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Occupational and environmental radiation and cancer*

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Epidemiologic evidence on the relation between occupational and environmental radiation and cancer is reviewed. Studies of pioneering radiation workers, underground miners, and radium dial painters revealed excess cancer deaths and contributed to the setting of radiation protection standards and to theories of carcinogenesis. Occupational exposures today are generally much lower than in the past, thus any associated increases in cancer will be difficult to detect. Pooling investigations of these more recently exposed workers, however, has the potential to validate current estimates of risk used in radiation protection. New information on the effects of chronic radiation exposure also may come from studies in the former Soviet Union of Chernobyl clean-up workers and of workers at the Mayak nuclear facilities. Studies of environmental radiation exposures, other than radon, are largely inconclusive, due mainly to the difficulties in detecting the low risks associated with low dose exposures. Thyroid cancer, however, has been linked to environmental radiation from the Chernobyl accident and from nuclear weapons tests. Low-level radiation released during normal operations at nuclear plants has not been found to increase cancer rates in surrounding populations. Radon, a human carcinogen, is the most ubiquitous exposure to human populations; remediating high residential-radon levels is recommended, recognizing that the exposure can never be removed completely because it occurs naturally. *Cancer Causes and Control* 1997, 8, 309-322

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Introduction

Ionizing radiation has been studied extensively as a human carcinogen for nearly a century. A wealth of knowledge derives from human populations irradiated for medical, occupational, or military reasons, and from experimental studies in animals and in cell culture.[1-4]

Ionizing radiation was first linked to adverse health effects over 400 years ago when Agricola[5] described a devastating lung disease that led to premature death of underground miners in the Black Forest region of eastern Europe. The culprit was determined many years later to be radon gas which accumulated to high levels in unventilated mine tunnels.[6] Since Roentgen discovered X-rays in 1895 and Becquerel discovered radioactivity in 1896, the medical, technical, industrial and other beneficial uses of radiation have become commonplace. However, at most, only about three percent of all cancers can be attributable to all sources of radiation exposure, predominantly from natural sources such as radon and cosmic rays. Even among Japanese survivors of the atomic bombings at the end of World War II, only about one percent of all deaths could be attributed to their radiation exposure.[7]

We discuss here the major epidemiologic studies of human populations exposed to occupational and environmental radiation. Studies of Japanese atomic bomb survivors and patients treated with radiation are reviewed elsewhere.[1,8] Emphasis will be on those investigations that

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have increased our knowledge of risk and our understanding of the mechanism of carcinogenesis.[9]

Most of our information on carcinogenic effects comes from populations exposed to greater than 20 cGy (20 rad). For comparison, a chest X-ray results in about 0.026 cGy to bone marrow; a mammogram adds about 0.300 cGy to breast tissue; natural background contributes about 0.100-0.300 cGy per year to the whole body; occupational limits are set at 5 cGy per year; the whole-body dose that would kill half the population within 30 days is about 400 cGy; and cancer patients are treated with 1,000-6,000 cGy. It is difficult for epidemiologic methods to detect effects at low levels; for example, the relative risk (RR) at 100 cGy (100 rad) whole-body exposure is about 1.40 which, even assuming linearity in the dose-response, implies an RR of 1.04 at 10 cGy and 1.004 at 1 cGy (1 rad). RRs below 1.1-1.2 cannot be detected readily and risk assessments usually are based on higher dose extrapolation and radiobiological principals. One remaining question for radiation epidemiologists to answer, however, is the extent to which radiation risk is modified when exposures are spread out over time.[10,11] Since cells have the ability to repair damage caused by ionizing and oxidative reactions, there may be a lowering of risk associated with the generally low-level protracted exposure received in most occupational and environmental situations.

Occupational exposure

Major sources of occupational exposure come from work associated with the nuclear fuel cycle, underground mining, and medical technologies (Table 1). Lung cancer is increased among radon-exposed miners, leukemia among early radiologists, and bone sarcomas among radium watch-dial painters. Quantitative risk data of useful precision are not yet available from studies of nuclear facilities workers. Studies of radiation workers within the former Soviet Union have the potential to provide new information on radiation risks.

Radiologists

Studies of pioneering radiologists from the early part of this century indicate that leukemia and skin cancer can result from repeated, presumably small, radiation expo-

