Epidemiologic Studies of Ionizing Radiation and Cancer: Past Successes and Future Challenges

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The health effects of radiation have been a focus for research since early in the 20th century. As the century ends, extensive experimental and epidemiologic evidence has been accumulated that addresses the adverse consequences of radiation exposure; epidemiologic studies of radiation-exposed groups from the general population and specific occupational groups provide quantitative estimates of the cancer risks associated with exposure. This report provides a perspective on the extensive epidemiologic evidence on the health effects of ionizing radiation and on likely needs for further epidemiologic research on radiation and health. Epidemiologic studies have proved informative on the quantitative risks of radiation-caused cancer but we now face the challenges of more precisely characterizing risks at lower levels of exposure and also of assessing modifiers of the risks, including dose rate, genetic susceptibility, and other environmental exposures. This report considers investigative approaches, such as pooled analysis of multiple data sets, that can be used to address these complex questions and the limitations of these approaches for addressing societal concerns about the risks of radiation exposure. — *Environ Health Perspect* 105(Suppl 4):883–889 (1997)

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Introduction

One hundred years have now elapsed since Roentgen's 1895 discovery of X-rays. In the ensuing years, radiation has become widely used for medical, industrial, and other purposes. The world's population has been exposed to radiation through its medical uses and by radiation-emitting products, employment in industries using radiation, accidents, and nuclear weapons. Moreover, it has been learned that most of the dose received by the general population comes from natural and not man-made sources (*1,2*). These natural sources include cosmic rays, terrestrial radiation, and internally deposited radionuclides (Table 1). Radon, the sixth decay product of uranium-238, is the largest contributor to population dose. Radon is ubiquitous in indoor environments, which it enters from the soil; its short-lived progeny includes two alpha-emitters, polonium-218 and polonium-214, which internally irradiate the lung when inhaled. Estimates of total radiation exposure for the United States (Table 1) show that radon contributes over half of the estimated effective dose, and man-made sources contribute less than 20% (*1*). Although sufficient data are not available for making similar estimates on a worldwide basis, the conclusions in the 1988 and 1993 reports of the United Nations Scientific Committees on the Effects of Atomic Radiation (UNSCEAR) (*2,3*) on the worldwide balance between exposure from natural and man-made sources were similar to that for the United States.

The health effects of radiation have been a focus for research since early in the 20th century. Radiation burns and radiation sickness were quickly recognized as early operators of X-ray machines suffered the consequences of high levels of exposure (*4*). The problem of radiation-caused skin cancers was also soon noted. By mid-century, the potential for external irradiation and internally deposited radionuclides to cause cancer at other sites was documented through the unfortunate experiences of the underground miners in Schneeberg and Joachimsthal in Central Europe, the radium dial painters in the United States, and the survivors of the Hiroshima and Nagasaki atomic bomb blasts in Japan.

Voluminous experimental and epidemiologic evidence is now available on the health effects of radiation. Throughout the world, government and nongovernment agencies have used the epidemiologic data to estimate the risks of radiation as a basis for setting limits for exposure; the complementing experimental data have been used to develop biologically appropriate risk models and to support assumptions made in analyzing and applying the epidemiologic findings. In the United States, the Biological Effects of Ionizing Radiation (BEIR) Committees of the National Research Council and committees of the National Council on Radiation Protection and Measurements (NCRP) have periodically developed estimates of the risks of various types of radiation exposure. Similar types of estimates have also been made by the International Commission for Radiological Protection (ICRP) and UNSCEAR. Increasingly sophisticated statistical approaches have been applied to the epidemiologic data for this purpose, and confidence in the risk estimates has mounted as the extent of the epidemiologic evidence and our understanding of biologic mechanisms have grown.

