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# COMMENTARY

# Evolving Strategies in Epidemiologic Research on Radiation and Cancer

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## INTRODUCTION

With the emergence of new imaging technologies and expanded access to large administrative databases and biospecimen banks, research teams of radiation epidemiologists, dosimetrists, statisticians and related scientists are adapting their use of fundamental research strategies for studying radiation and cancer. Five broad strategies have yielded numerous critical insights in the last three decades: assessing risks from environmental radiation releases; projecting radiation risks; following patients who have had radiotherapy; estimating organ doses with more sophisticated phantom models; and focusing on genetically susceptible individuals. We consider these five approaches in turn and discuss how findings might provide insight into biological mechanisms and translate into clinical benefit and improved public health.

## RADIATION RISK PROJECTION MODELING

Risk projection modeling makes use of the wealth of existing information on the long-term cancer risks after radiation exposure to project potential risks from specified exposure scenarios. Modeling allows for the timely estimation of risks and is particularly useful for low-dose scenarios because an infeasibly large sample size would be required to study these risks directly (*1*). It is not a new strategy; one of the earliest examples of its use was in the 1962 U.S. Federal Council Report on the health implications of exposure to fallout from above-ground nuclear testing. The committee estimated that there could be 0–2000 additional leukemia deaths in the U.S. as a result of these exposures (*2*). In recent years, however, risk projection modeling has moved from a rare to a ubiquitous strategy in radiation epidemiology. The reasons include the publication of user-friendly risk estimates for the U.S. population in the BEIR VII report and the increasing acceptance of the limitations of epidemiological studies for elucidating risks from low-dose exposures directly. Applications of the approach vary widely; examples include estimation of the proportion of childhood leukemias attributable to background radiation exposure (*3*), the number of future cancers related to CT scans in the U.S. (*4*), and the risks to European countries from the Chernobyl accident (*5*).

The risk models used in these calculations rely most heavily upon the results from the Life Span Study of the Japanese atomic bomb survivors (*6*) because this is one of the few studies that can provide organ-specific risk models that account for age at exposure, time since exposure and sex. Breast and thyroid cancer risk models are the exception because they can make use of the pooled data from medically exposed populations (*7, 8*). Additional pooled models for other cancer sites will help to improve the modeling, for example, the planned pooling of a number of studies of brain cancer after radiation exposure. Further research into the joint effect of radiation and other cancer risk factors (e.g., smoking) could also improve the models by helping us understand how to transfer risk models from the Japanese atomic bomb survivors to the exposed population of interest, which typically has different ''underlying'' cancer rates. Because risk projection involves a large number of assumptions, we need to calculate the range of potential estimates under varying assumptions. Researchers at NCI and SENES Oak Ridge have developed an interactive risk calculator that formally incorporates and quantifies subjective uncertainties in the assumptions as well as statistical uncertainties in the model parameters. A web-based version of the software NCI RadRAT (Radiation Risk Assessment Tool) will be made publicly available later in 2011 (Fig. 1).

## HYBRID COMPUTATIONAL PHANTOMS FOR RADIATION EXPOSURE RISK ASSESSMENT

Radiation dosimetry is a central component of radiation risk assessment. Organ- or tissue-specific estimated doses and associated uncertainties from large numbers of exposed individuals are essential for epidemiological studies of non-