Table 1. Studies of cancer following occupational exposure to radiation

Study	Excess cancers	Comments
Pioneering radiologists[12-16]	Leukemia, skin	Fractionated doses cumulating to large levels can cause cancer. Actual doses uncertain. Little evidence for risk among recent practitioners.
Radiologic technologists[17-20]	None to date	Average doses low among recent technologists. Little evidence of breast cancer risk. Studies ongoing. Genetic susceptibility being evaluated.
Radium dial painters[25-31]	Bone sarcomas Sinus sarcomas	Very high dose to bone, but not bone marrow; low leukemia risk. Radon likely cause of mastoid carcinomas.
Nuclear workers[39-41,43,44]	Possible leukemia	Recent combined analyses suggest small leukemia association but apparently at high doses, 40 cGy. Workers may be exposed to other hazards such as asbestos and chemicals. Strong healthy-worker effect usually seen.
Nuclear shipyard workers[33-38]	None	Apparently very low doses. Mesothelioma risk attributed to asbestos.
Plutonium workers[45-49]	Possible lung	Except for new studies of Russian workers, number of exposed workers and plutonium doses both small.
Weapons test participants[55-57]	Possible leukemia	Leukemia increased after only one test in US, not others. Most US and UK series indicate no or little risk.
Underground miners exposed to radon[58-62,65-71,148,149]	Lung, no other cancers	Linear dose-response across 11 studies: no age at first exposure modification. Decreasing risk with time since exposure. More than additive interaction with smoking. Inverse dose-rate effect not present at low exposures. Miners also exposed to other contaminants such as arsenic, diesel exhaust and blasting fumes. Molecular evaluations of lung tumor.
Chernobyl clean-up workers[50-54]	Few reports to date, no thyroid increase in Estonian workers	No reports of excess leukemia or other cancers. Several studies planned or just initiated.

sures received over a period of many years.[12] In 1902, just seven years after X-rays were discovered, skin cancer on the hand of a radiologist was linked to radiation.[3] The first convincing evidence that leukemia could be caused by radiation also came from studies of radiologists.[13] Cumulative dose during these early years was likely quite high (and well over 100 cGy) and severe depression of white blood-cell counts was not uncommon. Radiologists entering their profession in later years after radiation protection guidelines were established have not experienced increased cancer risks.[14-16]

Radiologic technologists

Radiologic technologists who likely received much lower total doses than radiologists have not been reported to be at increased risk of leukemia[17] or breast cancer.[18] A survey of 145,000 radiologic technologists in the United States should provide new information on radiation risks, accounting for genetic susceptibility[19] and other cancer risk factors.[20]

Airplane crews

Recent studies of female flight attendants find elevated risks of breast cancer.[21,22] While increased exposure to cosmic radiation from transcontinental flights was suggested as one possible contributing cause, other important factors such as reproductive histories and disruptive menstrual periods have yet to be evaluated. A recent cohort study of male civilian airline pilots from Canada[23] found significantly low standardized mortality ratios (SMR) for all cancer and cancers of the lung, rectum, and bladder, and significantly high SMRs for prostate cancer and acute myeloid leukemia.[23] Airline crews are exposed to a variety of physical and chemical carcinogens, in addition to slightly higher cosmic-ray levels. Commercial pilots and flight crews might receive annual doses in excess of 5 mSv (a six-hour flight, *e.g.*, from New York to San Francisco, would result in about 0.04 mSv).[24]

Radium dial painters

Women employed in the US radium dial industry before 1930 would use their lips to make fine points on their paint brushes. This habit resulted in the ingestion of large amounts of bone-seeking ^{226}Ra (mean to bone, 17 Gy) and resulted in excess bone sarcomas and head carcinomas many years later.[25,26] Radon gas emitted as a decay product of radium was implicated as the cause of cancers in mastoid air cells or paranasal sinuses (head carcinomas). Age at first exposure did not influence risk. Leukemia was not increased among US[27] or English dial painters.[28] Since radium is a bone-seeker, it remains primarily within the bone matrix and the bone marrow receives little exposure.

A straight line dose-response adequately fits the head carcinoma data, but the osteosarcoma data were more complex. The dose-response for osteosarcoma appeared sigmoid in shape, with no risk at low doses, increasing risk at higher doses, and a diminution in risk at the highest doses. Marshall *et al*[29,30] proposed that two successive initiating events and a later promoting event were required for osteosarcoma development. The initiation events would remove the ability of a cell to stop dividing (aside: this proposition was made years before the discovery of tumor suppressor genes), and the promotion event would be a signal for the cells to divide associated with natural remodeling of bone. The model also allowed for the competitive effects of cell killing. Recent analyses provide additional insights into the dose-response relationship.[31] Consistent with studies of cancer patients treated with high dose radiation,[32] bone cancers occurred only after extremely high doses, suggesting that tissue destruction and subsequent biological response are contributing factors.

Workers at nuclear shipyards

Nuclear workers at a naval shipyard in Portsmouth, New Hampshire (US) were reported to be at an increased risk of cancer and leukemia,[33] but the findings were not confirmed in a subsequent cohort study.[34] Several sources of bias were revealed, including inaccurate exposure status ascertained from next-of-kin by newspaper reporters. Further, relatives of workers who died from cancer were more likely to be located and interviewed, which, coupled with a lower all-cause mortality among nuclear workers, produced the spurious result.[35] Radiation work also was not linked to leukemia or lung cancer in case-control studies.[36,37] Recently, workers at eight nuclear shipyards were found not to be at increased risk of any cancer, except mesothelioma which was attributed to probable asbestos exposure.[38] Such studies, despite the large numbers involved, do not necessarily exonerate radiation as an occupational hazard. While reassuring, they indicate that at the relatively low doses involved, the level of risk is accordingly low and perhaps not detectable by epidemiologic methods.

