Epidemiologic Studies of the Effects of Exposure to Ionizing Radiation

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1. Introduction
Epidemiology is the study of health and disease in populations; its methods have been used to address a range of topics including evaluation of the health effects of exposure to ionizing radiation. This review will provide a discussion of the use of epidemiological methods in studies of radiation health effects, followed by a discussion of the findings of several important epidemiologic studies of the effects of exposure to ionizing radiation.

2. Epidemiologic Methods
All epidemiologic studies must address concerns about the accuracy of measurements of exposure and disease, and the appropriateness of comparisons between groups of people. These issues affect the validity of findings of studies of atomic bomb survivors, workers in the nuclear industry, and communities environmentally exposed to radiation.

2.1 Exposure Measurement
Accurate categorization of individuals into exposure groups is necessary if any association between exposure and disease is to be accurately assessed. Even if disease rates increase with increasing radiation dose, an association cannot be detected if enough people are inaccurately categorized by dose level, diluting any real differences in disease rates between dose groups.

In the Life Span Study of atomic bomb survivors, estimation of the exposures received by over one hundred thousand survivors has occupied researchers for more than forty years.[1] The level of radiation exposure received by an individual from the bombing was affected not only by where the person was situated geographically, but also their body position at the time of the explosion, whether they were shielded from the explosion, the type of shielding material, atmospheric humidity, patterns of movement and activities immediately after the explosion (due to concerns about residual radiation), ingestion of radioactive material, and bomb design.[2-4] Exposure misclassification, such as may result from incomplete information, and from inaccurate survey data elicited from a highly traumatized population, could produce errors in dose response estimates. Dose estimates for the National Academy of Science's BEIR III report were based on exposure histories for 109,000 people collected by the Atomic Bomb Casualty Commission and dose reconstruction efforts. In the National Academy of Science's BEIR V report, dose estimates were revised and doses (specifically neutron doses at Hiroshima) were lower than previously reported.[5 6]

In an occupational setting, a researcher may have better information about external radiation exposure. Workers at some nuclear facilities have been issued personal dosimeters to monitor penetrating radiation exposures, a seemingly ideal measurement situation. However, changes over time in who was monitored, the sensitivity of dosimeters, and the frequency of reading dosimeters could affect the reliability of recorded doses.[7-10] In the early years of operation of many nuclear facilities, dosimeters were read daily or weekly to help identify workers with higher exposures. But frequent reading may not allow dosimeters to be sufficiently exposed to reach the detection threshold. Doses well below exposure standards have not been of regulatory concern, but are of epidemiological interest, especially when they are accumulated over many years. It is typically assumed that workers wore their dosimeters at all times while at work, and that the external radiation dose recorded on a film badge reflects a radiation exposure that occurred at a horizontal angle (since the angle of exposure can affect the dose recorded by the badge) to the front of the worker.[11] In actuality it is rare that a worker is exposed to a uniform radiation field,[12] and some workers might have removed their badges before performing tasks which entailed high exposures in order to ensure that their recorded external exposures were below standards which would otherwise require them to stop work. Other errors might be expected because of difficulties in matching hundreds of thousands of dosimeter readings collected over many decades to thousands of workers, and errors of equipment and technicians that read the instruments.[10]

In both occupational and environmental settings, internal exposure to radionuclides is even more difficult to assess than external radiation exposure. Ingested or inhaled alpha- and beta-emitting radionuclides have greater density of ionization than gamma or x-rays, but they have little penetration, so the relevant dose is delivered to a particular organ or cells within the organ. Knowledge about retention of radionuclides has been used to estimate exposures, and information from excreta samples (urine/fecal analysis) or field data (nose swipes, air samples, skin and clothing contamination estimates) are traditionally employed to estimate body burdens of workers. Estimates can also be made using whole-body counters that detect the penetrating radiation emitted by the internally deposited particles. However, most epidemiological studies have used crude indicators to identify those people likely to have been exposed to internal radionuclide contamination. In occupational settings, exposure categories might be based on job titles, area monitoring data, or history of monitoring for internal radionuclides, while in environmental settings, exposure categories might be determined by geographical location and patterns of environmental contamination.

The proper classification of people in a study by level of exposure requires not only good measurement of exposure, but also correct decisions about which periods of exposure are etiologically relevant. Sometimes only the doses received up to a certain number of years in the past are considered in forming exposure groups based on the assumption that cancers take time to develop and that recent exposures are not relevant to disease (so-called "lag" or "latency" analyses). Chronic exposures might have a greater opportunity to impact an organism during especially susceptible states; or it may be that only high dose rate exposures are relevant to the onset of later disease. Thus, a further difficulty in interpreting radiation-cancer associations, beyond the measurement process itself, is that mechanisms of radiocarcinogenesis are not sufficiently well understood to provide a sound theoretical basis for knowing in advance what should be measured.

Comparability of groups with different levels of exposure is important in order to be able to attribute differences or similarities in disease rates between groups to radiation *per se*. This is accomplished both through the design of the study and through statistical analysis of the data. The assumption is that well-designed studies can provide estimates of the radiation-cancer dose response relationship that characterize the change in cancer rates for each unit change in radiation.

Studies of survivors of the atomic bombing of Hiroshima and Nagasaki have played a dominant role in the assessment of radiation health effects.[6] Biased conclusions about radiation-cancer associations could occur if groups with different degrees of radiation exposure are not comparable in other respects. Differences among survivors of different levels of exposure may relate to long-term effects of radiation on immune function.