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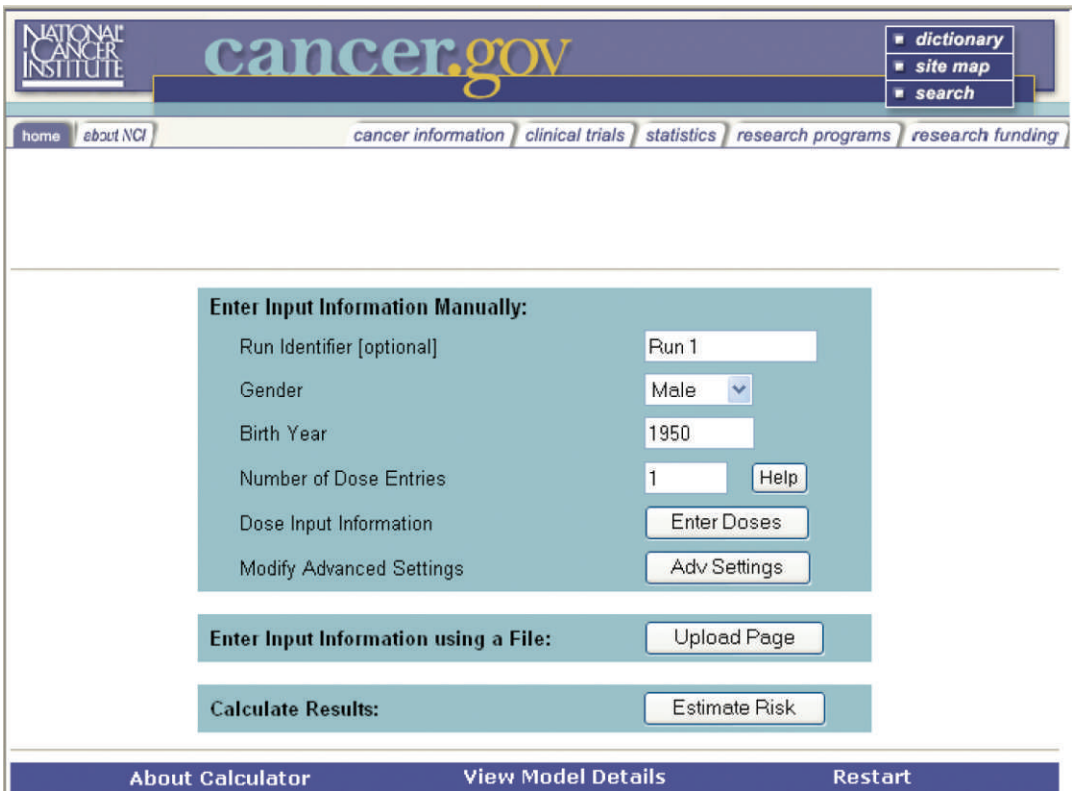


**FIG. 1.** Radiation risk assessment tool.

uniform radiation exposure and provide the critical data required for modeling radiation dose response. There are two ways to determine organ doses in radiation exposure: measurement and calculation. Measurement consists of placing dosimeters in a physical phantom that represents a patient's body and then reading the dosimeters after irradiation under specified conditions. However, measurement can be very expensive, may require substantial man-hours of effort, and is not flexible because of the need for repeated irradiations under a wide range of conditions. By contrast, computer models of the human body, called computational human phantoms, and of radiation sources can be used to simulate the conditions of irradiation. Compared to measurement, calculation is cost-effective, requires fewer man-hours, and is much more flexible. Therefore, the estimations of organ dose rely heavily on the computer simulations in which computational human phantoms are used in combination with Monte Carlo radiation transport techniques.

The last 50 years have seen little change in the Monte Carlo transport algorithms, but the capacity and speed of the computation resources have undergone significant changes and notable expansion, and substantial improvements have been made in the computational human phantoms (Fig. 2). Computational phantoms have evolved from the 1950s when simple phantoms such as spheres, cylinders or their combinations were used. Stylized phantoms represented by simple mathematical surface equations were introduced in the 1960s to describe human anatomy more realistically (*9*). Improved anatomical realism was achieved in the 1980s by voxel phantoms that were developed from the tomographic images from patients (*10*). Over time, the early crude general dosimetry, based on stylized phantoms, became more refined and dosimetry became more individualized. Despite the improved anatomical realism of voxel phantoms, the stylized phantom continues to be the basis of current dosimetry employed in epidemiological studies of medical exposures because a complete series of reference pediatric and adult voxel phantoms have not been available.

