, this trend certainly cannot be explained by radiation exposure per

Table 2. Overview of Case–Control Studies on Association Between Residential Radon and Lung Cancer in the United States.

References	Gender	Cases, n	Controls, n	Dose, Bq/m^3	OR (95% CI)
Cohen[211]	Female	433	402	<37[a]	1.0 (reference)
				37-73	1.1 (0.79-1.7)
				74-147	1.3 (0.62-2.9)
				148-418	4.2 (0.99-17.5)
Cohen[212]	Female[b]	538	1183	4-29[a]	1.00
				30-43	1.01 (0.7-1.4)
				44-62	0.84 (0.6-1.2)
				63-90	0.90 (0.6-1.3)
				91-566	1.20 (0.9-1.7)
Darby and Hill[209]	Both	200	397	<25	1.00
				25-49	0.53 (0.24-1.13)
				50-74	0.31 (0.13-0.73)
				75-149	0.47 (0.20-1.10)
				150-249	0.22 (0.04-1.13)
				≥250	2.50 (0.47-13.46)
Cohen[213]	Both	3662	4966	<25	1.00
				25-49	1.13 (0.95-1.35)
				50-74	1.09 (0.89-1.34)
				75-149	1.16 (0.91-1.48)
				100-149	1.24 (0.96-1.60)
				150-199	1.22 (0.87-1.71)
				≥200	1.37 (0.98-1.92)
Environmental Protection Agency[214]	Both	4081	5281	<25	1.00
				25-49	1.13 (0.94-1.31)
				50-74	1.05 (0.86-1.27)
				75-149	1.14 (0.90-1.45)
				100-149	1.22 (0.95-1.56)
				150-199	1.19 (0.86-1.66)
				≥200	1.29 (0.93-1.80)
Static Maps[215]	Both	561	740	<25	1.00
				25-49	0.90 (0.64-1.25)
				50-74	1.02 (0.66-1.57)
				75-99	1.31 (0.68-2.53)
				100-149	1.40 (0.64-3.09)
				≥150	0.76 (0.36-1.61)

Abbreviations: CI, confidence interval; NA, not available.
[a]Recalculated from pCi/L (1 pCi/L = 37 Bq/m^3).
[b]Nonsmokers.

se. In addition, an important point is that there was widespread psychological trauma following the accident, which was caused by fear of radiation but not by the radiation exposure per se. Such trauma could likely affect the risk of certain psychosomatic diseases. In discussing the long-term consequences of the Chernobyl accident, Takamura and Yamashita[237] noted that this accident led to psychoemotional trauma and social instability, which caused far more adverse health outcomes than that caused by the radiation exposure. Indeed, the post-accident relocation resulted in a "deeply traumatic experience" for about 350 000 people displaced from their homes in the affected regions. Persistent misperceptions and myths with regard to the threat of radiation led to "paralyzing fatalism" among these people. An important point in this respect is also that most emergency workers (*liquidators*) and people who resided in contaminated areas received relatively low doses of whole-body irradiation, compared to those in natural background radiation levels.[238] More specifically, the mean effective dose was 100 mSv for liquidators (n = 240 000) and 33 mSv for evacuees of 1986 (n = 160 000).[137,235] Overall, no carcinogenic effects were observed in people exposed to radiation doses below 100 mSv following the Chernobyl accident.