Other issues of comparability arise in studies of workers exposed to low level radiation. Studies of occupational hazards often compare the mortality experience of workers to that of the general population using Standardized Mortality Ratios (SMRs). These analyses may be the only way to detect an excess of a rare disease in an industry which has poor information about individual workers' exposure. SMR analyses are most informative for evaluation of health effects known to result in relatively short survival times and high mortality rates. However, SMR analyses are of less use for studying common causes of death that are expected to be affected by a broad range of exposures and to differ significantly between a working population and the general public (it has been repeatedly noted that people hired to work at nuclear facilities tend to be a select group of people who have low mortality rates, as expected in a highly selective, well educated, well paid workforce).[13]

More useful are studies which compare workers with each other rather than with the general population and thus avoid problems of comparability between workers and non-workers. Comparison of mortality rates among workers with different levels of occupational exposure avoids the need to make comparisons to mortality rates in the general population. However, there is still reason for concern about appropriate comparisons. Workers that enter (and remain in) jobs involving radiation exposure may differ from workers in other jobs in terms of work skills and preparation. The use of medical exams to screen workers for dangerous or high-security jobs, and prohibition of smoking in some but not all work areas, may also lead to health differences that are associated with occupational exposure. For example, in one study, workers who were at risk of internal contamination with radionuclides had *lower* non-cancer mortality rates than workers who were not at risk of internal radionuclide exposure.[16] Since the radiation doses from occupational exposures accumulate over time, selective differences may be age-related. Workers who are healthy enough to remain employed for many years generally reach higher dose levels, while workers who leave employment early due to illness generally have lower doses; this can lead to a downward bias in estimates of radiation effects. Other problems may be the result of differential exposure to chemicals or smoking.

2.4 Summary

Issues of exposure measurement, disease classification, and comparability of study subjects (between exposure groups and between the study population and the more general population) are issues for concern in reviewing the following studies.

The effects of measurement errors, selection bias, over-reliance on mortality data, and limited periods of followup tend to bias studies towards finding no radiation-cancer association. Given these impediments, it is very difficult to detect associations between low level ionizing radiation and cancer. Findings which have been reported may be expected to be biased downwards. It should also be noted that epidemiology is used for different purposes in different circumstances. Often, epidemiological studies are conducted in order to identify a potentially hazardous agent. Such studies may use relatively crude indicators of exposure, and yet evaluate whether an agent is associated with a disease. However, studies of the effects of ionizing radiation are not done to identify a potential hazard; rather, these studies are conducted for the purpose of risk assessment--to quantify the risk associated with a relatively small increase in level of exposure. Evaluations of risk assessment require a higher quality of data. The current risk assessments of the effects of low level radiation are primarily based on questionnaire data elicited from atomic bomb survivors (and mortality data, similarly suffering substantial misclassification) which are relatively poor quality data; greater attention should be given to other sources of data which provide better quality data.

3. Studies of Atomic Bomb Survivors

3.1 Introduction

Recent reports of the US. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation, and the International Commission for Radiological Protection[17] focus on the Life Span Study (LSS) of survivors of the atomic bombings of Hiroshima and Nagasaki as the primary source of information for understanding radiation health effects. These reports, subsequently, serve as a primary resource for a number of other recent reviews on radiation health effects.[18-23]

3.2 The Life Span Study (LSS)

The results discussed in this section relate to risk estimates for cancer incidence and cancer mortality among A-bomb survivors. Other studies of A-bomb survivors have examined non-cancer effects, including cataracts, birth defects, and genetic effects which are passed between generations. Most reports of results of LSS analyses concern radiation-related changes in cancer mortality rates among the survivors, often reported as the estimated excess relative risk of cancer mortality per sievert (Sv) radiation dose (ERR_{1Sv}).

Overall, the increase in all solid cancer mortality reported in BEIR V was 45 percent per Sv ($ERR_{1Sv}=0.45$). Leukemia mortality showed larger associations, with the largest excess risks among survivors who were under 20 years old ATB. The effects of radiation on breast cancer mortality were also described as differing with age at time of bombing; excess relative risk was largest for those exposed before age 15, while for those exposed after age 15 effects decline with older age at exposure.[6]

The incidence of cancer (as opposed to cancer mortality) diagnosed between 1958 and 1987, among members of the LSS (79,972 A-bomb survivors) was reported in 1994.[24]

Analyses of leukemia incidence reported strong evidence of radiation-induced risks for leukemia, with ERR at 1 Sv for leukemia subtypes (ALL, AML and CML, respectively) were 9.1, 3.3 and 6.2.[25] The excess relative risk for all solid tumor incidence was 0.63 per Sv. Lung (ERR_{1Sv}=0.95), breast (ERR_{1Sv}=1.59), and thyroid (ERR_{1Sv}=1.15) were some of the sites with larger estimated associations. When considering all solid tumors, the authors noted a twofold greater relative risk for females than males, and decreasing relative risk with age at exposure, predominantly due to the large ERR associated with exposures at the very youngest ages. The estimated excess relative risk at 1 Sv for all solid tumors was 40% larger when evaluating cancer incidence (ERR_{1Sv}= 0.63) than when evaluating mortality data (ERR_{1Sv}= 0.45). These differences have been attributed to greater diagnostic accuracy of the incidence data and the lack of full representation of radiosensitive but relatively nonfatal cancers, such as breast and thyroid, in the mortality data.[26]

3.2.1 Differences in Radiosensitivity for Different Types of Leukemia

Since whole body exposure to external penetrating radiation may affect cells throughout the body, it has been suggested that all sites potentially may exhibit increased cancer incidence. In the study of atomic bomb survivors, sensitivity to leukemogenic effects of radiation has been described as exhibiting differences between myeloid and lymphatic leukaemia. Following exposure to A-bomb radiation the dose response curve for myeloid leukaemia was exceptionally steep; the extra cases of this disease were concentrated among deaths before 1970, and there still seem to be no cases of chronic lymphatic leukaemia among the other radiogenic cancers. Similar differences between two variants of the same disease have also been observed in other populations of high dose survivors (e.g. radiotherapy patients). Therefore they might be in some way related to immediate effects of high doses.

These immediate effects, which include a rapid increase in the number of circulating myelocytes and an equally rapid decrease in the number of circulating lymphocytes are short-lived (less than a week) and there follows a much longer period when there is an overall shortage of red and white blood corpuscles and a high risk of dying either from aplastic anaemia or from fulminating infections.

Given this sequence of events it is only necessary to assume that the initial myelocytosis (which probably saved lives) was accompanied by a rapid outpouring of mutant cells, to have both a simple explanation of the special relationship between myeloid leukaemia and radiation, and a reason why this relationship has only been observed in studies of late effects of high doses.