Recently, a new class of computational phantoms, hybrid phantoms, has been developed to take advantage of the mathematical flexibility and anatomical realism from both the stylized and voxel phantoms (*11–13*). Using a new mathematical format designated the Non-Uniform Rational B-Spline (NURBS), hybrid phantoms provide a high level of flexibility for modeling different body postures and sizes (Fig. 2). The hybrid phantoms also have more sophisticated anatomy (e.g., a detailed skeleton model) than the previous stylized and voxel phantoms. Hybrid phantoms have resolved several significant problems and provide more individualized organ dose estimations for persons of different ages and body dimensions (e.g., obese and thin individuals) and more accurate bone marrow dosimetry based on realistic skeleton models. The flexibility of the

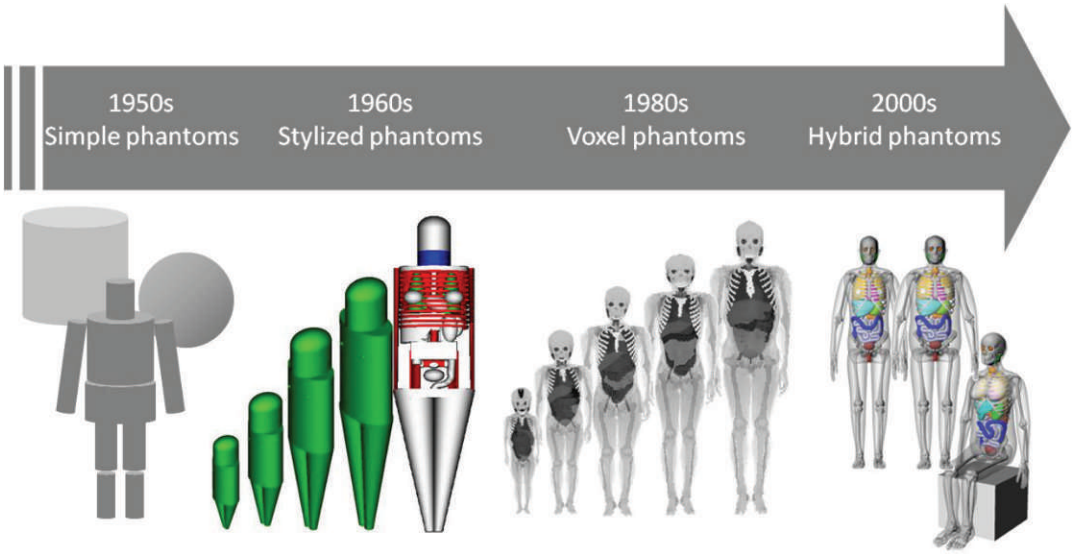


**FIG. 2.** Evolution of phantoms.

hybrid phantoms, coupled with Monte Carlo transport technique, will provide more accurate dose estimates and improved characterization of uncertainty in those estimates. The greater accuracy in dose estimates should result in improved risk estimation in epidemiological studies, with estimates for uncertainty incorporated within the risk analysis.

## INTENTIONAL AND ACCIDENTAL RELEASES OF RADIATION

The Life Span Study of Japanese atomic bomb survivors has taught us much of what we know about long-term risks from radiation exposures, especially at high dose rates. As of 2000, 45% of the cohort was alive. The number of deaths related to radiation in the survivors is estimated to peak around 2020. Ongoing follow-up and detailed risk assessment of the atomic bomb survivors will continue to add to knowledge about temporal patterns of radiation risk, organ-site-specific radiation risks, and interactions with non-radiation risk factors including smoking and other factors.

By following residents of the Techa River watershed who were exposed to releases of radionuclides from the Mayak nuclear facility, investigators are gleaning valuable information on the effects of radiation exposures that occurred at a low dose rate. Controversy remains with respect to how the same total dose affects radiation-related cancer risk at lower dose rates, and cohorts like the Techa River cohort provide the critically needed data.

The Chernobyl accident 25 years ago also provides extensive data on the effects of low-dose-rate exposure from radioactive fallout, including exposure to $^{131}$I. In a recent cohort study of Ukrainian residents who were exposed as children or adolescents (*14*). NCI researches found evidence of a strong, linear dose response for thyroid cancer risk using individual $^{131}$I dose estimates (Fig. 3). The persisting elevation of thyroid cancer risk in this population underscores the need to continue to follow these individuals to assess whether the excess risk persists or declines with time. A case-control study of leukemia among clean-up workers who, unlike residents, received primarily whole-body protracted external radiation found a significant increase in risk of total leukemia with evidence of an increase in leukemias other than chronic lymphocytic leukemia and in chronic lymphocytic leukemia (*15*).

