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Radiation Epidemiology: Old and New Challenges

by Roy E. Shore*

Over the last 40 years the amount of knowledge about human radiation effects has increased dramatically. During that interval, radiation epidemiologists have documented a number of additional types of radiation-induced cancer and have established rough estimates of the magnitude of cancer risks. Nevertheless, we currently have inadequate knowledge about a number of factors that help define the magnitude of radiation risks. These include questions of estimating risk over the lifetime, shapes of the dose-effect curves, magnitude of risks at low doses, potentiation between radiation and other agents, and the nature and role of host susceptibility factors. Data from various studies are used to illustrate these questions.

In the four decades since the New York University Institute of Environmental Medicine was founded, the knowledge base of radiation epidemiology has expanded greatly. Forty years ago there were indications that radiation caused bone cancer, leukemia, and lung cancer. That it also caused breast cancer, thyroid cancer, stomach and colon cancer, multiple myeloma, and many other types of cancer was yet to be learned. Thus, for several decades radiation epidemiology consisted mainly of finding new cancer sites for which radiation was a causal agent and making gross estimates of the amount of cancer induction at those cancer sites based on populations with high levels of radiation exposure. The data came chiefly from the Japanese atomic bomb study, series of patients who had had radiation treatment for a variety of medical conditions, and workers in mines with high radon levels.

The NYU Institute of Environmental Medicine began to play a role in radiation epidemiology about 25 years ago. A study of patients treated with X-rays for ringworm of the scalp during childhood was begun and has continued with intermittent follow-ups to the present. At that time there was some indication from case reports and clinical series (*1*) that large doses of X-rays to the thyroid gland caused thyroid cancer, but this study was among the first to show that low doses of radiation also caused thyroid tumors and that brain tumors were caused by radiation (*2,3*). Perhaps the most important contribution of the study was to bring data to the attention of the radiation protection community indicating that skin cancers could be caused by low to moderate doses of X-rays. It had previously been thought that large doses on the order of 1000 rem or more were required to produce skin cancer risk. This study showed that 300 to 600 rem to the scalp and 50 to 250 rem to the face and neck produced a striking increase in basal cell carcinomas (Fig. 1).

While the principal target organs for radiation carcinogenesis are now defined reasonably well, radiation epidemiologists face a number of new challenging questions. What is the temporal pattern of cancer induction, so as to estimate lifetime risk? What are the shapes of

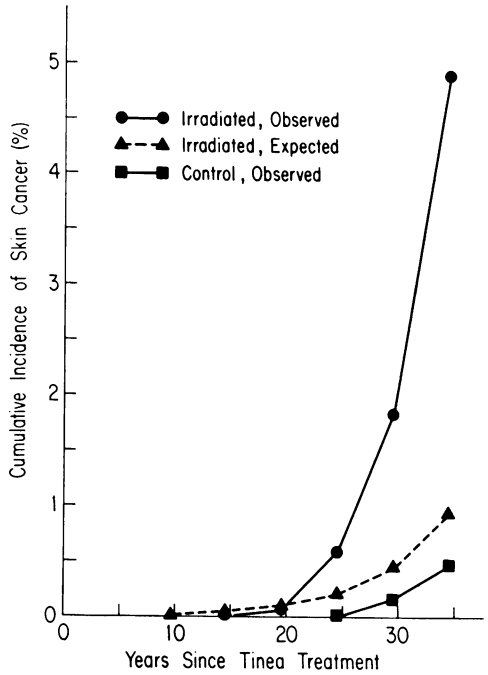

FIGURE 1. Cumulative incidence of skin cancer by years since treatment for ringworm of the scalp (*Tinea capitis*) for X-irradiated and nonirradiated patients.

*Institute of Environmental Medicine, New York University Medical Center, 550 First Avenue, New York, NY 10016.

dose-response curves for tumor induction in various organs, and what are the magnitudes of the effects at low doses? Are there other environmental exposures that potentiate or inhibit radiation effects? Are there important host-susceptibility factors and, if so, what are they? Data from our epidemiologic studies and others will be used to illustrate these questions.