The total absence of chronic lymphatic leukemia among the other radiogenic cancers of Abomb survivors is less easily explained. It is clearly not the result of lymphocytes being insensitive to stochastic effects of radiation (see OSCC data), or insensitive to nonstochastic effects[27] or the result of lymphocytes being less at risk of spontaneous mutations than myelocytes (since lymphatic and myeloid forms of leukaemia and other immune system cancers are equally common). However, between 20 and 70 years of age myeloid forms of leukaemia are much commoner than lymphatic forms, and after 70 years of age the position of the two groups is reversed.[28] By 70 years of age the proportion of chronic cases among lymphatic leukaemias is as high as the proportion of acute cases among juvenile forms of lymphatic leukaemia. So it is possible that the remarkable contrasts between myeloid leukaemia and chronic lymphatic leukaemia in Abomb data are partly the result of what happened to the high dose survivors in the first week after the bombing[27] and partly the result of intervals between induction and death exceeding 50 years in some cases of chronic lymphatic leukaemia.

3.3 Effects of Fetal Irradiation Reported in Studies of A-bomb Survivors

Studies of British and American children have repeatedly shown that the number of early cancer deaths following fetal involvement in obstetric x-ray examinations is excessive. Nowadays this finding is accepted as evidence of a causal association between fetal irradiation and childhood cancers. But there was prolonged opposition to this hypothesis and there still remain a few objectors.

This extreme reluctance to accept an obvious interpretation of a straightforward observation was a direct consequence of there being no comparable findings for children who had survived prenatal exposure to A-bomb radiation, and RERF repeatedly coming to the conclusion that in the 'in utero cohort' the only late effects of the radiation were teratogenic (stunted growth and microcephaly) rather than carcinogenic. But it is now clear that these are false impressions caused by there being gross underrepresentation of near conception exposures in the in utero cohort, and there being high rates of general mortality and infant mortality for at least a year after the bombing.

Young embryos are far more at risk of dying from stochastic effects of radiation than mature fetuses; during the latent phase of all cancers with in utero origins, especially leukemias, there is mounting sensitivity to infections. Therefore, these 'competing causes of death' can explain why, in the in-utero cohort, there was a not only a shortage of young embryos but also no cases of childhood leukemia; and only one case of microcephaly among the survivors who were under 8 weeks of fetal age when exposed. Those A-bomb survivors exposed in utero who survived to adulthood have, however, demonstrated excess cancer incidence later in adult life.[29-32]

There is one school of thought which assumes that sensitivity to brain damage effects of radiation is a relatively late development which leaves young embryos (under 8 weeks of fetal age) at no risk of this damage. This is still the line taken by ICRP. But given the unusual age distribution of the in utero cohort, there is every reason to believe the rarity of microcephaly cases in the youngest age group of A-bomb survivors is an artifact caused by extra in utero deaths.

3.4 Genetic Effects
Since ionizing radiation may damage chromosomal material, preconceptual exposure may lead to mutations in genetic material that will be transmitted to the exposed person's children. While such effects are expected based on studies of irradiation of animals, no genetic effects of the A-bomb radiation have thus far been observed.[33] The population examined to study such effects (F1 cohort) was assembled by the Atomic Bomb Casualty Commission. Even so it was restricted to the offspring of persons whose risk of dying before ABCC arrived on the scene was both exceptionally high and strongly dose related. Whether the extra bomb-related deaths had a disproportionate effect on carriers of defective genes will never be known. But what we do know is that at least until 10 years of age the F1 cohort has had an exceptionally low death rate for all causes (SMR=0.72) and neoplasms (SMR=0.81).[34]

3.5 Limitations of Data from Hiroshima and Nagasaki
We have already outlined some reasons for concern common to all epidemiologic studies, which related to comparability of popualations at risk and to exposure and disease measurement. As we noted, exposure measurement in studies of a-bomb survivors relied on questionnaire data collected over a period of many years after the bombing. Patterns of exposure were extremely complex due to sheilding by buildings and terrain, and little attention has been given to the contribution of delayed, residual or induced radiation to the doses received by survivors presumed to have little or no radiation exposure.[27] Recent comparisons of exposure estimates based on the questionnaire data used in the LSS to biological indicators of dose (such as chromosomal aberrations) suggest substantial exposure misclassification.[35] Evaluation of death certificate records also suggest substantial problems of disease misclassification. A recent report noted overall percentage agreement between death certificate and autopsy diagnoses in the LSS data was only 52.5%, with 25% of cancers diagnosed at autopsy missed on death certificates.[14] These are issues which affect the internal validity of a study.

Validity, however, may also be evaluated with respect to the appropriateness of using results from one study population to make conclusions about people in other situations-- this is called external validity. Some researchers have questioned whether it is appropriate to use results drawn from the LSS, a study population of five-year survivors of an atomic bomb detonation, to form conclusions about the effects of radiation in contemporary populations exposed to environmental or occupational exposures. One reason to question the validity of such conclusions relates to the difference in exposure patterns. The pattern of exposure from an atomic bomb blast is significantly different from exposure patterns in occupational and environmental settings. In contrast to studies of atomic bomb survivors, concerns about occupational and environmental exposures are related to the effects of long term exposure to low level radiation, at low dose rates.

Stewart and Kneale have also raised concerns about selective survival of people after the atomic bombing. Stewart and Kneale have presented evidence which suggests that differential mortality from the time of the bombing in 1945 until the assembly of the population for epidemiological study in 1950 produced more highly selected groups of robust individuals at higher than at lower exposures.[36] Premature deaths of people who were sensitive to the acute effects of radiation may have led to the selective removal of those who were more sensitive to the later effects of radiation as well. Consequently, when follow-up began five years after the bombing only a select population of less radiosensitive persons may have been left.[36-38] A recent survey of mortality in Nagasaki during the period 1945-1950 has also suggested potential selective survival among A-bomb survivors.[39] This situation raises questions about the applicability of estimates of radiation-cancer associations among A-bomb survivors to other populations.