Workers at nuclear installations

Studies of workers at nuclear installations have the potential to validate the risk estimates obtained from high dose and high dose-rate investigations. Radiation doses are recorded for most workers and cumulative exposure for some might reach levels where any adverse effects could be detected. While there have been many studies of workers at individual nuclear facilities,[1,8] it is the combined datasets that are most informative.

A combined analysis of nearly 40,000 workers at three US nuclear facilities[39] provided no evidence for radiation-related risks. The excess RR estimate per Sv (the sievert is a unit of dose effectiveness and is about 1 Gy for X and gamma rays) was 0.0 for all cancers, and it was nega-

tive for leukemia (-1 per Sv). Another pooling of data from multiple studies involved 75,000 employees in three nuclear establishments in the United Kingdom.[40] Excess RR estimates per Sv were -0.02 for all cancers and 4.2 for leukemia. The leukemia risk, however, was apparent only at one facility, Sellafield, where cumulative exposures over 40 cSv occurred and where potential exposure to toxic chemicals may have been higher than elsewhere because of fuel reprocessing activities. Exposure to other hazardous agents, such as asbestos, may have been responsible for increased cancer of the pleura. More recently, 95,673 nuclear industry workers in three countries were analyzed[41] and leukemia, but not other cancers, was significantly elevated. Overall, only about nine of the 3,976 cancer deaths could be attributable to radiation. Combined worker studies may have difficulty in providing risk estimates of useful precision if the ranges of exposures remain small.[42] Studies of electrical utility workers at nuclear power stations also have the potential to provide useful information on radiation risks because of relatively higher exposures than workers at weapons or reprocessing facilities.[43,44]

Workers exposed to plutonium

Plutonium at one time was considered one of the most toxic elements known, with cancers of the lung, bone, and liver clearly increased in animal studies.[4] Human data, however, are sketchy. Workers at Los Alamos (New Mexico, US) who were heavily exposed to plutonium during the Manhattan Project (nuclear reaction research during WW II) have not died at a higher rate than expected, but the numbers were small.[45] Also, three lung cancers developed in long-term smokers, and one osteosarcoma was diagnosed. Other studies of large populations of workers exposed to lower levels of plutonium find little correlation between plutonium intake and cancer mortality.[39,46] Recently, however, apparently high-dose plutonium and gamma ray exposures have caused excess lung cancers among 2,346 workers at the Mayak radiochemical and plutonium production plants in Russia.[47,48] Further studies of these workers involved in early weapons production have the potential to provide new information on human risks from plutonium exposures.[49]

Chernobyl clean-up workers

Although it has been over 10 years since the Chernobyl accident, few epidemiologic studies have been published. Over 600,000 workers were sent from the 15 republics in the former Soviet Union to clean-up the environment and entomb the damaged reactor. Because of the need for emergency action, occupational exposures as high as 35 cGy were permitted, suggesting that ongoing health studies might be informative.[50] To date, blood studies for biodosimetry suggest that the average dose for all workers may be about 10 cGy, with only a small proportion of clean-up workers receiving more than 20 cGy.[51] Thyroid screening of 2,400 Estonian clean-up workers with ultrasound and subsequent needle biopsy of nodules revealed no increase in thyroid disease that could be correlated with radiation dose.[52,53] The risk of leukemia also was not increased. Nonetheless, larger studies may provide information on the effects of protracted exposures.[54]

Nuclear weapons test participants

Participants at nuclear weapons tests conducted by the US[55,56] and the UK[57] were not at overall increased risk of dying from cancer. Estimated exposures were relatively low and less than 1 cGy on average. A small excess of leukemia (10 observed *cf* four expected) was seen at one US test, SMOKY, but in none of the others (46 *cf* 52.4). An elevated SMR for leukemia among UK participants was due to a significant deficit among comparison subjects and not an excess among the exposed. Compared with the general population, participants at nuclear weapons tests were healthier and less likely to die.[1]

Underground miners exposed to radon

Radioactive radon is an inert gas which can migrate from soils and rocks and accumulate in enclosed areas, such as homes and underground mines. When inhaled, the decay of the short-lived, α-particle-emitting progeny can damage epithelial cells in the lung and cause lung cancer.[4,58-60] Exposure in miners is estimated in units of Working Level Months[a] (WLM). Indoor levels of radon are measured in Becquerels per cubic meter, Bq/m^3 (or picoCuries per liter (pCi/l)) which is a count of the number of radioactive decays occurring in a specified volume.

