# Late Health Effects of Ionizing Radiation: Bridging the Experimental and Epidemiologic Divide

Author(s): Elaine Ron and Peter Jacob
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# INTRODUCTION

# Late Health Effects of Ionizing Radiation: Bridging the Experimental and Epidemiologic Divide

Elaine Ron[a] and Peter Jacob[b,1]

[a] *Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, Maryland; and* [b] *Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Radiation Protection, Neuherberg, Germany*

Radiation sciences aim to characterize, quantify and understand the relationship between a disease and radiation exposure. In epidemiology, human data are used to assess risks from occupational, environmental/accidental and medical radiation exposures, whereas experimental studies on animals or cells provide data to help understand the mechanisms of radiation-associated disease. A conference entitled ''Late Health Effects of Ionizing Radiation: Bridging the Experimental and Epidemiologic Divide'' was held 4–6 May 2009 in Washington, DC to identify important gaps and controversies in radiation research and to stimulate more integrated research through interdisciplinary approaches. Invited speakers from the fields of radiobiology, dosimetry, epidemiology and biostatistics presented research findings on experimental and observational effects from low-dose and low-dose-rate radiation exposures, non-targeted radiobiological effects and how they influence models of carcinogenesis, and radiation-related cancer and non-cancer diseases. This volume of *Radiation Research* includes 11 papers based on conference presentations that explore recent advances in our understanding of the late health effects of ionizing radiation. The papers cover results from cellular, animal and epidemiological studies as well as implications for radiation protection.

More than 100 years ago, scientists discovered that radiation exposure can lead to cancer, with the earliest observations being of radiation-related leukemia and skin cancer. After the atomic bombings of Hiroshima and Nagasaki, interest in radiation-related health effects increased and radiation research progressed rapidly. Since then, we have learned much about the mechanisms of radiation carcinogenesis and substantially improved the precision of estimates of radiation risk. Of particular relevance is the Life Span Study (LSS) cohort of about 100,000 atomic bomb survivors who have been followed for over five decades. This cohort has yielded substantial information regarding radiation carcinogenesis and more recently non-neoplastic diseases. Years of studying patients treated with radiation for benign or malignant diseases has also led to new observations on the relationship between radiation and a host of adverse health outcomes including cancer, cardiovascular diseases, growth and developmental disorders, mental impairment, obesity, thyroid dysfunction, and cataracts. By conducting large, well-designed collaborative studies of radiation workers, cancer and other diseases have been linked to low-dose and low-dose-rate protracted exposures. Experimental work to explain the causal mechanisms for the epidemiological findings has flourished over the last few decades.

The relationship between ionizing radiation and cancer has been the focal point of epidemiological and experimental research for a long time, and most of this research concerned moderate- to high-dose whole-body exposure, e.g. the atomic bomb survivors, or partial-body exposure from radiotherapy. However, because low-dose and protracted exposures are more relevant for radiation protection for the general public, research has been shifting toward studies of occupational cohorts and persons exposed to environmental radiation or multiple diagnostic X-ray examinations. Quantifying risks from protracted occupational exposures has assumed new significance because of the need to reassess the appropriate dose and dose-rate effectiveness factor (DDREF) to be used for radiation protection. In the most recent ICRP radiation protection guidelines (*1*) a DDREF of 2 was used, whereas a DDREF of 1.5 was used in the NAS BEIR VII report (*2*). The determination of the DDREF values was mainly based on radiobiological studies with cell cultures and animals and data from the LSS. It remains an open question whether risk estimates from the LSS are applicable to occupational or medical exposures

[1] Address for correspondence: Helmholtz Zentrum München, Institute of Radiation Protection, Ingolstädter Landstrasse 1, Neuherberg, Bayern 85764, Germany; e-mail: jacob@helmholtz-muenchen.de.