However, even in spite of such strong contra arguments, several authors still claim that there are catastrophic long-term radiogenic consequences of the Chernobyl accident. For example, Yablokov et al[239] claimed, based on LNT-based calculations, that 985 000 additional deaths occurred globally in 1986 to 2004 which could be attributed to Chernobyl. This apparent exaggeration of potential adverse effects is obviously due to the biased methodology used. More specifically, the article summarily rejects central postulates of present day radiation epidemiology that require proof of the radiation dose–effect relationships. The article selection is largely unbalanced, and papers where radiation effects were not observed

are completely ignored.[240,241] In most papers referenced by Yablokov et al,[239] an ecological approach was applied since direct dose measurements were lacking in these studies. As such, a cohort or case–control design for the various studies could not be constructed. Moreover, in trying to reveal any changes potentially attributed to Chernobyl, cancer incidence and mortality were most intensively investigated in affected populations after 1986. Therefore, diagnostic and health screening services were not similar in "clean" and "contaminated" regions, and diversity in incidence/mortality in various areas might not reflect actual health differences, but rather may be due to a systematic bias resulting from the screening effect. Indeed, as shown for sporadic thyroid carcinomas, an apparent incidence of radiation-associated thyroid cancers can be substantially related to the intensity and modalities of screening.[144, 242] For example, in South Korea, after implementation of screening procedures in 2000, the apparent incidence rose by 15-fold in subsequent years.

There are also apparent problems in attempting to define trends in health indices over time. The economic depression following the breakdown of the Soviet Union in 1991 caused a collapse of the health-care system and sharply increased mortality rates in post-Soviet countries.[243] Of note, the increase in mortality was more pronounced in the Far East of Russia, which obviously was not affected by the Chernobyl accident.[244] Furthermore, in most studies reviewed by Yablokov et al,[239] it is impossible to distinguish the effects of low and high radiation doses. In those studies where external radiation doses were documented, the effects of radiation were insignificant in the low-dose range. One example is the research by Ivanov and coworkers[245-247] where solid cancer incidence was investigated in emergency workers who worked in the 30-km zone around the Chernobyl nuclear power plant in 1986 to 1987. These workers were exposed to a very wide range of cumulative doses (1-300 mGy).[246] Data from this study indicated rather a hormetic dose–response relationship with the cancer risk rate below the level found in the general population (standardized incidence ratio [SIR] = 0.87) in low-dose (mean, 79 mGy) groups as opposed to an increased risk (SIR = 1.27) in the high-dose (mean, 194 mGy) group.

When discussing the applicability of the LNT hypothesis to radiation exposures from the Chernobyl accident, Jaworowski[248] concluded that LNT-based assumptions were counterproductive in this case. These assumptions are in conflict with observations from Russia, indicating that there was a 5% decrease in solid cancer incidence among the population residing in most contaminated areas compared to the general population of Russia and a 15% to 30% decrease in solid cancer mortality among emergency workers in Russia.

The second worst nuclear accident in history after Chernobyl occurred at the Fukushima Daiichi (Fukushima I) Japanese power plant in 2011 following earthquake and subsequent tsunami. Although both the Chernobyl and Fukushima Daiichi accidents were classified as level 7, the worst level on the International Nuclear Event Scale of the International Atomic Energy Agency, the actual conditions and damage scales differed significantly.[249] Similar to the Chernobyl case, large amounts of radioisotopes, including ^{131}I, were released in Fukushima and the surrounding prefectures. However, radiation doses to the thyroid gland were much lower in Fukushima, mainly because food restriction was timely ordered by the Japanese authorities. As a result, the average individual dose to the thyroid gland was <1 mSv only, with a maximal dose of 33 mSv. Therefore, it is not surprising that no increased incidence of clinical thyroid cancers was observed over the 5 years following the accident.[250] Later, massive screening of exposed children and teens (above 300 000 persons aged 18 years and younger) with novel ultrasensitive sonographic equipment yielded alarming 30-fold increase in thyroid cancer incidence. However, sample screening (with the same equipment and protocol) of cohorts of *unexposed* children also yielded 10- to 60-fold increase.[145] As discussed above, this increase in incidence is undoubtedly a result of overdiagnosis.