Nevertheless, the health effects of radiation remain a topic of widespread societal concern in spite of the deepening scientific knowledge. Risks of medical radiation, nuclear facilities, and occupational exposures have been questioned repeatedly as to their acceptability; on the other hand, these radiation exposures arise from essential societal applications of technology and there is concern that the public could be made too phobic of radiation by exaggerated risk estimates. Consequently, there has been sustained questioning of the epidemiologically based risk models. For example, the recent recognition of the magnitude of radon's contribution to

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Abbreviations used: BEIR, biological effects of ionizing radiation; ERR, excess relative risk; high-LET, high linear energy transfer; IARC, International Agency for Research on Cancer; ICRP, International Commission for Radiological Protection; low-LET, low linear energy transfer; NCRP, National Council on Radiation Protection and Measurements; UNSCEAR, United Nations Scientific Committees on the Effects of Atomic Radiation

Table 1. Average annual effective dose equivalent of iodizing regulations to a member of the U.S. population.

Source	Dose equivalent[a]		Effective dose equivalent	
	mSv	mrem	mSv	%
Natural				
Radon[b]	24	2400	2.0	55
Cosmic	0.27	27	0.27	8.0
Terrestrial	0.28	28	0.28	8.0
Internal	0.39	39	0.39	11
Total natural	–	–	3.0	82
Artificial				
Medical				
X-ray diagnosis	0.39	39	0.39	11
Nuclear medicine	0.14	14	0.14	4.0
Consumer products	0.10	10	0.10	3.0
Other				
Occupational	0.009	0.9	<0.01	<0.3
Nuclear fuel cycle	<0.01	<1.0	<0.01	<0.03
Fallout	<0.01	<31.0	<0.01	<0.03
Miscellaneous[c]	<0.01	<1.0	<0.01	<0.03
Total artificial	–	–	0.63	18
Total natural and artificial	–	–	3.6	100

[a]To soft tissues. [b]Dose equivalent to bronchi from radon progeny. The assumed weighting factor for the effective dose equivalent relative to whole-body exposure is 0.08. [c]U.S. Department of Energy facilities, smelters, transportation, etc. Data from the National Council on Radiation Protection and Measurements (*1*).

population dose has sparked national programs to reduce indoor levels. At the same time, critics have labeled such programs premature and called for more definitive evidence that this known occupational carcinogen causes lung cancer in the general population (*5*). They question the estimation of risks for the population with linear models derived from studies of miners. In the United States and some European countries, research has also been directed at electromagnetic fields and nonionizing radiation generated by power lines, appliances, and video display devices, including computer monitors. While nonionizing radiation is not considered in this review, attention given to this topic by the media may have raised the public's concern about radiation in general.

Even though the evidence on the health risks of radiation is more extensive than for most other environmental causes of disease, a strong rationale for further epidemiologic and experimental research is evident. The public is asking for a more confident assurance of the safety of radiation exposures, and changing technology has created new radiation sources that need investigation. Management of wastes from nuclear power generation and the clean-up of sites of weapons development and production have brought out the potential for exposures of workers and of the general population. The long half-lives of some of the radioisotopes that have been generated pose an unprecedented need for safe storage over thousands of years.

This report provides a perspective on likely needs for further population-based research on radiation and health; this research will take place on a background of advancing understanding of the mechanisms by which radiation causes cancer and of the genetic determinants of susceptibility. The article also forecasts areas in which epidemiologic investigation will be needed and the challenges that will be faced in these investigations. Selected examples are used to illustrate these predictions. The article does not attempt to comprehensively review the current status of the full range of evidence on radiation and disease; a number of comprehensive reviews on this topic are available (*6–8*).

Epidemiologic Findings on the Risks of Ionizing Radiation

Ionizing radiation is perhaps the best-characterized human carcinogen. We understand the physical nature of the agent; we have an ever-deepening knowledge of the mechanism of carcinogenesis; we have well-developed animal models of radiation-caused lung cancer; and we can estimate cancer risks from radiation with a reasonable degree of certainty. Exposures can be measured and doses of energy delivered to tissues can be calculated. This extensive knowledge has guided the development of radiation protection standards through the work of the BEIR committees and committees of the NCRP and ICRP.