Interest in the effects of exposure to radon and radon decay products (progeny) among underground miners was heightened in the 1940s and 1950s with the expansion of the uranium mining industry. Initially, there was doubt whether radioactive radon (half-life 3.8 d) in mines could produce sufficient doses to induce lung tumors. However, in 1951, William Bale, working with John Harley at the US Atomic Energy Commission New York Operations Office, showed that the α particles emitted from radon decay products (principally polonium-218 and polonium-214, with a combined half-life of under 30 min) could result in meaningful doses to lung tissue when the radioactive particles attached to bits of dust and remained in the lung.[61] Formal epidemiologic studies in the US and

[a] One working Level (WL) equals any combination of radon progeny in one liter of air which results in the ultimate emission of 130,000 million electron volts (MeV) of energy from α particles. WLM is a time-integrated exposure measure and is the product of time, in working months (170 hours), and working levels.

elsewhere in the 1950s and 1960s subsequently provided precise information about the health consequences of radon inhalation.

To date, there have been 11 cohort studies of underground miners in which radon exposure was estimated for individual workers. These studies included different types of hard rock mines (uranium, iron, fluorspar, tin), and were summarized recently in a pooled analysis of 65,000 men accruing nearly 1.2 million person years of observation and over 2,700 deaths from lung cancer.[58,59]

Similarity of results from the pooled analysis was remarkable. Except at the very highest cumulative exposures, the dose-response relationships were generally linear, although risk estimates differed for the individual cohorts. Age at first exposure did not influence subsequent risk, even among children exposed under age 10 years (mostly Chinese miners). The dose-response relationship, as measured by the excess RR per WLM (ERR/WLM) coefficient, decreased with time since exposure and with age at observation. An 'inverse dose-rate' effect (protraction enhancement) was also apparent; that is, for equal total exposure, lung cancer risk was increased at lower exposure rates (and longer exposure durations) compared with higher exposure rates (and short exposure durations).[62] This inverse dose-rate effect, however, effectively disappeared at total exposures below about 50-100 WLM, *i.e.*, at levels comparable to domestic exposure situations. An explanation of this diminution is based on biophysical principals, since at low total exposure, a cell cannot 'experience' a dose-rate effect when the probability of more than one traversal of a cell by an α particle is low.[63,64] Joint RRs for exposure to smoking and radon progeny are consistent with a multiplicative but not additive relationship, although the best estimate is a sub-multiplicative relationship. In the pooled miner analysis, the ERR/WLM coefficient for never-smoking miners was three-times the ERR/WLM coefficient for ever-smoking miners, as might be anticipated from a sub-multiplicative relationship between radon-progeny exposure and smoking. About 40 percent of all lung cancer deaths were attributed to radon-progeny exposure, 70 percent in never-smokers and 40 percent in smokers.[59] The temporal relationship between radon-progeny exposure and cigarette smoking also appears important, with a greater RR occurring when the initiation of cigarette smoking precedes the radon exposure than when radon exposure precedes smoking.[65,66]

Miners are exposed to other contaminants that might impact on radon risk estimates. Airborne arsenic in mines was a significant risk factor for lung cancer. The effect of adjustment for arsenic exposure on radon risk coefficients was mixed, reducing the radon risk estimate in one study,[67] but having little effect in another.[68] Exposure to silica in mine dusts had little apparent effect on radon risk coefficients.[69,70] Other mine exposures such as diesel exhaust, blasting fumes, and other heavy metals have not been evaluated.

Lung cancer is the only site shown to be associated with the inhalation of radon and its progeny. No excess leukemia or lymphoma has been reported among miners who were heavily exposed to uranium or radon and its progeny.[71] Much lower levels of radiation exposure associated with environmental contamination from uranium mill tailings also have not been linked to increased cancer risks.[72] High levels of ingested uranium dust, however, have been implicated as a nephrotoxin.[4]

Environmental exposures

Natural background radiation contributes the vast majority of total population exposure, with radon heading the top of the list. Other sources of environmental radiation include radioactive fallout from nuclear weapons test and from nuclear reactor accidents such as Chernobyl. Normal operation of nuclear reactors releases minimal amounts of radioactivity into the environment. High levels of radioactive wastes, however, were released in the former Soviet Union causing massive environmental contamination (Table 2).

Indoor radon exposure

Although it has long been recognized that radon causes lung cancer among underground miners, the possible hazard of exposure to radon at the generally low levels found in homes was not appreciated until more recently. Indoor radon accounts for over half of all radiation exposures received by the general population, and, based on extrapolations from high-dose miner studies, may cause between 6,000 to 36,000 lung cancer deaths per year in the US.[58,59] In homes, mean radon concentration is 46 Bq/m^3 (or 1.3 pCi/l)[73] which for radon at 50 percent equilibrium with its decay products results in a radon progeny level of 0.006 WL, approximately 50 to 100 times lower than the lowest WL reported in mines.

