Ionizing Radiation: Future Etiologic Research and Preventive Strategies

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Estimates of cancer risks following exposure to ionizing radiation traditionally have been based on the experience of populations exposed to substantial (and known) doses delivered over short periods of time. Examples include survivors of the atomic bombings at Hiroshima and Nagasaki, and persons treated with radiation for benign or malignant disease. Continued follow-up of these populations is important to determine the long-term effects of exposure in childhood, to characterize temporal patterns of excess risk for different types of cancer, and to understand better the interactions between radiation and other host and environmental factors. Most population exposure to radiation occurs at very low dose rates. For low linear energy transfer (LET) radiations, it has been assumed that cancer risks per unit dose are lower following protracted exposure than following acute exposure. Studies of nuclear workers chronically exposed over a working lifetime provide data that can be used to test this hypothesis, and preliminary indications are that the risks per unit dose for most cancers other than leukemia are similar to those for acute exposure. However, these results are subject to considerable uncertainty, and further information on this question is needed. Residential radon is the major source of population exposure to high-LET radiation. Current estimates of the risk of lung cancer due to residential exposure to radon and radon daughters are based on the experience of miners exposed to much higher concentrations. Data indicate that lung cancer risk among miners is inversely associated with exposure rate, and also is influenced by the presence of other lung carcinogens such as arsenic in the mine environment. Further study of populations of radon-exposed miners would be informative, particularly those exposed at below-average levels. More direct evidence on the effects of residential exposure to radon also is desirable but might be difficult to come by, as risks associated with radon levels found in most homes might be too low to be quantified accurately in epidemiological studies. — Environ Health Perspect 103(Suppl 1):245–249 (1995)

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Introduction

Epidemiological studies of populations exposed to ionizing radiation have provided considerable quantitative information concerning the risks of radiation-induced cancer (1–3)—more, perhaps, than is available for any other human carcinogen. Such data are invaluable for setting radiation protection policy and evaluating the late effects of medical exposures. Epidemiological data also complement experimental evidence as a basis for learning about mechanisms by which cancers develop. Yet, important unanswered questions remain regarding lifetime risks of radiation-induced cancer, the magnitude of risks from chronic low-dose-rate exposures, risk from low-level radon exposures in the home, determinants of host susceptibility, and molecular mechanisms of radiation carcinogenesis. The epidemiological data are strongest for populations exposed to high doses of radiation at high dose rates, but such exposures are uncommon in the general population. Implementation of effective preventive strategies requires better understanding of cancer and other health risks associated with low-level exposures. Full understanding of lifetime cancer risks attributable to irradiation requires long-term follow-up of exposed populations, including those irradiated at young ages.

Atomic Bomb Survivors

The single most important source of information about radiation-induced cancer in humans has been the Life Span Study (LSS) cohort of survivors of the atomic bomb explosions in Hiroshima and Nagasaki, for which the latest comprehensive reports document cancer incidence through 1987 (4,5). Continued follow-up of this study population is essential if we are to understand lifetime risks of exposure during childhood and adolescence. This is illustrated in Figure 1, which is for solid tumors occurring among males (5). Panel A shows the fitted excess relative risk (ERR) of solid tumors at a dose of 1 Sv as a function of time since exposure, separately for three different ages at exposure. For ages 30 and 50 years, the ERR was approximately constant with increasing time, but for age 10 at exposure, it decreased with time from initially high levels. Some observers have interpreted this decrease in relative risk as evidence that excess risk disappears with time among persons exposed during childhood. However, the pattern looks different when data for the same people are plotted on the absolute risk scale (Figure 1C). Even for those age 10 at exposure, the absolute risk increased with time since exposure. Data in Figure 1D are expressed in terms of attained age rather than in years since exposure. The absolute excess risk at a given attained age (Figure 1D) was almost identical for those who were age 10 at exposure and those age 30 at exposure. The age 10 at exposure group had only reached age 50 or so as of the last follow-up, and we do not know how patterns of risk will change as these people...
pass through ages of high cancer incidence. Studies of atomic bomb survivors now under way at the Radiation Effects Research Foundation in Japan should be continued so that this opportunity for lifelong follow-up is not missed.