Quantitative estimates of the risks have been derived primarily from epidemiologic studies of radiation-exposed populations. For low linear energy transfer (low-LET) radiation, the study of the atomic bomb survivors of Hiroshima and Nagasaki has been a principal data source. This is a prospective cohort study involving follow up of approximately 93,000 survivors of the atomic bombings and 27,000 additional persons who lived in the two cities in 1950 but were not present at the time of the blasts. The population was not enrolled until 5 years had passed since the bombings, so survival for at least 5 years was mandatory for enrollment in the cohort. For each person, radiation exposure was estimated based on location at the time of the blast, shielding, and other factors. Unique features of the population include its size, the virtually instantaneous delivery of exposure at the time of the blast, and the lengthy follow up. Initially, the participants were followed for cancer mortality (*9*), but incidence has now been added (*10,11*).

Excess occurrence of cancer is assessed by comparing the number of cancers among cohort members exposed to radiation with projections of expected numbers of cases based on the experience of the participants who were not exposed. Quantitative estimates of risk are made by applying regression models that calculate the relationship of the excess risk beyond background with exposure to radiation (or with estimated organ dose). This approach was followed by the BEIR V Committee (*7*) and in subsequently reported analyses of mortality for 1950 to 1987 (*8*) and for cancer incidence for 1958 to 1987 (*10,11*). In the relative-risk models used in these analyses, the risk coefficients describe the relative increment in risk beyond background per unit of exposure. Positive coefficients are evident for most sites of solid tumors; leukemias, except for chronic lymphocytic leukemia, were also in excess. Tracking cancer incidence adds information on sites for which cancers are infrequently fatal—thyroid, skin, salivary gland, and new leukemias and lymphomas. The excess risk coefficients derived from this study remain a principal basis for estimating risks of radiation-associated cancer.

We have also gained substantial methodologic insights from the studies of atomic bomb survivors. The data set has been a challenge to analysts and an impetus for the development and application of new models for longitudinal analysis (*9*). The lengthy follow up of the cohort provided

opportunity to characterize the time dependence of risk and to determine if the excess should be considered additive or multiplicative to the background risk. The general tendency for the data to be better fit by multiplicative models has led to the now universal application of relative risk models (*12*) and the extension of those models to include time-dependent effects. Throughout the study there have been concerns about error in the exposure estimates and misclassification of cancer diagnoses; in fact, dose estimates were revised in 1986 and questions have been subsequently raised as to the assumptions underlying these most recent revisions (*9*). These concerns have sparked the application of statistical methods for considering the consequences of errors in diagnoses (*13*) and exposure and dose (*14*).

For low-LET radiation, data from numerous additional epidemiologic studies now also supply site-specific estimates of cancer risk. The participants in these studies have been exposed either through therapeutic radiation or through their jobs. For cancer of the breast, for example, the 1994 UNSCEAR report lists 10 populations in addition to the atomic bomb survivors (Table 2). These studies generally indicate excess incidence of breast cancer, although there is a wide range of risk coefficients and substantial imprecision in some of the risk estimates. However, these studies differ substantially in the quality of the dose estimates and population characteristics that may modify the risk of radiation. For most other cancer sites, risk estimates are also available from a number of studies (*7,8*). The availability of risk estimates from studies other than the atomic bomb survivors has generally strengthened confidence in estimates for specific sites while deepening the characterization of uncertainty. These additional risk estimates have also proved useful in assessing uncertainty associated with extending estimates from the atomic bomb survivors to other populations.

To increase the informativeness of epidemiologic studies, the data from individual studies can be combined to more precisely quantify risks; metaanalysis uses the data at the level of the individual studies, while pooled analysis combines the data for individuals in different studies. Increasingly sophisticated techniques have been used to combine data from different studies. The random-effects models that have come into use for combining data simultaneously consider the effect of being in a particular study and the effect of the exposure(s) of interest, e.g., radiation.