Probably the easiest thing to learn about the temporal pattern of radiogenic cancer risk is the length of the minimum induction period. It is well documented for leukemia that the minimum period is roughly 2 years, whereas for most solid tumors it takes 10 or more years before any appreciable excess risk is observed (*4*). In our study of children X-irradiated for ringworm of the scalp, a long minimum period of over 20 years was seen for skin cancer induction (Fig. 1). A likely explanation for the long period may be that excess cancers do not begin to appear until the ages at which spontaneous cancers also become common at the same site—in the case of skin cancer during their 30s. Another finding illustrates this point. In our study of women given X-ray therapy for acute postpartum mastitis, mainly at ages 20 to 35, excess breast cancers began to appear 10 to 15 years after irradiation (*5*). However, among women who had been given irradiation during infancy for alleged enlarged thymus glands, excess breast cancers did not occur until over 30 years after irradiation (*6*).

A second question about the temporal patterns of risk pertains to the persistence of risk over the lifetime. Although statistical models are a useful aid in estimating lifetime risks, the only sure way to determine them is by observing irradiated groups for long periods of time. At present, the follow-up periods of major studies have not been long enough to define the lifetime risks associated with some of the prime cancer sites such as the breast, thyroid, and gastrointestinal tract. The risk of leukemia is largely defined, because leukemias appear in a wave that tapers off to virtually background levels by about 30 years postirradiation (although the length, height, and timing of the wave of leukemia are somewhat dependent on type of leukemia and age at irradiation) (*7*).

For solid tumors, one of the main questions in defining lifetime risks is whether radiation multiplies the natural age-specific risks (multiplicative risk model), or, instead, adds a constant increment of risk at all ages (absolute excess risk model). The multiplicative risk model predicts several times as much lifetime risk as the absolute excess model when the current estimates of cancer risks are projected out for the remaining lifetime, since most background cancer rates rise steeply with age and a multiplier therefore predicts larger and larger risks as people grow older.

Analyses of the Japanese A-bomb data have suggested that for a number of cancer sites such as breast cancer, the multiplicative risk model provides a better fit to the data than the absolute excess risk model (*8,9*). In contrast to those findings, several studies of radon exposure and lung cancer among miners have recently reported that a multiplicative risk for lung cancer tapers off at older ages (and/or after exposure ceases; the two factors are difficult to disentangle) (*10–12*). In our study of thymus-irradiated children, the temporal pattern of thyroid cancer risk fit an absolute excess risk model but not a multiplicative model (*13*). Thus, there does not seem to be any one temporal pattern of risk that will apply to all types of cancer induced by ionizing radiation.

A central question is whether small doses and/or several small dose fractions yield as much tumor risk per unit dose as do larger, acute exposures for low LET (Linear Energy Transfer) radiations such as X-rays or gamma rays. Many radiobiological studies suggest that the effect is smaller (per unit dose) for small exposures (*14*). However, our studies of breast cancer in women irradiated for acute postpartum mastitis showed a linear dose-response curve, until it bent over at the highest doses. Most of the other data available for radiogenic breast cancer support a linear dose-response curve as well (*8*), although one study appears to be an exception to this (*15*). Our study of infants irradiated for enlarged thymus glands showed essentially a linear dose-responsive curve for thyroid cancer (Fig. 2) (*13*). The other dose-response data available for thyroid cancer, primarily the Japanese A-bomb study, also support a linear relationship (*16*).

One concern in the radiation protection community is the possibility that radiation effects may be potentiated by exposure to other environmental carcinogenic cofactors. Several such potentiations have been shown experimentally (*17*). However, there are few human data on the subject. The best studied is the interaction of smoking and radiation exposure with respect to lung cancer