In an average home, yearly exposure results in approximately 0.2 WLM (0.1 cGy to lung), resulting in an approximate lifetime cumulative exposure of 10-20 WLM (5-10 cGy) (NAS 1991). Subjects resident for a lifetime in a home at the EPA action level (150 Bq/m^3) might accumulate 40-80 WLM (20-40 cGy). Indoor concentrations vary widely among countries; in Great Britain, the mean concentration is about 20 Bq/m^3 (0.5 pCi/l), while in Sweden it is 96 Bq/m^3 (2.6 pCi/l). Some areas in China have exceptionally high levels related to dwellings being built underground.[74]

Indoor radon studies differ from the majority of radiation studies in design, *i.e.*, they are case-control investigations and not cohort studies. The most relevant

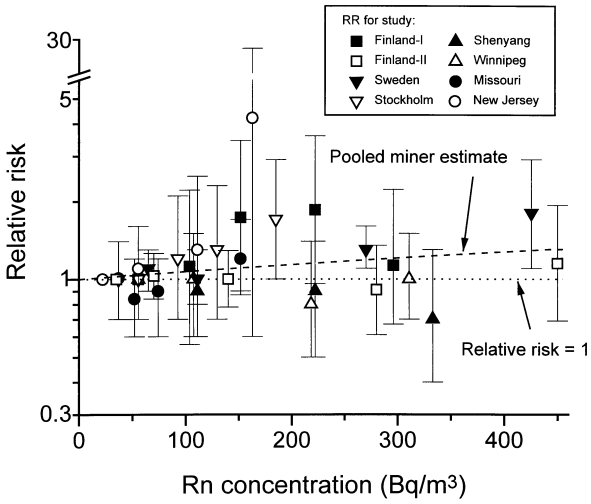
Table 2. Studies of cancer following environmental exposure to radiation

Study	Excess cancers	Comments
Indoor radon[4,74-85,90,91,152-155]	Lung cancer evaluated	Studies consistent with both risks predicted from miner studies and with no risk. Exposures low. Dosimetry imprecise. Migration adds complexity. Future combined studies may prove informative. Major source of radiation exposure to world population.
Fallout, nuclear weapons[103-114]	Thyroid, possible leukemia	Clear increases of thyroid cancer among Marshall Islanders exposed to high doses. Data from studies around Nevada Test Site and in Scandinavia generally noninformative due to low exposures. High exposures around Semipalatinsk might be studied.
Nuclear facilities, environment[115-122,126-132,134]	Childhood leukemia not confirmed	Ecologic surveys raised concern but had severe limitations. Analytic studies fail to link cancer with radiation releases. Preconception effect unconfirmed.
High background radiation, excluding radon[1,92-102]	No evidence for cancer increase	Doses so low that difficult to detect small risk. Ecologic studies severely limited. China studies find no thyroid excess based on clinical screenings.
Chernobyl reactor accident, surrounding population[50,137-147]	Childhood thyroid cancer but not leukemia	Massive release of radioactive iodides likely responsible for remarkable increase but as yet only ecologic correlations. Screening and endemic goiter may have contributed.
Techa River release of radioactive waste[49,148]	Leukemia	Under study. Possible reduction in risk related to low dose rate.

epidemiologic studies of lung cancer are those that have incorporated long-term measurements of radon to estimate exposure. Eight major case-control studies have been reported, along with a pooled analysis of three of the studies (Table 3). Results of these studies, with over 3,700 cases, have been inconsistent, although some were interpreted as positive or 'weakly' positive. Figure 1 contrasts the RRs from eight studies with the predicted RRs for constant residential exposure between the ages of 35 and 65 based on extrapolation from miners.[75] For example, the estimated RR based on miners for an individual living 30 years in a home at 150 Bq/m^3 (about 4 pCi/l), which would occur in less than five percent of US houses, is 1.15.

A case-control study in Stockholm[76] showed a positive association between lung cancer and radon levels, although the association was weakened appreciably when adjustment for occupancy within the home was made.[76] A national study in Sweden found a positive association between radon and lung cancer based on comprehensive measurements and large numbers.[77] In New Jersey (US), lung cancer risk was increased more than twofold among women living in homes with radon levels greater than 150 Bq/m^3 (4 pCi/l), but there were only six cases and two controls with such exposure.[78] A comprehensive case-control study of 308 women diagnosed with lung cancer in China[79] found no association between lung cancer and increasing radon exposure. Year-long measurements of radon were made in current residences, and 20 percent of the readings exceeded 150 Bq/m^3, the level above which

Figure 1. Relative risks of lung cancer by radon levels from eight indoor case-control studies.[81]



remedial action is suggested in the US. Similar negative findings were obtained in a large study in Canada of 738 lung cancer cases[80] and in a study of 538 incident lung cancer cases in Missouri among nonsmoking women.[81] A recent study in Finland[82] was based on 517 matched case-control pairs selected among long-term residents of single-family homes and also was negative. Some