Several recent analyses are illustrative. The International Agency for Research on Cancer (IARC) combined data from seven cohort studies of nuclear workers comprising nearly 96,000 persons exposed to generally low doses of low-LET radiation (below) (*15*) and an earlier report described a pooled analysis of data from workers at U.S. Department of Energy facilities (*16*). The IARC analyses pooled data assembled from 95,673 workers in seven cohorts in the United Kingdom, Canada, and the United States. Mortality from leukemias, exclusive of chronic lymphocytic leukemia, was significantly increased while mortality from all cancers exclusive of leukemia was not. Using Poisson regression and a linear model for excess relative risk (ERR), the ERR was estimated as 2.18 per Sv (90% confidence interval CI, 0.1, 5.7) for the leukemias and as –0.07 per Sv (90% CI –0.4, 0.3) for all cancers except leukemia. The leukemia risk was consistent with projections from the BEIR V model. The analyses did not show a significant association of radiation dose with all cancer mortality but CIs were wide, even without full consideration of uncertainty in the ERR estimates.

In other pooled analyses, Ron and colleagues (*17*) assessed risk of thyroid cancer following exposure to ionizing radiation. Data from five cohort studies were combined; for every subject in the cohorts, information was obtained on dates of birth and exposure, type of exposure, number of exposures, individual thyroid dose estimates, and development of thyroid cancer. The data for those exposed under age 15 were combined and analyzed with Poisson regression models. The individual studies had all shown significantly increased risk but confidence limits on the risk estimates were wide. The pooled ERR per G was 7.7 (95% CI 2.1–28.7). The CIs, calculated with a random effects model, incorporated the uncertainty from variation among the cohorts.

For high linear energy transfer (high-LET) radiation, there is also a wealth of information, derived from studies of underground miners exposed to radon (*6,18*). At least 12 cohort studies incorporate estimates of exposure to radon progeny. The BEIR IV report provided a model for lung cancer risk associated with radon exposure, based on four of the cohorts; more recently, Lubin and colleagues combined data from 11 studies (*19,20*).

This extensive epidemiologic database on populations exposed to low- and high-LET radiation leaves no doubt as to the carcinogenicity of radiation and provides quantitative risk estimates that are

Table 2. Epidemiologic studies of ionizing radiation and breast cancer incidence.[a]

Study	Observed cases	Expected cases	Mean dose, Sv	Average excess relative risk, Sv^{-1}[b]
Life span study				
Age at exposure				
<20 years	122	62.8	0.28	3.32 (2.3–4.4)
>20 years	173	137.1	0.27	0.98 (0.4–1.6)
Time since exposure				
5–19 years	49	36.9	0.28	1.19
20–29 years	87	63.5	0.27	1.34
30–42 years	159	99.5	0.27	2.21
All	295	199.9	0.27	1.74 (1.1–2.2)
Massachusetts tuberculosis fluoroscopy	142	107.6	0.79	0.40 (0.2–0.7)
New York acute postpartum mastitis	54	20.8	3.70	0.43 (0.3–0.6)
Ankylosing spondylitis	26	16.1	0.50	1.24 (0.3–2.5)
Swedish breast irradiation	115	28.8	8.46	0.35 (0.3–0.4)
Cervical cancer case–control	953	1083.0	0.31	–0.2 (<–0.2–0.3)
Without ovaries	91	82.6	0.3	0.33 (<–0.2–5.8)
Contralateral breast				
Denmark	529	508.7	2.51	0.02 (<–0.1–0.2)
United States	655	550.4	2.82	0.07 (<–0.1–0.2)
Rochester thymic irradiation	22	7.8	0.76	2.39 (1.2–4.0)
Skin hemangioma	56	36.4	0.20	4.2 (1.8–7.2)
Scoliosis	11	6.1	0.13	6.37 (0.9–15)
Hodgkin's disease (Stanford)	25	6.1	–44.0	0.07 (0.04–0.11)