In short, we can use new dose estimation and new statistical techniques, but we need to continue tracking populations exposed to intentional or accidental releases of radiation, because such populations provide direct human data on exposure to radionuclides such as $^{131}$I and the impact of dose-fractionation effects. Continued follow-up will improve the precision of radiation risk estimates and effect modifiers of radiation exposure. Pooled analyses combining data from several studies provide more precise risk estimates associated with different types of radiation, particularly for specific organ sites.

## THERAPEUTIC RADIOTHERAPY AND CANCER RISK

Quantifying the contribution of radiotherapy to the risk of developing cancer not only provides vital information for patients who undergo such therapy and their physicians but also advances our understanding of the fundamental mechanisms of radiation carcinogenesis. Patients who receive therapeutic irradiation for various benign and malignant conditions experience a range of ionizing radiation exposures outside the treatment area due to scatter. The study of these exposures provides important insight into radiation-related carcinogenesis at radiation doses that often

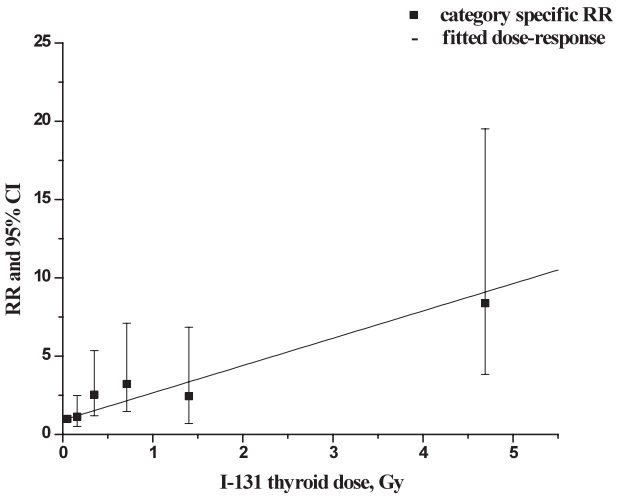


**FIG. 3.** Dose–response relationship between incident thyroid cancers and $^{131}$I dose estimates: A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident in Ukraine. The solid line represents fitted relative risks (RR) based on the linear ERR model and the squares with vertical lines represent category specific RRs with 95% confidence intervals for mean $^{131}$I dose per category. The fitted linear dose response was adjusted to pass through the lowest $^{131}$I category. The ERR was adjusted for gender, oblast of residence at first screening examination, and continuous attained age.

are substantially higher than those in other settings (1–>40 Gy) but delivered in small fractions. Direct evaluation of the radiation dose–response relationship at these higher doses has proven critical, because a non-linear relationship has been shown to most accurately describe the data in this dose range (e.g., 1–>40 Gy) for certain malignancies, such as leukemia and thyroid cancer (*16*, *17*). In addition, second cancers are a leading cause of morbidity and mortality among the nearly 12 million cancer survivors in the United States (*18*), yet data on the etiology of second cancers are sparse.

Measurement of cancer risks from radiotherapy has faced major challenges. To date, most studies of second cancers have been descriptive, often relying on data from population-based cancer registries. These studies have provided important evidence that cancer survivors typically have a higher risk of subsequent malignancy than the general population (*19*). However, because most descriptive studies are characterized by limited or no information on radiotherapy exposures, other treatments, or other cancer risk factors, their primary utility lies in identification of groups of cancer survivors at increased second cancer risk and generation of hypotheses that direct the development of specific analytic studies (*20–22*).

Medical record-based analytic studies overcome some of the limits of registry studies, and they have provided critical insights into the late effects of radiotherapy and chemotherapy. Although initial studies focused primarily on the most common radiation-induced malignancies (e.g., leukemia and cancers of the thyroid, breast and brain), recent efforts have quantified the radiation dose–response relationship at higher doses for other cancer sites such as the lung (*23–29*). These studies also have provided key information on potential modifiers of radiation-related risks, such as age at exposure and cigarette smoking. Most analyses have found that the risks are lower than those observed after the single acute exposure in the Japanese atomic bomb survivors, though there is some suggestion that the joint effects of radiation and some other factors (e.g., cigarette smoking) (*29, 30*) on subsequent cancer risk may differ for radiotherapy compared with lower-dose radiation exposures.