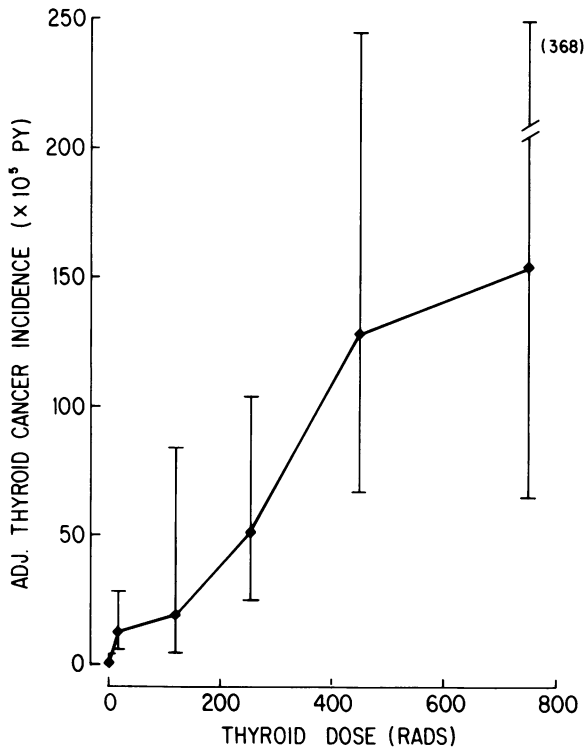

FIGURE 2. Thyroid cancer incidence in relation to X-ray dose in a population given thymic irradiation in infancy and sibling controls.

risk. Some, but not all, studies have found evidence for potentiation by smoking (*11,12,18,19*).

In searching for potentiating factors in the postpartum mastitis study, we evaluated whether breast cancer risk from radiation was potentiated by exogenous estrogens, but found no evidence for it (*20*). In our scalp ringworm study, a large excess of skin cancers was found in the irradiated group as compared with a control group who received only topical medications for the disease, indicating a clear effect due to ionizing radiation. But the data suggested that ultraviolet radiation was an important cofactor with the X-radiation in producing skin cancers. The distribution of skin cancers on the head indicated a radiogenic effect that was four times as large (per cm^2 of skin area per rem) on the sun-exposed face and neck as on the hair-covered scalp (Fig. 3).

For purposes of radiation protection or of targeted screening of high risk individuals, it is important to identify host susceptibility factors. If certain identifiable subgroups are at unusual cancer risk following radiation exposure, then the exposures to them should be minimized or care taken to monitor them closely for early signs of disease.

With regard to radiogenic breast cancer, we have found two suggestions of subgroups with elevated risk. Women in the postpartum mastitis study received radiation treatment for breast infections/inflammation associated with childbirth or lactation. Even after controlling for age at treatment, women who were irradiated around the time of their first childbirth subsequently had a greater excess risk (per rem) of breast cancer than women who were irradiated at the second or later pregnancies. The findings from other epidemiological studies indicate that the age at first childbirth is an important risk-modifying factor for breast cancer. Thus, our finding complements the other findings in indicating that the first childbirth is somehow biologically important in defining breast cancer risk. The study also showed that irradiated women who developed benign breast disease (usually subsequent to the radiation treatment) were at very high risk for breast cancer. This suggests they should be carefully monitored for incipient breast cancers.

As another example, in the scalp ringworm X-ray study, sensitivity to ultraviolet exposure appears to be an important susceptibility factor for radiation-induced skin cancer, for no skin cancers were seen among the 25% of the irradiated group who were black. Furthermore, questionnaire information on complexion factors showed that light-skinned persons who freckle or sunburn easily had the greatest excess of radiation-induced skin cancer.

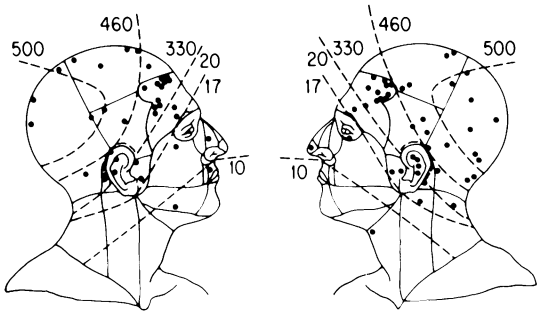

FIGURE 3. Locations of skin cancers and skin doses in rads among patients given X-ray therapy for ringworm of the scalp (*Tinea capitis*).

The last 40 years of radiation epidemiology have provided a strong base of fundamental information about radiation risks, but many interesting and challenging questions remain. It is to be hoped that in the next 40 years we will be able to apply the principles and techniques of cancer biology and radiobiology to produce or confirm new biological insights. The wedding of biochemical and molecular approaches to field studies may help define groups who are at very high risk of radiation-induced cancer and will no doubt increase our understanding of human cancer.

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