Table 3. Case-control studies of indoor radon and lung cancer

Author (ref) Year	Location	Subjects	Rn concentration[a]	Rn extremes	Summary of overall results
Blot *et al*[79] 1990	Shenyang, China	Females: 308 cases and 362 controls	Median of 85 Bq m^{-3}, mean of 118 Bq m^{-3}	20% > 148 Bq m^{-3}	Categories < 74, 74-147, 148-295, ≥296 Bq m^{-3} with RRs 1.0, 0.9, 0.9, 0.7
Schoenberg *et al*[78,151] 1990,1992	New Jersey (USA)	Females: 433 cases and 402 controls	Median of 22 Bq m^{-3}, mean of 26 Bq m^{-3}	1% > 148 Bq m^{-3}	Categories < 37, 37-73, 74-147, ≥148 Bq m^{-3} with RRs 1.0, 1.1, 1.3, 4.2. *P*-value for test of trend 0.04; highest category had 6 cases and 2 controls
Ruosteenoja[152, 153] 1991, 1996	Finland-I	Males: 238 cases and 434 controls	Mean of 220 Bq m^{-3}	40% > 174 Bq m^{-3}	Quintile categories < 80, 80-126, 127-173, 174-274, ≥275 Bq m^{-3} with RRs 1.0, 1.1, 1.7, 1.9, 1.1. *P*-value for test of trend > 0.05
Pershagen *et al*[76] 1992	Stockholm, Sweden	Females: 210 cases and 191 hospital and 209 population controls	Mean of 128 Bq m^{-3}	28% > 150 Bq m^{-3}	Categories < 75, 75-110, 111-150, 151+ Bq m^{-3} with RRs 1.0, 1.2, 1.3, 1.7. *P*-value for test of trend 0.05. No trend after adjustment for residential occupancy or BEIR IV weighting of exposure[b]
Pershagen *et al*[77] 1994	Sweden	Males and females: 1,281 cases and 2,576 controls	Mean of 107 Bq m^{-3}	25% > 117 Bq m^{-3}	Categories ≤ 50, 50-80, 80-140, 140-400, > 400 Bq m^{-3} with RRs 1.0, 1.1, 1.0, 1.3, 1.8. *P*-value for test of trend < 0.05
Létourneau *et al*[80] 1994	Winnipeg, Canada	Females: 250 cases and 250 controls; males: 488 cases and 488 controls	Means of 120 and 200 Bq m^{-3} for bedrooms and basements	24% > 144 Bq m^{-3}	Categories (estimated) < 72, 72-144, 145-287, ≥288 Bq m^{-3} with RRs 1.0, 1.0, 0.8, 1.0 using bedroom and 1.0, 0.8, 0.9, 0.6 using basement measurements
Alavanja *et al*[81,83] 1994	Missouri (USA)	Female nonsmokers: 538 cases, 1,183 controls	Mean of 67 Bq m^{-3} for cases and for controls	7% > 148 Bq m^{-3}	Quintile categories < 30, 30-43, 44-62, 64-91, ≥91 Bq m^{-3}, with RRs 1.0, 1.0, 0.8, 0.9, 1.2
Auvinen *et al*[82] 1996	Finland-II	Males and females: 517 matched case-controls pairs, residents of one single family home for 19+ years	Median of 67 Bq m^{-3} mean of 100 Bq m^{-3}	9% > 200 Bq m^{-3}	Categories < 50, 50-99, 100-199, 200-399, > 400, with RRs 1.0, 1.0, 1.0, 0.9, 1.15

[a] Most studies incorporated one-year measurements as the principal source of exposure data. The Swedish study used three-month winter measurements, and the Finland-I study used two-month winter measurements. The New Jersey and Stockholm studies used measurements of less than one-year duration for 9% and 13% of subjects, respectively.

[b] Residential exposures were weighted with exposures 5-15 years prior to the index date given full weight and ≥ 15 years before given half weight.

estimates of the population attributable risk are less than two percent, but they were based, in large part, on negative studies.[82,83]

Combined analyses of radon datasets have been conducted to help clarify apparent discrepancies. A pooling of data from three studies in Sweden, New Jersey, and China involved nearly 1,000 lung cancer cases among women.[84] Results were consistent with no association with cumulative radon measures, although results were also consistent with miner extrapolations. These ambiguous results are associated in part with the very low RR to be detected at indoor radon levels, *i.e.*, between 1.1 and 1.3. However, a recent meta-analysis[85] of the eight case-control studies to date produced a dose-response of borderline significance that overlapped closely with predictions from miner studies.

Ecologic studies of home radon exposure have been uninformative. Over 15 published ecologic studies have failed to demonstrate consistent correlations between population lung cancer rates and measures of radon exposure; some studies have shown a positive association between lung cancer rates and mean radon levels, while other studies have shown negative or no associations.[86] One ecologic study,[87] showing an inverse relationship between county measures of radon and lung cancer mortality, has attracted a great deal of attention. With the overwhelming influence of cigarette smoking, population migration, uncertain relevance of population lung cancer rates, the imprecision of summary radon values as a measure of exposure within geographic units, and the small level of excess risk from radon exposure, ecologic studies are of little use in addressing quantitative issues of radon risk. Moreover, Greenland and Robins[88] demonstrate how the inclusion of area-level regressors variables, in particular smoking, will not adjust for confounding at the level of the individual when the risk model is non-linear and smoking effects are synergistic, as is the case with radon-progeny exposure. Further, RRs from the indoor studies (Figure 1) make clear that a negative dose-response relationship,[87] is not consistent with the analytic studies and can be rejected.[85]