[a]Data based on UNSCEAR, Annex A, Table 8 (*8*). [b]90% CI in parentheses derived from published data for the life span study and using exact Poisson methods for the other studies.

sufficiently precise for calculating risks of exposures in the workplace and of diagnostic uses of radiation. Current approaches for limiting radiation exposures have long been grounded in these risk estimates and there is little controversy about the risks at the selected exposure limits. On the other hand, the inferences from the epidemiologic evidence as to the risks at the lower range of the exposure distribution have become highly controversial and the data have proved less informative on issues of increasing importance from the public policy perspective. The pooled analyses that have been reported to date show that epidemiologic studies can be informative about lower exposures if sufficient data can be amassed. Pooled analyses, like the IARC report on nuclear workers, can be used to gauge whether or not projected risks deviate appreciably from observed risks.

Future Challenges for Understanding the Risks of Ionizing Radiation

Dose–Response Relationship at Lower Doses

For the purpose of public health protection, exposure– or dose–response relationships derived from epidemiologic studies are used to estimate the burden of radiation-related cancer for the general population and exposed occupational groups. These estimates are subject to uncertainty because they are based on extrapolation of dose-response relationships to ranges of dose lower than those at which the observations were made. For this purpose, linear no-threshold models for the relationship between dose and cancer risk are widely used; this type of model has been viewed as biologically plausible and conservative in protecting public health because risk is attributed to all levels of exposure (*21*). Some have viewed this model as greatly exaggerating the risks and contributing to public fear of radiation (*22–24*). Some have called for a reconsideration of using the linear no-threshold model for policy purposes, arguing that the science is not consistent and proposing that practical thresholds may be found (*25*). The mounting evidence on adaptive responses to radiation is an additional consideration in regard to the effects of lower radiation doses (*8*). Some have proposed that lower doses of radiation may carry no cancer risk or may even reduce risk (hormesis) (*26,27*). On the other hand, the 1994 UNSCEAR report (*8*) concluded that the information on adaptive responses of cells did not have implications with regard to late effects such as cancer induction.

Using current epidemiologic approaches, directly characterizing radiation risks at doses typically received by the general population is a formidable and virtually unaddressable challenge. To gain sufficient precision to provide a meaningful characterization of risk, extremely large study populations are needed. For example, Land (*28*) estimated sample size needs for a theoretical cohort study designed to detect excess risk associated with an average tissue dose from a single mammographic examination of 1 centigray to each breast. Power was not adequate for sample sizes of less than 100 million. For leukemia, a sample size of 16 million was projected for adequate power and the same exposure. Characterizing the shape of the dose–response relationship would carry even more demanding data requirements. Errors in exposure and the confounding influences of other causes of cancer further complicate the assessment of dose–response relationships at lower doses.

Determining the risks of indoor radon is another topical example. To date, the principal approach for estimating the risks of indoor radon has been extension of the dose–response relationship observed in underground miners of uranium and other ores to the generally lower exposures of the general population. Extrapolation to the population's average exposure is across at least one or two orders of magnitude of cumulative dose. To more directly estimate the risk of indoor radon and thereby avoid the uncertainty associated with using the miner data, case–control studies of lung cancer in the general population have been undertaken. These studies involve comparison of estimated exposures to indoor radon with exposures of controls who do not have lung cancer. Exposures are estimated by making measurements in current and past residences with the implicit assumption that current concentrations reflect those that gave rise to past exposures. There is certain to be error because of this assumption and this approach is further limited by the difficulty of accessing all prior residences in most studies. Residential mobility also reduces the variance of exposure and thereby increases the needed sample sizes beyond projections based on the distribution of concentrations in homes. In spite of these methodologic problems, there are a number of case–control studies of indoor radon, some of substantial size, that are either completed or in progress (*12*).