Most likely, the primary public health problem following the Fukushima accident is chronic psychological stress, as well as stress-related lifestyle disorders, such as obesity, hypertension, type 2 diabetes, and dyslipidemia in displaced people, all of which may result in an increased risk of cardiovascular disease in the future.[251]

Discussion

Summary of Epidemiological Studies: Limitations and Opportunities

There were several methodological issues and limitations in most of the epidemiological studies addressing the long-term effects of low-dose radiation. By generalizing results from occupational studies, it should be concluded that statistically significant detrimental health effects of occupational low-dose radiation exposure were not often observed. In particular professional groups, these effects can be influenced by confounding factors such as smoking and/or alcohol consumption. A common trend observed in the majority of occupational cohorts around the world is that mortality from most causes of death is typically lower in these cohorts than that in the general populations. Although such outcomes are likely influenced by the HWE,[77,78] no quantitative estimations of HWE have been performed and several authors believe that radiation hormesis induced by low-dose radiation could be involved.[18,252,253] Further progress in such occupational studies is expected from the use of advanced analytical tools. The radiation-related risks may likely be better addressed in individual-level studies (eg, by introducing the omics-based technologies[254,255]) than in population-level studies. Implementation of such innovative approaches can likely improve our understanding of causative mechanisms underlying health effects in cohorts occupationally exposed to radiation.

Follow-up of patients subjected to diagnostic or interventional radiology may certainly give extremely valuable information on the biological effects of low-dose irradiation. In most of these studies, increased incidence and mortality from

cancer were observed. The main drawback of such studies is the formidable task of accounting for confounding factors—since the very fact that a person was sent to treatment places him in a higher risk group. An additional important limitation is that, in such studies, individual cumulative doses demonstrated a great deal of intersubject variability, that is, exposed groups usually included individuals who received doses differing by orders of magnitude. Therefore, these groups were extremely heterogeneous and consisted of patients exposed to low, moderate, or even high doses. In those cases where exposures were in the low-dose range only, they tended to result in either no or beneficial health outcomes. Indeed, low-dose radiotherapy is suggested to be a novel promising therapy to treat various cancer and noncancer pathological conditions.

Regarding studies on the effects of environmental radiation exposure, one of the most important methodological issues is the "ecological fallacy" which occurs when conclusions regarding individuals are based on the analysis of group data only. Indeed, ecological studies typically do not include estimates of individual radiation exposure; instead, aggregate population estimates or surrogate indicators such as geographic location are commonly used to define population dose for the group of individuals.[6] It is assumed, for example, that persons residing near a nuclear power plant receive higher radiation doses than those who live far away from a facility and that everyone within the exposed area is equally exposed. In most cases, however, there is a significant variability in individual exposure levels within the population at risk; thus, the association of the disease with the exposure level can be substantially underestimated or overestimated. Moreover, no information is usually available in ecological studies about potentially confounding factors. Therefore, no causal inferences may be made, as a rule, from the results of such studies. Limitations of the ecological approach can be overcome by using a cohort study that compares the experience of several groups of patients who are concurrently followed prospectively or by constructing a case–control study by comparing individuals who have the disease (the "cases") with individuals who do not have such pathology but are otherwise similar (the "controls"). Both these approaches are preferable but not always possible since they require the reconstruction of individual doses.

Finally, regarding studies on the radiation effects in participants of nuclear tests ("atomic veterans"), exposed population ("downwinders"), and uranium workers, one cannot ignore a significant incentive for cancer overdiagnosis. According to the US Radiation Exposure Compensation Act, downwinders diagnosed with cancer are eligible to tax-free compensation of US$50 000, atomic veterans of US$75 000, and uranium-processing workers of US$100 000.

Ethical, Economic, and Regulatory Considerations

As mentioned already in the Introduction, there is no solid evidence that exposure of up to 500 mSv/y (2 mSv/d) causes harm of any type. We discussed in the section "Occupational Exposure" that a dose rate of 500 mSv/y should be considered safe (ie, tolerance level) based on human data. The present limits are much lower: 20 mSv/y (25 times lower) for occupational exposure and 1 mSv/y (500 times lower) for the public.