in populations that did not experience the devastating conditions at the time of the atomic bombings and have different lifestyles and genetic backgrounds. Information derived from direct comparisons of risks observed in populations exposed to occupational or medical radiation and the LSS is becoming increasingly relevant with the ongoing improvement of low-dose-rate epidemiological studies. In an analysis of cancer risks in nine radiation worker populations compared to subsets of the atomic bomb survivors with similar age and gender distributions, the risks for protracted occupational exposures were not lower than those for the acute exposure experienced by the atomic bomb survivors (*3*). Advances in exposure assessment and other aspects of epidemiological research have furthered our ability to study low-dose and low-dose-rate radiation exposures. In this volume, Linet *et al.* (*4*) discuss radiation-associated cancer risks among medical workers exposed to low-dose radiation, often delivered over several decades, and call attention to the need for additional dosimetric and epidemiological studies. They point out that while radiation exposure to most radiation workers has been reduced substantially over time, this trend may not hold true for doses to physicians carrying out fluoroscopically guided procedures because these procedures involve large radiation doses and the physicians remain in the room while they are performed.

It is estimated that about 70 million CT scans are performed annually the U.S. (*5*). Thus the proper use of these examinations is a particularly important issue for radiation protection of the general population. Brenner (*6*) focuses on the low but not insignificant estimated cancer risks from computed tomography and how the use of these examinations can be reduced without sacrificing good medical care. In his paper, he discusses the three main ways to lower the population dose from CT examinations.

Since cells in different organs and tissues divide at different rates, it would be expected that organs would vary in their radiation sensitivity and therefore in their radiation-related cancer risks. While epidemiological studies often provide organ or site-specific risk estimates, they are usually based on a relatively small number of excess cases and therefore are quite imprecise, yet few studies have assessed the differences in these risks to determine whether they are real or whether they are the result of statistical variability. On statistical grounds it can be assumed that the distribution of the estimated organ-specific risk values is wider than that of the true values. Pawel *et al.* (*7*) suggested a method to adjust correspondingly the individual organ-specific risk estimates using empirical Bayesian methods. In this issue, Preston *et al.* (*8*) evaluated the variability in the site-specific risk estimates for the Mayak cohort of nuclear workers and the Techa River cohort of people who were exposed to radiation from the radionuclides contaminating the Techa River. Using maximum likelihood methods to compute site-specific excess relative risks, they found that the variability was extremely and probably unrealistically large. Applying empirical and hierarchical Bayesian methods to adjust the risk estimates for the statistical fluctuations reduced the variability among the individual cancer sites. This work outlines methodologies to estimate organ-specific risks more precisely. It can be expected that future work in this field will include the derivation of improved *a priori* distributions of the risk estimates.

Radiation sensitivity and carcinogenesis was another focus of the conference. Jeggo (*9*) gave an overview on the role of DNA repair proteins in maintaining genomic stability in response to double-strand break formation. A rare class of individuals with severe mutations in the double-strand break repair proteins displays genetic predisposition to the harmful effects of low-dose exposure. The author also describes how persons with mild defects in DNA damage response mechanisms could exhibit radiosensitivity at low and moderate doses ($<$500 mGy). In particular, individuals with mutations in the double-strand break-DNA damage response proteins may not adequately maintain genomic stability after exposure to low-dose radiation, making them more prone to radiation-induced cancer.

An area of radiation-related cancer research that is becoming more prominent is the role of stem cells and tissue turnover. Niwa (*10*) discusses how the concept of permanent stem cell residence in a tissue has changed so that today it is thought that stem cells, like progenitor cells, can be eliminated over time. Thus the loss of radiation-initiated stem cells over time could reduce the risk of developing radiation-related cancer years after exposure and can help explain the time since exposure-related declining excess relative risk observed in irradiated populations.

The mounting interest in non-cancer effects from radiation exposure was reflected at the conference, and several papers report on the relationship between radiation exposure and the development of subsequent deleterious health outcomes other than cancer. During the last few decades, evidence has been building that high-dose radiotherapy can cause damage to the cardiovascular and cerebrovascular systems, but more recently it has become apparent that low to moderate doses of radiation also increase the risk of cardio- and cerebrovascular damage.