Lubin, Samet, and Weinberg (*29*) estimated the sample sizes needed for case–control studies of indoor radon and lung cancer. Two hypotheses are of potential interest in such studies: the null hypothesis that indoor radon does not cause lung cancer; and the alternative hypothesis that the risk of indoor radon is substantially different from the projection based on the miner data. For public policy purposes, the latter hypothesis is of more interest because observational evidence alone will not suffice to dismiss indoor radon as a carcinogen in view of the extensive data available from miners and the state of our understanding of the biologic basis of radon's carcinogenicity (*6*). Under realistic scenarios of population mobility, these calculations showed that thousands of participants would be needed to address these hypotheses (Table 3). Measurement error further increases the needed number of cases and controls. In a recent extension of these analyses, Lubin, Boice, and Samet (*30*) considered the likely informativeness of 10 case–control studies of indoor radon and lung cancer, each with 700 cases and controls and each representing the evidence available at present. Their simulation

Table 3. Effect of measurement error and mobility pattern on sample size required to reject no trend with radon exposure, $\beta_0 = 0$, when the true trend is $\beta_1 = 0.015$.[a]

	Mobility pattern[b]					
	60 years		3 × 20 years		6 × 10 years	
f	Cases	Power[c]	Cases	Power[c]	Cases	Power[c]
0.00	251	0.90	529	0.66	938	0.46
0.30	288	0.86	656	0.58	1,303	0.37
0.50	365	0.79	916	0.48	2,050	0.28
1.00	973	0.48	2,987	0.23	8,002	0.14
1.50	4,186	0.22	13,934	0.12	39,456	0.09
2.00	29,542	0.12	100,308	0.08	287,644	0.07*

Abbreviations: β, excess risk coefficient in units of percent per working level month of exposure; f, proportional index of error on a logarithmic scale; data from Lubin et al., Table 5 (*29*). [a]Study based on a control-to-case ratio of 2. [b]Number of, and duration at, residences in 60 years (e.g., 1 residence in 60 years). [c]Power relative to a study with 251 cases, 502 controls, and no error in exposure ($f = 0$).

analysis showed that a set of studies of this size would provide little insight into radon risk. By the end of the century, the pool of case–control studies of indoor radon and lung cancer will include about 15,000 cases; separate pooled analyses of the North American and European studies are planned, followed by a global pooling. However, Lubin and colleagues (*30*) are pessimistic about the prospects of resolving issues of quantitative risk from indoor radon with pooled analyses of the case–control data.

Pooling of data from higher-dose studies of radiation-exposed workers and therapeutically exposed persons has proved informative because of the statistical power gained beyond that of the individual studies. The pooled analyses of data from underground miners are illustrative. The BEIR IV Alpha Committee (*6*) analyzed data from four studies (Colorado Plateau, Beaverlodge, and Ontario uranium miners and Malmberget iron miners) that included a total of 360 lung cancer deaths. Poisson regression analysis was used to fit a series of relative risk models to the individual data sets and to the combined data. The individual data sets were found to be consistent and the committee reported a preferred model based on the pooled data. The model was multiplicative but the effect of exposure varied with interval since exposure and with attained age. The model represented a significant departure from prior analyses, which had emphasized either simple attributable risk or relative risk models. The recent pooled analysis extended this approach to the 11 cohorts extant in the early 1990s that had individual exposure estimates and a significant number of lung cancer cases (*20*). The total population comprised about 68,000 men who had experienced 2700 lung cancer deaths during follow up. This larger sample size facilitated a more precise characterization of the risk of radon and added a term to the model for an effect of dose rate. Other illustrative analyses have been reported for nuclear workers (*15*) and for thyroid cancer following exposure to external radiation (*17*).

Such pooled analyses would appear to represent the optimum approach for future assessments of the cancer risks associated with lower levels of radiation. The anticipated pooling of the case–control studies of indoor radon and lung cancer has been facilitated by a series of workshops of the investigators and a similar high level of cooperation has been achieved for other pooled analyses.