4. Epidemiological Studies of Workers in the Nuclear Industry

*4.*1 Introduction

Occupational studies of radiation health effects offer the opportunity to study humans who have been exposed in a relatively uniform environment, who can be followed through employment records and occupational medical departments, and who can be traced through pension benefits and other record sources. Because occupational exposures are often higher than exposures of the general public, smaller sample sizes are needed than would be the case for environmental studies (presuming a linear dose response association.) Workers occupationally exposed to ionizing radiation are of particular interest because their chronic exposure to relatively low doses are more like environmental exposure situations than medical or A-bomb exposed populations. There has been much interest in the potential influence of dose rate on the carcinogenic impact of a given cumulative dose. Many studies of nuclear workers have focused on external penetrating radiation, in part because this source of exposure is easier to quantify using film badges than are doses from internally deposited radionuclides. A volume edited by Wilkinson summarizes much of the literature on epidemiological studies of nuclear industry workers.[13] A critical review of the US Department of Energy's epidemiology program has been published by Physicians for Social Responsibility;[5] and a review of studies of workers in nuclear weapons facilities internationally has been published by the International Physcians for the Prevention of Nuclear War and the Institute for Energy and Environmental Research.[40]

This review discusses the findings from selected occupational studies, focusing on results from cohort studies of US Department of Energy (DOE) nuclear weapons facilities, but also discussing results from studies of the United Kingdom's Atomic Energy Authority, and international 'pooled analyses' which combine data from nuclear weapons facilities from several countries.

These are primarily studies of cancer mortality; however, other adverse effects of radiation exposure may also be of interest. While research is limited on effects of occupational exposure to radiation other than cancer, some researchers have examined genetic effects (heritable effects) and the occurrence of chromosomal aberrations.

4.2 Studies of Nuclear Weapons Facilities Workers

The United States operates a large number of governmental nuclear facilities for the research and production of nuclear weapons. During the Manhattan project, workers at these facilities built the first nuclear reactors; the Atomic Energy Commission, and its successor agencies conducted monitoring of workers for internal and external exposure to radiation. Studies of workers in the US nuclear weapons facilities provide an important source of information about effects of low level exposure to ionizing radiation, since these workers have a long history of follow-up and relatively good exposure information. Occupational cohort studies of workers at Hanford and Oak Ridge National Laboratory have received attention because of reports of positive associations between estimated external radiation exposure and mortality due to specific cancers. Workers at the Rocky Flats facility have received attention because of reports of positive associations between internal exposure to radionuclides and cancer mortality. In occupational settings, cumulative doses tend to be much lower than doses received by atomic bomb survivors; consequently, associations between disease and external radiation in this section are reported as the excess relative risk per 10 mSv dose (ERR_{10mSv}).

4.2.1 Hanford

The Hanford facility, located in the state of Washington, is one of the largest cohorts of nuclear weapons facility workers, with particularly complete information on external radiation exposure. Reports on cohort studies of workers at the Hanford facility have focused on the effects of external ionizing radiation exposure; few workers have recorded internal radionuclide exposures. Early analyses of workers at the Hanford facility compared accumulated doses among Hanford workers who died from cancer to the doses accumulated among workers who died from non-cancer causes. Higher mean cumulative doses were reported among workers who died from cancer than among workers who died from other causes.[41]

These findings were followed by analyses by other researchers which reported lower cancer mortality among workers at Hanford than among the general population (SMR=0.86), and little evidence of dose response relationships between cumulative radiation and cancer mortality, with the exception of positive associations for multiple myeloma, Hodgkin's disease, and carcinoma of the pancreas.[42-45] Reporting on vital status follow-up of the Hanford cohort through 1986, Stewart and Kneale noted positive associations between radiation and cancer mortality, with exposures received after age 50 being most important to this relationship.[46] Gilbert et al., in contrast, reported negative associations between cumulative radiation dose (at all ages) and leukemia mortality (ERR_{10mSv}= -0.011) and all cancer mortality except leukemia (ERR_{10mSv}= -0.00).[45] Stewart and Kneale have argued that attention to time-related factors, such as age at exposure, year of exposure, and latency, are fundamental to explaining the differences in results between their research and that of Gilbert et al.[47 48] Stewart and Kneale have also reported analyses which, by comparing dose response associations for lung cancer and other respiratory diseases, suggest that confounding by cigarette smoking is unlikely to account for the radiation-cancer dose response relationships observed at Hanford.[49]

4.2.2 Oak Ridge National Laboratory

Oak Ridge National Laboratory (ORNL) is located in Oak Ridge, Tennessee. The association between radiation and cancer mortality among ORNL workers has been the subject of a number of analyses. Checkoway et al. conducted analyses of 8375 white male workers hired at ORNL between 1943 and 1972.[50] As in other DOE cohorts, all cause (SMR=0.73) and all cancer mortality (SMR=0.78) for these workers were lower than expected when compared to the general population;[5] however, elevated SMRs were observed for leukemia (SMR=1.49), cancer of the prostate (SMR=1.16), and Hodgkin's disease (SMR=1.10). Standardized rate ratios for leukemia increased with increasing external radiation dose and with longer latency assumptions, although no deaths were observed among those receiving the highest doses.

Wing et al. reported on the association between radiation and cancer mortality among ORNL workers hired between 1943 and 1972 with vital status follow-up through 1984.[16] Leukemia mortality was elevated in the cohort when compared to the general population (SMR=1.63). Examination of dose response associations between radiation and mortality among white male workers revealed that all cancer, lung cancer, and leukemia exhibited positive associations with external radiation dose. Associations were largest in magnitude for leukemia, intermediate for lung cancer, and smallest in magnitude for all cancer mortality. The magnitude of associations increased with longer lag assumptions. A 4.94% increase in all cancer mortality per 10 mSv dose was reported under a twenty year lag assumption (ERR_{10mSv}= 0.0494). Wing et al. noted that contrary to expectations about confounding due to cigarette smoking, associations between radiation and cancer mortality were smaller in magnitude for lung cancer mortality than for other smoking related cancers; and, radiation-cancer associations exhibited strong sensitivity to lag assumptions. Frome et al. also examined radiation-cancer association among white males employed at ORNL; using a linear excess relative risk model they reported ERR_{10mSv} of 0.0187, 0.0359, and 0.0627 for lag assumptions of 2, 10, and 20 years.[51]

Subsequent analyses report that the radiation-cancer associations among ORNL workers exhibits substantial modification of the effects of low-level radiation by the age at which exposure occurred.[52] Similar to Stewart and Kneale's findings for workers at the