**Medically Irradiated Populations**

It is important to continue to follow other irradiated groups in addition to those exposed at Hiroshima and Nagasaki. Studies of persons given radiotherapy for benign and malignant disease also have provided valuable information about cancer risks due to low-LET radiation. Ankylosing spondylitis patients treated with external-beam X-rays were one of the first such study populations to be described (6), and follow-up recently was updated (7). Figure 2 shows relative risk (RR) by time since irradiation for men who were 35 years old at exposure. The solid line represents lung cancer and the dotted line other solid tumors. Whereas the RR was more or less constant with increasing time since exposure among the Japanese atomic bomb survivors who were age 30 at exposure, the RR for spondylitics decreased, especially for lung cancer but also to a certain extent for other solid tumors. A different pattern was seen for cancer of the bladder following radiotherapy with X-rays for metropathia hemorragica (Table 1) (8), a condition that typically occurs among women between the ages of 45 and 50. These treatments delivered large doses to pelvic organs. The RR for bladder cancer increased with time following irradiation, but had this population been followed for only 15 to 20 years, this radiation effect might have been missed. Other pelvic organs displayed a different pattern of excess risk over time (Table 1) (8).

Results for different study populations complement each other, as they provide information about risks associated with different types of radiation exposure and possible modifying effects of host characteristics. Identical results are not necessarily to be expected among studies, and differences can provide important insights about mechanisms of induction of cancer by radiation.

**Nuclear Workers**

Whereas exposures experienced by atomic bomb survivors and persons given radiotherapy usually are of short-duration, occupational, environmental, and diagnostic medical exposures to ionizing radiation usually involve chronic or repeated exposure to low doses. These are the types of exposure that account for most of the radiation exposure in the general population (9), but cancer risks associated with protracted, highly fractionated exposures are less well understood.

Because animal data indicate that cancer risks from penetrating, low-LET radiation are lower when the dose is accumulated over a prolonged period than for acute exposure, risk estimates derived from human populations exposed briefly at high doses often have been divided by a dose-rate effectiveness factor when applied to populations receiving protracted exposures. Animal data have been interpreted to indicate that this factor might lie in the range 2 to 10, with greater support for the low end of this range (2). We are just now beginning to have enough data available on nuclear workers with protracted radiation exposures to test this hypothesis. Preliminary data do not support dose-rate factors as large as 10 (Table 2). Estimates of the excess relative risk per Sv for all cancers combined are very similar for nuclear

**Table 1.** Ratio of number of deaths observed (O) due to cancer among women treated with radiotherapy for metropathia hemorragica divided by the number expected (E), separately by time since irradiation.

| Site of cancer            | 0–4 | 5–14 | 15–24 | ≥25 | Total, ≥5 |
|---------------------------|-----|------|-------|-----|-----------|
| Bladder                   | 0.00| 1.12 | 1.45  | 4.37| 3.02      |
| Other pelvic organs       | 0.28| 1.62 | 1.20  | 1.23| 1.31      |
| All cancers               | 0.68| 1.16 | 1.06  | 1.21| 1.15      |

*Expected values were calculated based on mortality rates for the Scottish population. Analysis was limited to ages ≤85 years. \( p < 0.001 \), \( p = 0.007 \), \( p = 0.02 \). Data from Darby et al. (6).
Table 2. Excess relative risk estimates for all cancers combined and for leukemia (exclusive of chronic lymphocytic leukemia) for nuclear workers from the United Kingdom and United States and male atomic bomb survivors age > 20 at the time of bombing.

| Cancer Type | Excess relative risk per Sv, 95% CI |
|-------------|----------------------------------|
| All cancer  | 0.23 (<0, 0.83)                  |
| Nuclear workers (U.K. and U.S.) | 0.33 (0.11, 0.60) |
| Atomic bomb survivors (men exposed at ages > 20) | 1.7 (<0, 5.9) |
| Leukemia (excluding CLL) | 6.2 (2.7, 13.8) |
| Nuclear workers (U.K. and U.S.) | 0.33 (0.11, 0.60) |
| Atomic bomb survivors (men exposed at ages > 20) | 1.7 (<0, 5.9) |

CLL, chronic lymphocytic leukemia. Data from UNSCEAR (3).