Dose–Rate Effects

Typical radiation exposures of the general population are sustained at lower dose rates than those received by participants in the epidemiologic studies. At the extreme, the radiation from the atomic bomb blasts in Hiroshima and Nagasaki was received instantaneously. The radon-exposed underground miners received exposures across a range of a few months to their full working lifetimes, while radon exposure indoors is continuous. Consequently, to project radiation risks for the general population, an assumption is needed as to the effect of differing dose rates for the observed populations and the general population.

For low-LET radiation, risk estimates derived at high doses and high dose rates are reduced by the dose–rate reduction factor (*7,8*). While some studies provide information on consequences of dose rate, the dose–rate reduction factors have been empirically derived and their biologic and epidemiologic basis remains uncertain (*31*). It is not realistic to anticipate that epidemiologic evidence will characterize dose–rate reduction factors at the doses of greatest concern for typical population exposures.

For high-LET radiation, there is both experimental and epidemiologic evidence that lower dose–rate exposures have increased risk (inverse dose–rate effect) (*12,20*). The recent pooled analysis of data from underground miners showed that the excess relative risk of lung cancer increased as the exposure rate decreased. However, the lowest dose-rate category in this analysis is about two orders of magnitude above the typical exposure rates for the general population. Thus to estimate the risk posed by residential radon, assumptions are needed not only on the shape of the dose–response relationship but also on the magnitude of the dose–rate effect at typical environmental exposures. A simple extrapolation of the estimated dose–rate effect from the miner data would lead to unrealistically high risk estimates. Brenner (*32*) has proposed a biophysical model that postulates a dependence of the dose–rate effect on dose; this model leads to the conclusion that a dose–rate effect should not be present at low doses. A recent analysis of data from the 11 cohorts of underground miners is consistent with this postulated dependence of the inverse dose–rate effect on dose (*19*).

Dose–rate effects will remain a key uncertainty in risk assessments. Large epidemiologic data sets can provide only a limited characterization of such effects at lower doses, as exemplified by the pooled analysis of underground miner data. Further guidance is needed from research findings on mechanisms of carcinogenesis.

Susceptibility

We are making rapid advances in our understanding of the molecular basis of carcinogenesis. Numerous genetic mutations associated with increased cancer risk have now been identified. The increasing availability of genetic markers of cancer risk brings the possibility of identifying persons at increased risk for radiation-related cancer in research studies and potentially for limiting exposures of those found susceptible. We have developed a research paradigm, now widely referred to as molecular epidemiology, that provides an approach to assessing the combined effect of radiation exposure and susceptibility determinants. For example, in cohort (longitudinal) studies, biological specimens can be stored as the cohort is established, or even while follow up is in progress, then analyzed for susceptibility markers for those developing cancer as well as for appropriately matched controls.

Breast cancer may prove to be one of the first successes of this approach. We recently learned that a gene, *BRCA1*, is responsible for a substantial proportion of premenopausal breast cancer cases. Using data from atomic bomb survivors younger than age 20 at the blast, Land (*33*) has shown that the pattern of age-specific risks of breast cancer is consistent with an interaction between radiation exposure and genetic susceptibility. The estimated ERR is far higher (ERR = 13.5) for women developing breast cancer before age 35 than in those who have a later diagnosis (ERR = 2.0). This pattern implies the existence of a radiation-susceptible subgroup. Land proposes that the role of *BRCA1* (or other genes) could be tested by using archival or other tissues.