Hanford facility, the association between external radiation and all cancer mortality was found to be strongest for exposures received at ages above 45 years(ERR_{10mSv}= 0.059).[53]

4.2.3 Santa Susana Field Laboratory

A cohort study of 4563 nuclear workers monitored for external radiation at the Santa Susana Field Laboratory. Rate ratios were calculated in order to estimate the effect of 100 mSv cumulative external radiation dose received after age 50; elevated rate ratios were observed for mortality due to all cancers (RR_{100mSv}= 1.77), lung cancer (RR_{100mSv}= 3.73), and solid tumors at radiosensitive sites (RR_{100mSv}= 3.03) .[54]

4.2.4 Rocky Flats

Rocky Flats workers have been examined in order to evaluate effects of external exposure to ionizing radiation, and internal exposure primarily to plutonium. Compared to Hanford and ORNL, estimates of external radiation exposure were relatively less complete. Rate ratios were calculated in order to compare employees with greater than, and less than, 10 mSv cumulative external radiation dose; elevated rate ratios (RR) were found for myeloid leukemia (RR=3.02), lymphosarcoma and reticulum cell sarcoma (RR=3.00), and liver cancer (RR=2.77).[55]

Attention was raised by the observation of positive dose response associations between internal exposure estimates and specific types of cancer mortality.[55] Standardized rate ratios increased as plutonium body burdens increased for all causes, all cancers, and digestive cancers. Wilkinson compared rate ratios for the group of white males exposed to greater than and less than 2nCi of internal contamination by radionuclides, reporting elevated rate ratios under a ten year lag assumption for workers with >=2nCi for all causes of death (RR=1.39) and all lymphopoietic neoplasms (RR=5.22). An excess of brain cancer was reported for the cohort as a whole (SMR=1.19). In an unpublished paper,[56] Wilkinson reported that SMRs were noted to increase when latency periods of 5, 10, 15 years were considered. Elevated SMRs under a 15 year lag were noted for liver (SMR=2.89), brain (SMR=2.93), leukemia (SMR=2.49), lymphopoietic (SMR=1.43) and benign or unspecified neoplasms, which were all intracranial (SMR=5.85).

4.2.5 Los Alamos and Lawrence Livermore Laboratories

Los Alamos National Laboratory (LANL) is located in Nevada. LANL workers were examined to evaluate the effects of external and internal exposure to ionizing radiation[57] Wiggs et al. examined 15,727 white males at Los Alamos, presenting SMRs which were lower than expected for all cancer mortality (SMR=0.64) and all cause mortality (SMR=0.63). External radiation exposure was evaluated by comparing rate ratios for workers with different levels of cumulative external radiation dose. Overall, little association was observed between categories of cumulative external exposure and cancer mortality; however, positive trends were observed for Hodgkin's disease, brain neoplasms, cancer of esophagus, and kidney cancer. Evaluation of internal exposure to radionuclides was done by comparing workers with plutonium exposure greater and less than 2nCi, excluding those workers never monitored. Elevated rate ratios (RRs) are found for lung cancer (RR=1.78), and bone cancer (1 case observed/ approximately zero expected), brain cancer (RR=1.20), bladder cancer (RR=6.39), and lymphoma (RR=1.29).

The only published studies of the incidence of non-fatal cancers among US nuclear weapons facility workers are analyses of malignant melanoma among LANL and Lawrence Livermore National Laboratory (LLNL) workers. A threefold melanoma incidence excess was reported among LLNL workers.[58] A subsequent study examined occupational and non-occupational factors in much greater detail, and reported that exposure to radioactive materials and being present at a nuclear test were important predictors of melanoma incidence among these workers.(AJE, 1997) In the studies of LANL workers, melanoma incidence for workers from 1969-78 was compared to New

Mexico rates.[59] Six cases of melanoma were identified among the workers where 5.69 were expected.[60]

An unpublished report examined the incidence of different types of cancer among LANL workers using a tumor registry for the period 1969-78.[61] Sites identified as of particular interest were lymph nodes, lung, liver, and bone. For men, Standardized Incidence Ratios (SIRs) were as follows: liver cancer=1.11; bone cancer=2.04; lymphosarcoma=2.49; confidence intervals were wide. All cancer incidence, as in other studies of DOE workers, was low, particularly due to a deficit of smoking related cancers. Similar to the published studies of malignant melanoma incidence, this study would be expected to underestimate cancer incidence among LANL workers, due to underascertainment in the tumor registry, failure to identify cases which occurred among workers who migrated out of the area, and the ability to only consider incidence among those employed at the time of study.

4.2.6 Pantex, Savannah River, and Mound

Data on external and internal exposure to ionizing radiation are less complete at most other DOE facilities; SMR analyses are emphasized for analyses of Pantex,[62] Savannah River Plant,[63] and Mound.[64] These studies demonstrate the expected problems of selection bias through the observation of below expected mortality rates for all causes and all cancers. One approach that has been used in SMR analyses is to investigate subgroups of workers hired in early historical period; these workers will have the longest duration of followup (allowing for a longer latency period) and typically also received higher doses of external and internal radiation. In Cragle et al.'s analyses of Savannah River Plant[63] elevated SMRs for leukemia were observed among the workers hired before 1955. Among workers at Mound hired before 1960 elevated SMRs were observed for lung cancer mortality.[64]

4.2.7 Nuclear Facility Workers in the United Kingdom

Overall, data for workers employed in the United Kingdom's Atomic Weapons Establishment demonstrated strong evidence of selection bias among the 22,552 workers employed between 1951 and 1982 (mortality was 23% lower than the national average for all causes of death and 18% lower for cancer). Data on external radiation exposure is highly incomplete for this cohort; only 42% of these workers were ever monitored for radiation exposure during their employment.[65]

Two recent study of workers at British Nuclear Fuels facities reported that among radiation workers there were positive associations between low level external radiation exposures and leukemia mortality (ERR_{10mSv} =0.0418); for cancers other than leukemia, in contrast, there was little evidence of a dose-response association.[66 67]

4.2.8 Meta-analyses and Multi-facility Analyses

Wilkinson and Dreyer reported on meta-analyses of radiation-leukemia associations using results reported from published studies of workers at seven facilities. They calculated an relative risk for leukemia of 1.5 (adjusted for age and calendar time) among workers with cumulative occupational doses of 10 mSv or greater, compared with those with cumulative doses of less than 10 mSv; and, a relative risk of 1.8 among individuals with 10-50 mSv (1-5 rem) when compared with those who had cumulative doses less than 10 mSv. They concluded that the combined data indicate a small elevated risk of leukemia for doses of ionizing radiation under 50 mSv.