Data on other (non-treatment) cancer risk factors are far too sparse in medical record-based studies, yet we know that most second cancers result from genetic, lifestyle and environmental risk factors, as shown in a recent study estimating that fewer than 10% of second solid cancers are due to radiotherapy in adulthood (*30*). Emerging studies therefore need to focus simultaneously on the multiple contributors to second cancers and the potential interactions among them. Richer data from electronic medical records and interconnected sources on well-defined populations should provide the information needed to elucidate the causes of second cancers and the long-term effects of high-dose fractionated radiation exposure.

## GENETIC SUSCEPTIBILITY TO RADIATION

Some individuals may be more genetically susceptible to the effects of radiation than others, as seen in populations with certain rare hereditary disorders, such as ataxia telangiectasia. The known genetic variants associated with these cancer susceptibility syndromes affect a very small proportion of the general population. On the other hand, multiple genetic pathways have been implicated in studies of radiosensitivity (including DNA damage repair, radiation fibrogenesis, oxidative stress and endothelial cell damage) (*31*), so it is likely that some of the contribution to radiation susceptibility is polygenic, with elevated risk resulting from the inheritance of several low-penetrance risk alleles (the ''common-variant-common-disease'' model).

The few studies to date examining common genetic variants associated with risk of radiation-induced cancer have mainly employed the ''candidate-gene'' approach to examine whether single nucleotide polymorphisms (SNPs) affect risk. This method assumes prior knowledge of one or more functional SNPs. A series of nested case-control studies of breast cancer in U.S. radiologic technologists, for example, has suggested that common variants in genes involved in DNA damage repair (*32, 33*), apoptosis (*34*) and proliferation (*35*) may alter the risk of radiation-related breast cancer from diagnostic radiation procedures. However, none of these results have been convincingly replicated to date. This is not surprising given the challenges facing gene-radiation interaction studies. For one, sample sizes need to

be sufficiently large to detect interaction, particularly in the context of low-level radiation exposure. Additionally, high-quality exposure assessment for both radiation and potential confounding factors (such as chemotherapy) is essential to reduce misclassification. Finally, the complexity of the underlying biology makes it exceedingly difficult to identify true causal variants through the candidate gene method. The ''genome-wide association study'' (GWAS), which uses genetic markers (tag-SNPs) across the genome to identify regions of interest, is a more agnostic approach that has been successful in identifying novel cancer susceptibility regions for several cancer sites, and it may be informative in the context of radiation sensitivity.

Identifying genetically high-risk individuals to reduce radiation exposure to these individuals when possible remains a very pertinent research strategy. However, ascertaining this variation is not straightforward. It is essential that studies addressing this question have large sample sizes and high-quality exposure information, with sufficient power to adequately address variation in demographic and treatment factors. With the rapid advancement of technology to query the genome, studies of radiation-associated genetic susceptibility must carefully assess the available technologies and choose the technology appropriate for the specific study question(s) being asked.

## CONCLUSION

We see ahead a continuing expansion of radiation exposure to the population from medical tests and treatments. Recent events in Japan also remind us that future nuclear accidents are a real threat. Cancer epidemiologists must respond by developing and adapting a variety of flexible research strategies. The most useful of these strategies fall into two broad frameworks. The first employs statistical modeling, both of the doses received and the cancer risks incurred, using the data we have accumulated from past studies. Risk projection, computational phantoms and newly discovered genetic susceptibility will play increasingly prominent roles. The complementary framework is field studies: directly measuring doses and cancer occurrence in groups who have been exposed, some from new treatment techniques, some from nuclear reactor accidents, and some from other sources. Both the modeling and the measuring approaches will engage a variety of scientific disciplines, and the ongoing comparison of the results of each will help direct the field and generate new research strategies.

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