Investigating Clusters

The landscape of the developed world is now dotted with nuclear facilities: nuclear power plants, uranium processing plants, factories and laboratories concerned with weapons development and manufacturing, and areas of waste storage. The 1988 UNSCEAR report (*3*) identified 417 nuclear reactors in use for power production in 26 countries at the end of 1987. Contamination has been found at long-abandoned sites of factories where radiation was used, and tailings piles (stacks of residual ore and waste products) and

radiation-containing lagoons remain in areas where uranium was mined. The visible presence of these nuclear facilities invites concern about the health consequences of living in nearby locations. Given the numbers of such locations, clusters of cancers with spatial distributions consistent with causation by radiation or other exposures linked to nuclear facilities are inevitable. The sequence of investigations that followed the identification of excess incidence of childhood leukemia and other cancers in Seascale and other villages near the Sellafield nuclear site in the United Kingdom is illustrative (*34*). The cluster, first reported in a television program, was quickly followed by confirmation of increased leukemia mortality rates for one of the adjoining districts (*34*). This single cluster has prompted a remarkable series of descriptive and analytic investigations and remains unexplained. The single explanation linking the cluster to the nuclear facility—paternal exposure to radiation—has not been sustained by studies elsewhere (*35*). Other clusters, including a clustering of brain cancer noted in Los Alamos County, New Mexico, have also received widespread attention.

A research methodology is needed for prospectively identifying such clusters and evaluating their public health significance. Without such a methodology, apparent clusters (which may not be actual clusters) will almost certainly be recognized, and public concern and media attention will demand investigations that may tax local resources.

Assuring Safety

Accidental radiation releases, some of catastrophic proportions like Chernobyl, have been widely documented. Releases of radiation into the general environment have been investigated at a number of locations including, for example, Denver, Colorado, adjacent to Rocky Flats; the area adjacent to Three Mile Island; and regions exposed following the Chernobyl disaster. The effects of fallout on the community have also been investigated. These investigations, undertaken with some knowledge of the quantities of radiation released and the likely doses received, have several potential purposes: providing evidence to the public of the consequences of exposure; providing assurance to the public that the projected doses were, in fact, low, and that adverse effects could not be documented; and providing an opportunity to test dose-response relationships extrapolated from higher doses. The conduct of some of these studies of exposed populations has been largely motivated by the need to offer reassurance to the public and to show evidence that an investigation has been undertaken. Land (*36*) and McMahon (*37*) have cautioned against studies of populations with doses only slightly higher than background, both arguing that an unfavorable signal-to-noise ratio assures uninformative and even misleading results. New approaches to sharpen the specificity of studies at low doses may obviate this justifiable concern.

The experience gained from these studies shows the limitations faced by observational studies at low doses. For example, Hatch et al. (*38*) investigated cancer near the Three Mile Island nuclear plant. Modeled dispersion of emissions was used to estimate population doses. The average increment-to-background dose was estimated to be about 0.1 mSV, about 10% of the annual dose. The upper limit was at about a doubling of annual dose. The findings showed no changes in cancer incidence indicative of an effect of the radiation releases from the plant, but confidence limits around risk measures were extremely wide because of the small numbers of cancer cases. Reassurance for the public can be found in the point estimates of risk, which show no consistent evidence of increase; the upper bounds of the CIs, however, extend well into a range of public health concern.

Unfortunately, accidental exposures continue. Each should be assessed for the need for surveillance and for more formal epidemiologic investigations. The exposed population needs to know the surveillance data. Unanticipated excesses of disease may then prompt follow-up investigation. For example, there has been a dramatic increase in childhood thyroid cancer in Belarus and the Ukraine following the Chernobyl accident (*39*). This excess calls for investigation, including reconstruction of doses and estimation of dose–response relationships.

Conclusions

This review has emphasized research questions and methodologic advances related to the cancer risk associated with radiation exposure. It has emphasized key uncertainties related to the risks of radiation using observational data: dose response, dose–rate effects, and susceptibility. Advances have been made in the epidemiologic approach to quantifying the risk of radiation exposure, and mechanistic research promises to further reduce uncertainties. We should be able to address public concerns about radiation with increasing confidence, although the rising emphasis on the risks of lower levels of exposure has increased the challenge.

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