Researchers have combined data for workers from ORNL, Hanford, and Rocky Flats in order to conduct 'pooled' analyses of the effects of external exposure to ionizing radiation.[68 69] Such pooled analyses have the advantage of increased statistical power since they consider large numbers of workers;[70] however, the heterogeneity of the cohorts (in the quality and completeness of data, the nature of work done at different facilities, and the types of exposures received at the facilities) raises concern about pooling.[13 51 71] A report by Gilbert et al. on these pooled analyses noted a negative association between external radiation and leukemia (ERR_{10mSv}= -0.01), and no association between radiation and all cancer mortality (ERR_{10mSv}= 0.00).[68]

Kneale and Stewart also reported on analyses that included workers from ORNL and Hanford, as well as at three other DOE facilities.[71] They concluded that when time-related factors were considered, a positive association existed between radiation dose and cancer mortality among workers at each facility. However, significant differences existed in radiation-cancer associations between the cohorts, suggesting that pooled analyses may be inappropriate because of the heterogeneity between cohorts. For workers at ORNL the association between radiation and all cancer mortality was strongest when considering cumulative dose received after age 45 under a 21 year lag assumption; for workers at Hanford this association was strongest when considering doses received after age 62 under a 17 year lag assumption.

International pooled analyses considered cancer mortality among workers at nuclear facilities in the United States, United Kingdom, and Canada. Cumulative radiation dose was negatively associated with all cancers except leukemia (ERR_{10mSv}= -0.0007), and positively associated with leukemia excluding chronic lymphocytic leukemia (CLL) (ERR_{10mSv}= 0.0218; or 2.18 per Sv); in all cases associations were smaller than those derived from extrapolation from A-bomb survivors.[72]

4.3 Summary of Findings from Occupational Studies

One way to address questions about the long-term health effects of low level exposure to ionizing radiation has been to study workers in the nuclear industry, many of whom were hired during the early development of nuclear reactors and the United States' atomic weapons program.[6] Summarizing what has been learned from these occupational studies, the National Academy of Science's Committee on the Biological Effects of Ionizing Radiation noted that no study has found "results which differ significantly from the null."[6] Similarly, discussing the literature on occupational exposures to radiation, researchers for the International Agency for Research on Cancer concluded that "in most studies the confidence intervals of risk estimates were compatible with a range of possibilities, from negative effects to risks an order of magnitude greater than those on which current radiation protection recommendations are based."[72 73]

Such "null" findings were interpreted by the authors as consistent with findings from the Life Span Study (LSS) of atomic bomb survivors.[72] The LSS has served, in this way, as an interpretative framework through which the results of other epidemiologic studies of workers exposed to ionizing radiation have been read.[74] The literature on occupational exposure to low level radiation, however, is not constituted only by findings that converge at consensus.[5 36 75-77] Stewart and Kneale, for example, have repeatedly demonstrated differences in the effects of radiation depending on time-related factors, suggesting that low doses of radiation received at older ages and under long latency assumptions, may be associated with substantial increases in cancer mortality.[46 71 75 78 79] Other researchers, reporting on occupational studies of exposure to ionizing radiation, have also reported associations substantially larger than the estimates derived from the study of A-bomb survivors.[16 52 80]

It has been suggested that studies which diverge from the findings of the LSS are likely to represent random error, problems of bias and confounding, and the proclivity of journals to print studies with positive rather than null findings.[6 19] Some have argued that interpretation of research findings on the effects of low level radiation should give primacy to the results of the LSS, relegating findings that diverge from these estimates to the domain of outliers and statistical aberrations.[6 19 81] Others contend that the LSS also suffers the problems of biases, that the literature on radiation health effects contains substantial inconsistencies, and that we should continue to look for the threads of continuity which stitch together the entire body of this research.[36 38 77]

Many of the published studies of occupational exposure to radiation have emphasized results that are methodologically weak over those which are suggestive of untoward health effects of low level radiation. Furthermore, the lack of adequate measurements of exposures, potential confounding factors, and biological outcomes all would tend to weaken the ability of occupational studies to detect real effects. Consequently, the findings of elevated cancer rates among certain groups of workers raise important questions about the possible adverse health effects of chronic low-level radiation exposure. These results suggest greater attention to results from studies of individually monitored workers with long term follow-up, further evaluation of factors such as age at exposure and latency, and greater acknowledgment of the tendency of these studies to be biased towards the null. Workers must be healthy enough to be employed, whereas the general population includes the infirmed, infants, children, and the elderly. Findings from occupational studies should provide cautionary information about the effects of exposures in the general population which may include people who are more radiosensitive than a working population.

5. Epidemiological Studies of Effects around Nuclear Facilities

5.1 Introduction

While environmental releases of radiation are of wide concern, epidemiologic analyses of the effects of these releases suffer from lack of available data on exposure magnitudes, pathways for exposure, and time-patterns of exposure. Furthermore, in a general population, complicated patterns of migration affect exposure patterns as well as follow-up to assess disease status. Daily patterns of travel, similarly may influence exposure magnitudes. Environmenal epidemiological studies generally rely on correlations between geographical patterns of exposure and disease incidence. Concern is typically raised in such studies by the potential for confounding factors to lead to spurious observed associations (due to differences in the geographical distribution of other cancer risk factors); critics less often note that confounding, in addition to migration and errors in dose estimates, could also lead to masking or underestimation of exposure effects. The studies reviewed here do not have quantitative measurements of radiation exposure adequate to allow estimation of changes in relative risk per unit exposure; rather these studies compare death or disease rates among populations presumed to have different levels of exposure. Environmental exposures are generally assumed to be low, consequently, differences in disease rates between populations are presumed to reflect very small differences in exposure magnitude.