While circumstances associated with underground mines have led some to question whether extrapolations from miner studies have direct relevance to residential situations,[89] at the current time such studies provide the best source of risk data for low dose extrapolation.[90] It also should be remembered, however, that cigarette smoking remains by far the single most important preventable cause of lung cancer, and smoking just a few cigarettes per day places one at higher risk than an underground miner working in an unventilated mine.[91]

Natural background radiation

Similar to the geographic studies of radon and lung cancer discussed above,[86] ecologic studies attempting to link cancer mortality with natural background radiation also have been uninformative.[3,92,93] Childhood cancer in England has been correlated with maternal irradiation from background sources,[94] and adult leukemia (but not lung cancer) with radon,[95] but again, such correlations are weak indicators of causality.[3,86,96] A recent survey of areas defined by postal codes found no overall association between childhood cancer and radon levels.[97]

Because radon-progeny appear to be attracted to electric fields, it has been proposed[98] that this concentration of α-emitters might explain the inconsistent associations reported between childhood leukemia and proximity to power transmission lines. However, because electric fields cannot penetrate buildings (where radon accumulates), this theory appears to have limited plausibility. The most extensive investigation on the possible health effects of naturally occurring radiation is being conducted in China.[99,100] on a stable population of 73,000 persons who received three times the amount of background radiation as 77,000 inhabitants of a comparison region. Cancer was not increased among residents of the high background area. Thyroid nodularity, a sensitive indicator of low-dose radiation effects, also was found to be similar among female residents of the high (14 cGy) and low (5 cGy) radiation areas based on clinical screenings of 2,000 elderly women.[101] Differences in chromosome aberrations in circulating lymphocytes indicated that the background radiation levels were different. Limitations of ecologic studies include the uncertainties of dose levels for individuals, migration patterns, selection factors for place of residence, geographic variations in the accuracy of cancer diagnoses, and the inability to control for confounding factors among individuals.[102]

Fallout from weapons testing

Marshall Islands. Natives of four atolls in the north Pacific, east of Bikini Island, were exposed accidentally to nuclear fallout in 1954.[103,104] Most of the exposure was from radioactive iodides and external gamma radiation. Among 253 exposed islanders, 60 (or 24 percent) developed thyroid nodules or thyroid cancer. Leukemia occurred in one exposed and in one nonexposed (n = 135) islanders. The earliest thyroid abnormality was detected nine years after exposure. Risk estimates are uncertain, however, because the large thyroid doses may have caused lethal cellular damage that decreased the number of cells at risk for malignant transformation. The contribution of the different radionuclides of iodine to risk is also uncertain. Most β particle energy from ^{131}I is thought to be deposited in the colloid of the large follicles without reaching the critical follicular cells, and the low rate of decay would further reduce risk by allowing repair processes to operate. In contrast, the shorter-lived and more

energetic isotopes (^{132}I, ^{133}I, and ^{135}I) contributed two to three times the dose of ^{131}I, and exposed the thyroid more uniformly and at a higher dose rate. Another study of 7,000 Marshall Islanders from 14 atolls reported a linear relationship between thyroid nodules and proximity to Bikini.[105]

Nevada Test Site. Several studies have attempted to link increased thyroid nodular disease with fallout exposure from detonations at the US Nevada Test Site in the 1950s.[106,107] Children living in counties which received differing levels of radioactive fallout (the so-called 'downwinders') were traced and clinical examinations conducted to reveal nodular disease. A comprehensive dose reconstruction program provided individual doses (primarily from I^{131}) based on milk and green vegetable consumption, radionuclide deposition, and milk production (mean 17 cGy; range 0-460 cGy). The reported results are inconsistent, reflecting the small number of exposed children studied, the relatively low doses experienced from fallout, and the uncertainties in dose estimation. Comparisons based on county of residence revealed no association with fallout. Based on a combined period prevalence of 19 neoplasms (benign, 11; malignant eight), a significant dose-response was reported. No association was evident for non-neoplastic thyroid nodules or for thyroid cancer evaluated separately. The small excess of thyroid neoplasms may reflect slight biases in dietary recall and disease ascertainment. Dosimetry was based on recall of dietary habits in the 1950s which were obtained in large part after the thyroid examination had been conducted and the status of disease determined. Conceivably, subjects with thyroid disease may be more reliable historians with regard to milk consumption 30 years ago than persons without thyroid disease. Further, selection for thyroid examination varied significantly by exposure; 32 percent of the Utah residents (a high fallout region) were referred for clinical exams *cf* only 17 percent from Arizona (a low fallout region). Thyroid nodularity is especially susceptible to detection by screening, and slight excesses could reflect an increased opportunity for detection.