Implementation of the present regulatory restrictions in the field of ionizing radiation is very expensive. It has been estimated that spending US$100 million on controlling radiation emissions might save 1 human life year[256]—provided the LNT is correct. Such high cost effectively causes loss of life, as a median medical program costs US$19 000 per life year saved.[256] For example, instead of one person saved, assuming LNT is true (and 0, if false), —five thousands of other patients can be saved. The effective loss of life due to radiation safety–related spending is not limited to underfunding of public life-saving programs. The fact is that wealthier people live not only wealthier but also longer: They use safer products (eg, cars), consume healthier food, have healthier lifestyle (eg, affording time for physical exercise), and more. It is difficult to estimate quantitatively the connection between public spending and statistical loss of life. The estimations differ from US$7 million per life[257] to US$70 million per life.[258] To put these figures into proportion, let us compare statistical life saving versus statistical loss of life for spending on nuclear protection.[259] Multiplying US$100 million per life year saved[256] by 11 years of average life shortening per cancer death—see BEIR[6]—yields US$1100 million ($1.1 billion) per *one* life saved. Public spending of US$1100 million leads to loss of 1100/70 $\sim$ 15 lives lost according to Viscusi[258] and to 1100/7 $\sim$ 150 lives lost according to Lutter and Morrall.[257] An additional study[260] concluded that the price tag of radiation protection is about 5000 times higher than that of protection of workers from all other (and more probable) events. It can be therefore said that per each statistical life saved by nuclear regulation (if LNT is valid), there are 15 to 5000 "statistical murders" (the term used by Graham).[256]

There are more issues connected to stringent regulatory policies and associated radiophobia—an irrational fear of radiation hazards. At Chernobyl and Fukushima, compulsory relocation led to social destruction and caused significant psychosomatic problems and life shortening. To illustrate, during the first year after Fukushima, more than 1000 evacuation-related deaths (of nonradiogenic origin) were officially registered among the evacuated population.[261] Moreover, it has been noted that "Predictions of hypothetical cancer incidence and deaths . . . cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures" (p. 1).[127] It should also be mentioned that the present regulation and policies essentially preclude development of low-dose radiation therapies in medicine, even though animal studies have shown potential for treatment of some noncurable diseases—for example, Alzheimer disease.[262] One should also remember that after Chernobyl, there were more than 100 000 unnecessary abortions in Europe among women who received negligible doses of radiation.[263] Finally, radiophobia contributes to motivating radiological terrorism and promoting

nuclear proliferation, providing strong incentives to terrorists and rogue states.[259]

Conclusions

Today, the radiation safety regulations are based on the LNT model, that is, the assumption that carcinogenic risks are proportional to the radiation exposure for all radiation doses and dose rates. However, LNT has never been a subject of scientific consensus, and the most recent epidemiological and radiobiological evidence is anticipated to completely deprive LNT of its high status. There is a growing body of evidence that low-dose radiation, such as used in X-ray imaging including CT, actually promotes health rather than poses risk. In light of the new data, LNT is considered at least doubtful (and often—obsolete) by a growing number of researchers. And even if one assumes that LNT is correct, there are growing concerns that the present unreasonably stringent radiation protection regulation is, by far, not the best way to protect the public health. So policy makers have already enough points for consideration.

Although a lot of information has been gained regarding the biological effects of low-dose radiation, there are many important issues that require further research by scientists. Certainly, caution should be exercised when changing the current practices. However, bearing in mind the social, economic, and ethical aspects of the current LNT-based regulations, and taking into account their extremely high cost (both economic and human cost) for society, there is little doubt that the ionized radiation–related regulation should be reconsidered: The exposure limits should be raised and the regulatory burden be lightened.

Authors' Note

A.V. and Y.S. conceived the idea for the manuscript and produced the first draft. A.K. and O.Z. were involved in creating figures and tables and also in critical review. All authors read and approved the final manuscript.

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