5.2 Epidemiological Investigations of Cancer Clusters Near Sellafield and Other Nuclear Weapons Facilities

Excesses of childhood leukemia were reported in the area around Sellafield in the 1980s. An investigation of this cluster of leukemia was conducted by Gardner et al. Using a case-control study method, information was collected about all known cases of leukemia and lymphoma among children in the area health authority between 1950-1985 and compared to information about local controls selected from the birth registry. A number of potential risk factors were examined, and father's employment at the Sellafield nuclear facility was identified as an important risk factor.[82-85] Furthermore, fathers of cases who had worked at Sellafield had larger cumulative preconception doses than fathers of controls who had worked at Sellafield.[82] A subsequent study examined followup through 1991, attempting to avoid criticisms which were directed at previous analyses by specifying, a priori, the outcomes of interest and geographic areas defining the study population.[86] Excess leukemia incidence was noted in the area, which the authors suggest might reflect occupational or environmental exposures.

In Scotland, excess childhood leukemia and non-Hodgkins lymphoma has been reported in the area around the Dounreay nuclear facility. The excess first reported in the 1980s has persisted with more recent followup through 1991;[87] a case-control study identified use of the local beaches as associated with childhood leukemia.[88] An analysis of leukemia and lymphoma incidence around seven nuclear sites in Scotland found a significant excess only around Dounreay.[89] Similarly, a case-control study of childhood leukemia near the La Hague plutonium reprocessing facility in France found evidence that environmental radiation exposure from recreational activities on beaches and from shellfish consumption could be associated with increased childhood leukemia among area residents.[90-92] In the US, analyses of cancer incidence and mortality around DOE facilities have been limited. Substantial efforts are currently focused on estimation of exposures received by populations around the Hanford facility and the Fernald facility. Cancer rates in the area near Oak Ridge, TN were compared to rates age-specific national rates, with larger increases found for the area around Oak Ridge.[93] A study of congenital malformations at birth among residents near the Hanford facility identified excess of neural tube defects and a deficit of cleft lip in the counties near Hanford when compared to rates for the neighboring states.[94] A case-control study of congenital malformations compared cases with congenital malformations with matched controls selected from the two counties nearest the Hanford facility; congenital dislocation of the hip and tracheoesophageal fistula were associated with employment of the parents at Hanford, but not with parental radiation exposure, while neural tube defects showed a significant association with parental preconception exposure. Other defects showed no evidence of such an association.[95]

Cancer around the Rocky Flats nuclear weapons facility has been the subject of a more detailed investigation which used environmental exposure estimates. Johnson evaluated cancer incidence patterns for the period between 1969-1971 in areas with varied estimated levels of contamination from plutonium and other radionuclides emitted by the Rocky Flats plant near Denver, Colorado.[96] He compared the cancer incidence rates of four geographic regions around Rocky Flats that were determined using isopleths from an area-wide survey by the AEC in 1970. There was a 24 % higher cancer incidence in males in Area I (highest exposure) vs. Area IV (lowest exposure), and a 15 % higher cancer incidence in Area II vs. Area IV. For females, there was a 10 % increase in cancer incidence in Area I, and 10 % increase in Area II. Johnson concluded that exposure of general populations to Pu and other radionuclides may have an effect on cancer incidence rates and that further study is warranted to investigate the poorly understood dose response relationship between Pu exposure and cancer in populations living near nuclear facilities.

In a re-analysis, Crump obtained similar results for 1969-71 and extended the analysis to 1979-81.[97] [98] Positive findings were diminished by adjustment for distance from the State Capitol. Crump argued that distance from the State Capitol was a measure of socioeconomic factors related to cancer incidence, however, he does not present findings for conventional measures of socioeconomic status, and provides no quantitative evidence for this assertion.

5.2.1 Studies of Cancer near Nuclear Power Facilities
Jablon has reported on cancer incidence around many of the commercial and governmental nuclear facilities in the US.[99] No clear association was found in this study; critics however note that this study gave no attention to patterns of exposure or population migration. Consequently the findings are likely to have suffered substantially from exposure misclassification which would tend to weaken the study's ability to detect any real effect.

Recent reports of excess adult leukemia incidence around the Pilgrim power plant in Massachusetts led to an investigation of association between proximity to the facility during years of 'high emission' and leukemia incidence; a positive dose-response association was observed.[100]

An analysis of childhood cancer incidence was conducted in 20 areas surrounding West German power facilities; while all cancer and acute leukemia incidence were not elevated in those areas within 15 km of nuclear facilites, increase acute leukemia and lymphoma was observed among those who lived within 5 km of the facilities.[101]

Beral et al. considered cancer around nuclear facililites in Britain, concluding that "the relevance of a single geographic cluster of disease can rarely be interpreted. Even when a prior hypothesis exists, the small number of cases which generally occur in a small area make the findings highly sensitive to reporting, diagnostic, or classification errors."[102]

5.3 Conclusions
Epidemiological techniques are well suited to documenting strong risk factors, such as regular cigarette smoking or high dose ionizing radiation, that show little or minor variation in impact in various population subgroups. However, due to the importance of environmental contamination and the potentially large population receiving exposure,

radiation epidemiology must now focus on weaker relationships at lower exposure levels, where poor measurement and the presence of unmeasured differences between exposure groups become major potential problems. Relatively small differences in disease occurrence, such as those that are suspected in the case of many environmental radiation exposures, are difficult to detect [McMichael, 1989]. But small increments in disease incidence can have a great population impact when many people are exposed.[103]

Environmental releases of radioactive material may be of particular concern because the effects of radionuclide exposures are believed to be modified by many substances. For example, gastric absorbtion of plutonium tends to be very low in occupatonal settings; however, in the presence of fluoride, chlorine, or carbonate ions, the gastric absorption of plutonium rises to near 100% absorption. Consequently, environmental releases of radionuclides that contaminate drinking water, which is often chlorinated and may contain fluoride and carbonate ions, may lead to very high levels of internal contamination. Through the food chain, radionuclides may be incorporated and uptake increased as well. Furthermore, in contrast to adult workers, rates of absorbtion of radionuclides tends to vary with age, and may be extremely high for nursing infants.