Table 3. Excess relative risk for lung cancer among underground miners, by average rate of exposure to radon and radon daughters. Mines are listed in descending order by estimated average exposure rate.

| Mine                                    | Average exposure rate, WLM/year | Excess relative risk, %/cumulative WLM |
|-----------------------------------------|---------------------------------|-----------------------------------------|
| Port Radium (Northwest Territories)²  | 105                             | 0.3                                    |
| Newfoundland⁴                          | 67                              | 0.9                                    |
| New Mexico²                            | -16                             | 1.1                                    |
| Ontario²                               | -10                             | 1.3                                    |
| Malmberget (Sweden)²                   | 5                               | 3.6                                    |
| Beaverlodge (Saskatchewan)³            | 5                               | 3.3                                    |

WLM, working-level month. *Howe et al. (13). *Morrison et al. (14). *Samet et al. (15). *Kusiak et al. (16). 
*Radford and St. Clair Renard (17). *Howe et al. (18).

workers and atomic bomb survivors, while leukemia risk estimates differ by a factor of about three to four (4, 5, 10, 11). Again, these data are preliminary, and the estimates have wide confidence intervals. It is important to continue studies of nuclear workers and make further comparisons of this nature.

Radon

Another topic causing much public concern at the present time is the risk of lung cancer due to exposure to radon (²²⁲Rn) in the home. Radon and its short-lived daughter products are the largest source of radiation exposure to the general population (2). Until now, estimates of the risk of radon-induced lung cancer have been based on studies of underground miners, most of whom were exposed at relatively high levels. Extrapolation of these risk estimates down to the dose range more typical of residential exposures would suggest that there are, perhaps, 15,000 radon-induced lung cancer deaths per year in the United States (12). However, there are enormous uncertainties in those estimates.

One of the uncertainties concerns the effect of exposure rate. Table 3 summarizes results from six studies of underground miners listed in decreasing order of average exposure rate. The Port Radium (Northwest Territories, Canada) and Newfoundland miners worked in mines that, on average, had the highest ambient concentrations of radon, and the Malmberget (Sweden) and Beaverlodge (Saskatchewan) miners on average experienced the lowest concentrations of radon. There is a nearly monotonic inverse association between average exposure rate and estimates of the excess relative risk per cumulative working-level month (WLM). (A working level is defined as any combination of short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3 x 10⁵ MeV of potential α energy, which approximately equals the α energy released from the decay of daughters in equilibrium with 100 picocuries of ²²²Ra (1). A working-level month is defined as the exposure resulting from inhalation of air with a concentration of 1 working level of radon daughters for 170 working hours) (1). Most of the public’s exposure to radon is accrued at a very low exposure rates, lower than any of the rates for miners shown in Table 3. Failure to take account of a dose-rate effect could, therefore, result in a substantial underestimate of risk to the general population.

Detailed analyses of lung cancer mortality among 4320 uranium miners from West Bohemia revealed a 20-fold decrease in the excess relative risk per WLM with increasing average exposure rate (Table 4) (19). The men in this study worked in 19 different mine shafts, and radon concentrations varied widely, both from shaft to shaft and also within any particular shaft over time, as engineering changes were introduced to improve ventilation and reduce the radon concentration. Most men worked in a variety of mine shafts, and detailed data were available about the average radon concentration to which each man was exposed for every month he was employed in the mines. In trying to understand and model the exposure rate effect among these miners, it was discovered that it was entirely attributable to the small proportion of men who were ever employed in a mine shaft with a concentration of radon daughters of 10 working levels (WL) or more, which is an extremely high concentration.

When these men were omitted from the analysis, the association between RR and exposure rate completely disappeared, even though the average exposure was still quite high (Table 4). It would be interesting to determine whether a similar phenomenon occurs in other studies of radon-exposed miners. If it does, then a better data set for extrapolating to the general population might be obtained by omitting those men who at any time were exposed to a very high concentration.