Evidence of elevated risks of radiation-associated cardiovascular diseases comes from studies of cancer survivors (*11–13*), atomic bomb survivors (*14, 15*), and nuclear (*16, 17*) and medical radiation workers (*18*). In this volume, Azizova and colleagues (*19*) extend what is known about the relationship between radiation exposure and cerebrovascular diseases. They report a significant dose–response trend for cerebrovascular

disease incidence, but not mortality, among 12,000 nuclear workers who were employed by the Mayak nuclear facility in the Russian Federation. These workers were exposed to external $\gamma$ radiation and/or internal plutonium, and dose–response trends were demonstrated for both types of exposure. The reason for the different results for the incidence and mortality data is not clear but might be due to the greater statistical power for the incidence analyses because of the substantially larger number of cases. Stewart *et al.* (*20*) review the underlying mechanisms for the epidemiological findings. They note that at high doses, such as those used to treat cancer, radiation causes inflammatory changes in the microvasulature that lead to myocardial damage. Since the myocardium is made up of cells that have limited regenerative capacity, this damage can result in excessive myocardial cell death and fibrosis. Inflammatory processes are also implicated in radiation-related stroke.

Studies of atomic bomb survivors, who were exposed to doses considerably lower than those received by cancer patients, indicate that radiation can impair the immune system as demonstrated by a clear link between radiation dose and the observed decades-long damage in T-cell function (*21*). In this volume, Kusinoki *et al.* (*22*) show that radiation-related reduced T-cell-mediated immunity causes enhanced inflammatory responses, which in turn results in cardiovascular disease and other age-related diseases. They suggest that additional research on possible interactions between radiation-related and age-related immunological changes may help explain the life-long elevated risk for several non-cancer diseases observed in irradiated populations.

With almost 80% of childhood cancer patients now surviving 5 years or more, the late health consequences of their treatment are becoming more of a concern. Investigators from the Childhood Cancer Survivor Study (CCSS) of over 10,000 patients and 3,000 sibling comparison subjects have published numerous papers on the dose–response relationship between radiotherapy and subsequent cancers (summarized by Armstrong *et al.* in this volume), but this study also provides important information on the long-term non-cancer health effects of radiotherapy and chemotherapy. In a clinically examined subset of the study, Armstrong *et al.* (*11*) note that survivors are at higher risk of obesity after high cranial radiation doses ($>$20 Gy) than their nonirradiated siblings. They also report that radiation exposure to the chest increases the risk of lung fibrosis and other indications of pulmonary damage and that treatment with high-dose radiation is associated with an overall increase in developing a variety of subsequent chronic medical conditions, many of them life-threatening, compared to sibling comparison subjects. Head and neck irradiation was associated not only with thyroid nodules and hypothyroidism but, among a small group of patients, hyperthyroidism was also related to their radiation treatment.

The association between head and neck irradiation and benign thyroid diseases in many different populations was described by Ron and Brenner (*23*). They found compelling evidence for a long-lasting linear dose response for benign nodules at low to moderate doses. Studies of persons exposed to radioactive iodine from the Chernobyl accident have added to our limited knowledge regarding functional thyroid diseases and autoimmune disorders; however, taken in the aggregate, results were not always in agreement. The authors suggested that the inconsistent findings may be related to the greater difficulties in studying these diseases in epidemiological investigations.

Shore *et al.* (*24*) demonstrate that current thinking regarding radiation-related cataracts needs to be revised to incorporate recent findings from several different irradiated populations indicating that lens opacities occur after radiation doses of less than 1 Gy, a dose substantially lower than previously thought. These data clearly signify the need to reassess current radiation protection guidelines, which are based on assuming a threshold at much higher doses.

Radiation protection recommendations come primarily from epidemiological studies, with the Life Span Study of atomic bomb survivors being the main data source. Epidemiological data are essential since only they are completely relevant to human beings exposed to radiation under actual conditions. Yet inconsistencies among studies exist and questions remain including how to transfer risk estimates from population to population and from one radiation source or type to another, what the health effects are at low doses, whether there are radiation-sensitive subgroups and if so how to identify them, how age and gender influence radiation effects, and how organs and tissues differ in terms of radiosensitivity. To answer some of these questions, the underlying mechanisms of radiation-induced cancer and other diseases or effects need to be better understood. The conference on ''Late Health Effects of Ionizing Radiation: Bridging the Experimental and Epidemiological Divide'' was held to help bring the many disciplines in radiation research together to search for integrated ways to address these complex problems. While the conference did not provide immediate answers, it encouraged communication and future collaborations.

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