6. *Epidemiological Studies of Nuclear Accidents*

*6.*1 Introduction

In addition to putting nuclear workers at an increased risk of harmful effects of mutations, the nuclear industry has exposed the public to accidental releases of radiation from its facilities: notably the accidents at Windscale and Rocky Flats in 1957; at Chelyabinsk in the USSR in 1958; at Three Mile Island in 1979, and at Chernobyl in 1986. In cases of accidental (as opposed to routine) environmental releases of radiation from nuclear facilites, epidemiological investigations have typically been hampered by poor dosimetry data. Studies of cytogenetic damage may offer some information about an invididual's exposure, but such approaches are poorly suited to systematic investigation of populations. Radiation readings used to estimate exposure have been insufficient to reconstruct the complex movement of radionuclides through the environment, while individual differences in lung function, patterns of work and movement, age, sex, and diet may have significant impact on doses from environmental releases of radiation. On each of these occasions of accidental radiation releases, it would have been appropriate to identify a cohort of more heavily exposed persons and arrange for systematic recording of subsequent mortality and morbidity (as in the case of A-bomb survivors). But on each occasion the world was told either that the dose was too small to have any stochastic effects, or (in the case of Chernobyl where there had been some deaths from nonstochastic effects of the radiation) that a short-lived isotope of iodine might have caused a few cases of thyroid cancer.

*6.*2 Three Mile Island

The accident at the Three Mile Island (TMI) nuclear facility near Harrisburg, PA, which began on March 28, 1979, resulted in environmental releases of ionizing radiation. The reported maximum radiation dose to a person in the general population was less than average annual background levels, and no health effects were expected to be detectable (1). However, there were unofficial reports of erythema, hair loss, vomiting and pet death near TMI at the time of the accident, and of excess cancer deaths during 1979-84 (2,3). Investigators from Columbia University examined estimated doses to the population in the ten-mile area and collected information on incident cancers for the years 1975-1985. Non-Hodgkin's lymphoma showed a statistically significant (two-tailed $p<0.05$) relationship with accident doses, all cancers and lung cancer were also significantly associated with accident doses. However, because of the lack of strong associations for childhood and highly radiosensitive cancers, the possibility of uncontrolled confounding, and the estimates of low doses and short follow-up, the authors concluded that observed associations did not reflect an accident effect (4,5).

Those findings were reconsidered, accounting for methodological problems in earlier reports. Associations between accident doses and incidence rates of leukemia, lung cancer and all cancer were assessed with adjustments for age, sex, socioeconomic characteristics, and pre-accident variation in incidence. Accident doses were positively associated with cancer incidence. Associations were larger in 1984-85 than in 1981-85, largest for leukemia, intermediate for lung cancer, and smallest for all cancers combined. Adjustment for socioeconomic variables resulted in larger associations. Results support the hypothesis that radiation doses are related to increased cancer incidence. If these associations reflect radiation from the accident they are not consistent with previous low-level release estimates.

6.3 Chernobyl

The nuclear accident at the Chernobyl power station on April 26, 1986 resulted in a large-scale release of radionuclides (particularly radioactive iodine), estimated at 4×10^{18}

Bq.[104] Radionuclides were released over several days, with contamination affecting air, water, soil, and food. In the first decade after the accident a viewpoint widely expressed has been that the psychological outcomes (related to stress or radiation-phobia) have been the prominent effect of the accident.[104 105] However, after nearly a decade of followup, despite the poor enumeration of exposed populations, the problems of data collection in the former Soviet Union, and limited dosimetry data, studies reported that the incidence of thyroid cancer among children and adolescents in the region was orders of magnitude higher than expected,[106] with excesses also of mental retardation, evidence of increases in other cancers.[107] Adults in the region, and liquidators who participated in cleanup from the accident, exhibit substantially increased incidence of chromosomal aberrations.[107]

The effects of the Chernobyl accident on the health of populations outside the former Soviet Union is subject to continued investigation and debate. The highest levels of contamination outside the former Soviet Union were recorded in Bulgaria, Austria, Greece and Romania, followed by other countries of Central, Southeast and Northern Europe.[108] Reports of excess trisomy 21 in Berlin,[109 110] neural tube defects in Turkey,[111-114] and changes in perinatal mortality in Germany,[115 116], are contrasted with reports of no changes in pregnancy outcomes in Sweden,[117] and no increase in childhood leukemia in Sweden, Finland, or Greece.[118-123] A review of recent studies concluded that despite reports of some effects in several countries, there is little evidence after the first decade of followup of a major impact of the Chernobyl accident on cancer in Europe;[108 123 124] however, these conclusions must be tempered by the fact that given the inadequacies of dose estimates for these populations, and the focus on rare outcomes (specific birth defects, and childhood leukemia), such studies may have little power to detect an effect.

7. Conclusion

Findings from radiation epidemiology are the subject of important debate. Very low level doses of ionizing radiation have been demonstrated in laboratory settings to damage chromosomal material (and the repair of damaged DNA always has the potential to be unsuccessful or inaccurate).[125]

However, the effect of low level radiation exposure on cancer incidence in populations is difficult to quantify with epidemiological methods. Epidemiological studies tend to suffer from poor measurement of exposures and misclassification of study subjects (persons presumed to have no exposure, or little exposure, may actually have received high doses). Furthermore, movement of people across local and national borders makes long term follow-up (which must span decades to study cancer effects, or generations to study genetic effects) difficult and nearly always incomplete. These problems affect studies of atomic bomb survivors as much as studies of Chernobyl's victims; and, the tendency of these problems is to bias studies towards an underestimate of the true consequences of radiation exposure.[126]

Given the limitations of the available data for epidemiologic research on low level radiation, studies of nuclear workers offer some of the best information about potential long term effects of low level radiation exposure. Many of these workers have individual, quantitative estimates of external ionizing radiation exposure, and several decades of mortality follow-up. Studies of nuclear workers pertain primarily to the effects of radiation on adult males. Among these workers it appears that sensitivity to the effects of low level radiation may increase with older age (findings reported from analyses of workers at Hanford, Oak Ridge National Laboratory, and Santa Susana Field Laboratory); estimated dose-response associations are an order of magnitude larger than estimates derived from studies of atomic bomb survivors.

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