Even if exposure rate effects can be sorted out, there are other difficulties associated with using radon risk estimates for miners to extrapolate to residential exposures. Among these is the possible role of other carcinogens in the mine environment. In a large study of Chinese tin miners exposed to both radon and arsenic, it was shown that the apparent risks of radon exposure were substantially reduced when adjustment was made for arsenic exposure (20). The role of arsenic and other carcinogens until now has not been studied in great detail among radon-exposed miners. However, Tomášek et al. (19) were also able to examine the question to a certain Table 4. Estimates of excess relative risk of lung cancer among West Bohemian uranium miners, separately by average rate of exposure to radon and radon daughters.²

| Average exposure rate, WL | Excess relative risk per WLM² | Men with exposure rate < 10 WL only |
|--------------------------|------------------------------|-----------------------------------|
| < 2.0²                  | 1.00²                        | 1.00²                              |
| 2.0-3.9                 | 0.41                         | 0.94                              |
| 4.0-5.9                 | 0.24                         | 1.17                              |
| ≥6.0                    | 0.05                         | —                                 |

Risk (trend) < 0.001 NS

Abbreviations: NS, not significant; WL, working level; WLM, working-level month. *Estimates are presented both for the entire cohort and after excluding men who ever worked in a mine shaft with a concentration exceeding 10 WL. Data from Tomášek et al. (19). §Relative to reference category. ©Reference category.
was restricted to men who were only exposed at rates below 10 WL. Although this does not prove that arsenic played a role in the etiology of lung cancer in these men, it is consistent with what one would expect if it did and points to the need for more thorough exploration of the possible role of other exposures among radon-exposed miners in the future. Venitt and Biggs (21) suggested that mycotoxins might also contribute to lung cancer excesses observed among miners. Other sources of uncertainty in generalizations from the experience of miners to the residential environment include risks of exposure to infants and children, and to females as well as males, and joint effects of radon exposure and smoking (22).

Because extrapolation of radon risks from exposed miners to the general population clearly is going to be difficult and uncertain however carefully it is done, it seems important to collect data bearing directly on the question of risks of residential radon. Such studies need be large, as radon exposures tend to be low. In a recently published Swedish study (23), investigators obtained an overall risk estimate that is very much in line with the predictions based on the miner data, but the confidence interval was wide (Table 5). Several other large case-control studies are in progress. It probably will be necessary to pool results from multiple studies to get a more definitive answer about risks from residential radon. Even then, however, it is questionable whether risks associated with radon levels encountered in most homes can be evaluated directly because it is difficult for epidemiological studies to distinguish low-level effects from bias (24). The task would be simplified if radon-induced tumors could be identified, such as through a characteristic mutation in a particular gene (25–27).

**Chernobyl**

The reactor accident at Chernobyl in April 1986 resulted in the release of large quantities of radioactive materials to the environment and was a catastrophe of enormous proportions in terms of disruptions in peoples’ lives (28). The full extent of the health effects will be difficult to document for several reasons, including uncertainties about exposures for individuals and difficulties in ascertaining health outcomes in an unbiased manner. Nearly half the surveyed people from villages between 30 and 300 km from Chernobyl reported having had an illness that they attributed to radiation exposure, but early clinical and laboratory studies did not find evidence to corroborate these perceptions (28). With regard to cancer, particular attention should be paid to the risk of thyroid cancer among people exposed as children. There is concern that a large increase in thyroid cancer seen among children in Belarus might have been caused by exposure to radioactive iodines from the accident (29).

### Table 5. Estimates of the excess relative risk of lung cancer due to residential exposure to radon and radon daughters, separately by smoking status.

| Smoking status, cigarettes per day | Excess relative risk per 100 Bq m⁻³ | 95% CI |
|-----------------------------------|------------------------------------|-------|
| Never smoked                      | 0.07 (0.0, 0.35)                   |       |
| <10 per day                       | 0.16 (0.0, 0.54)                   |       |
| ≥10 per day                       | 0.19 (0.0, 0.61)                   |       |
| Total                             | 0.10 (0.0, 0.22)                   |       |

Data from Pershagen et al. (23).

**Summary**

Future epidemiological studies of radiation-exposed populations should aim to cover new ground and not simply revisit the question of whether radiation causes cancer, which has been answered in the affirmative for most though not all types of cancer (2). There is particular need for good quantitative information about risks from chronic low-dose-rate exposures, including radon in the home. An essential component of risk quantification is good dosimetry. The public often overestimates risks of exposure to ionizing radiation relative to other common and more hazardous exposures. Residential, occupational, and diagnostic medical exposures are potentially controllable but only at a cost. While it is desirable to avoid unnecessary radiation exposures, it might be contrary to society’s best interest to undertake extreme protective measures that would effect only a small reduction in risk.
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