Several ecologic studies[108-111] also have attempted to link leukemia with fallout from the Nevada Test Site. In an early correlation study,[108]increases in childhood leukemia apparently were balanced by decreases in other childhood cancers. Further, the elevated leukemia risk appeared to be the result of an anomalously low rate of leukemia in the comparison regions and not an association with fallout.[110] A more recent case-control study of 1,000 individuals who died of leukemia in southwest Utah, however, found a weak, but nonsignificant, association between estimated bone marrow dose and all leukemia.[112] There was no association found for exposure *in utero*. While acute leukemia following childhood exposure was increased, similar levels of risk for chronic lymphocytic leukemia (CLL), a tumor not shown to be elevated after irradiation, tempers the causal interpretation.

An ecologic survey[113] of childhood leukemia within Nordic countries could not convincingly link trends with fallout from nuclear weapons tests in the former Soviet Union. Estimates of bone marrow dose were less than annual doses received from natural background radiation. The ecologic design, coupled with such low exposures, had little change to provide substantive information on radiation risk. Fallout in southern Siberia and in Khazakastan from the Semipalatinsk nuclear testing site, however, may have resulted in large population exposures.[114]

Cancer around nuclear installations

A great deal of interest was focused on reports of childhood leukemia being excessive in regions of the UK which included nuclear installations, although there were no general increases in cancer overall.[115] Attempts to replicate these findings in the US,[116] France,[117,118] Germany,[119] and Canada[120] were unsuccessful. More refined analyses in the UK found little evidence that childhood leukemia was related to proximity to nuclear facilities, except for the Sellafield installation.[121] A rather remarkable study[122] found that childhood leukemia was increased around sites selected for nuclear facility construction in the UK, but had not been completed. An infective agent associated with large migrations of people into these areas has been proposed as one possible explanation for the childhood leukemia clusters.[123-125] These ecologic correlation analyses are severely limited because radiation dose to individuals is unknown, but is likely much below natural background radiation;[126] and unknown factors associated with migration, selection for residence, and occupation could play a major role in cancer occurrence and registration. Other studies around nuclear facilities have failed to provide clear insights into the reasons, other than chance or gerrymandering, for apparent clusterings of childhood cancer.[127,128]

A case-control study,[129] however, indicated that paternal exposure among Sellafield workers might explain the cluster. Similar studies at the Dounreay (UK) nuclear facility,[130] in Scotland,[125] and Canada[131] failed to replicate the preconception findings. The geographic distribution of the paternal dose received prior to conception of over 10,363 children born to fathers who worked at Sellafield also added doubt to the causal nature of the association. Childhood leukemia was not increased in areas, other than Seascale (UK), despite higher preconception exposures.[132] Further, the potential exposure hypothesis

was not consistent with comprehensive studies of cancer risk among children of atomic bomb survivors.[133]

Preconception radiation of the fathers appears to have been a provocative but unsubstantiated hypothesis to explain the Seascale cluster.[134] An equally provocative hypothesis is the possibility that childhood leukemia may occur as a rare response to an infectious agent whose transmission is enhanced when relatively isolated populations suddenly come in contact with large numbers of people migrating into their habitat.[123-125]

Nuclear reactor accidents and Chernobyl

The nuclear reactor accident at Three Mile Island (Pennsylvania, US) resulted in minimal population exposure. In contrast to Chernobyl, there was a containment vessel which prevented release of radioactivity into the environment. The cancer risk was accordingly negligible.[135] Ecologic surveys have not linked increased cancer rates[136] or cancer mortality[116] with residence near Three Mile Island. The accident at Chernobyl, however, resulted in a massive release of radioactivity into the environment.[50] Childhood leukemia has not been limited to this environmental contamination,[137-140] indicating a low dose to bone marrow.[141] Infant leukemia was correlated with possible *in utero* exposure to radiation from Chernobyl;[142] but, as in all ecologic surveys, actual exposure to individuals was unknown and the findings were also at odds with the study of *in utero* exposure from the Nevada Test Site.[112] Initial analytic studies[143] of thyroid cancer were negative, but the follow-up may not have been sufficient. Subsequent descriptive studies revealed an abrupt increase in childhood thyroid cancer in Belarus and the Ukraine[144] which may be only partially the result of increased medical surveillance and reporting.[145] It appears, also, that only a few children actually died from thyroid cancer. While it is becoming clear that an unusual increase of thyroid cancer in children has occurred,[146,147] the absence of radiation dose estimates, the possibility of surveillance bias, and the possible enhancement of a radiation effect in iodine deficient areas will have to be carefully evaluated.[141] New comprehensive studies of thyroid cancer in Belarus, Ukraine, and Russia, coupled with detailed dose reconstruction investigations, however, now indicate that valuable information on radiogenic thyroid cancer following the reactor accident may be forthcoming.[50]

Studies of populations in the southern Urals, Russia, are also ongoing. In 1957, a storage tank at the Chelyabinsk nuclear facility (the Kyshtym accident) exploded and released large amounts of radioactive waste into the Techa river. Prior to the accident, high-level radioactive wastes from the Mayak facility were dumped into the river.[148] Leukemia has been reported to be in excess among the 28,000 residents and doses as high as 400 cGy were possible. These studies have the potential for providing new information on the effects of ionizing radiation delivered chronically over time.[49]

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