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LEUKEMIA MORTALITY AMONG RADIATION-EXPOSED WORKERS

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Leukemia is a neoplastic disease of the hematopoietic (blood-forming) system, characterized by uncontrolled proliferation of white blood cells. Leukemia comprises many clinically distinct subtypes, but they have been grouped into four predominant subtypes according to the eighth and ninth revisions of the International Classification of Diseases: acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL).[88,89]

Although several agents found in occupational settings (including benzene and other solvents, and nonionizing radiation) have been associated with leukemia risk, none has been as intensely studied as ionizing radiation in the form of x-ray or high-energy photon exposures. While much of this information derives from observation of populations exposed briefly or episodically to relatively high radiation doses, studies of workers exposed occupationally over longer periods of time have also provided important information about the leukemogenicity of low-level, protracted radiation exposures. This review describes the epidemiologic evidence for the leukemogenic effects of ionizing radiation exposure among nuclear workers. The design and results of these studies, as well as quantitative risk estimates per unit dose, are summarized in this review. Known limitations, and methods to circumvent them, are also detailed. Finally, the expected contributions to this research area, in the face of epidemiologic limitations, are critically evaluated.

HISTORY

The relationship between exposure to low linear energy transfer (low-LET) ionizing radiation, including x-rays and gamma rays, and leukemia was first established from observations among occupationally exposed workers. Clusters of leukemia among radiation workers were investigated in Germany before World War I, but before the development of rigorous tools for chronic disease epidemiology, the evidence remained largely anecdotal.[45,59] The first epidemiologic evidence of the leukemogenicity of ionizing radiation exposure resulted from occupational studies of U.S. and British radiologists.[55,57,70,74] Radiologists employed before 1940 exhibited approximately three times the age-adjusted mortality rate for leukemia as other physicians.

The three-fold elevations in risk observed among early radiologists are assumed to derive from exposures to relatively high doses (although individual dosimetry estimates are unavailable). Recent studies among medical radiation workers have found generally low relative risks for leukemia among those monitored for exposure to ionizing radiation,[23] or employed more recently in the field.[81] These exposures are thought to be lower than those of early radiologists,[23,81] although exposure monitoring data are incomplete for these cohorts.

Many of the epidemiologic studies upon which current radiation standards are based derive from relatively high instantaneous or fractionated exposures of special populations, including the Japanese atomic bomb survivors of Hiroshima and Nagasaki, and patients therapeutically exposed for the treatment of ankylosing spondylitis.[16,62] A limitation of these studies is their relevance to the occupational or environmental setting, where exposures are generally lower and of longer duration. Recent estimates from the Japanese A-bomb cohort suggest an excess relative risk (ERR) of 2.6% (95% confidence interval [CI]: 0.8–8.6%) at 10 millisievert (mSv), for individuals exposed at age 20 or older, with fewer than 25 years follow-up after exposure.[62] The dose-related leukemia risk decreased with increasing time since exposure.

Although precise estimates of the dose-response relationship for leukemia and low-LET ionizing radiation are available from these studies, there remain questions of great importance that must be addressed from research in other cohorts. For example, follow-up did not begin in the A-bomb cohort until 5 years post-detonation. For most cancers, the missed follow-up in the first 5 years is of little relevance due to their long latency following exposure. However, leukemia risk, with latency considerably shorter than that of other cancers, is likely to have been underestimated by the lack of early follow-up. Dose was not measured, but was estimated from reconstructions of locations of tens of thousands of individuals in Hiroshima and Nagasaki at the moment of the blast. The relevance of epidemiologic findings for a traumatic radiation exposure in the cohort of war-time Japanese residents to U.S. nuclear industry workers has also been questioned.[76]

Military Workers

Military workers in the U.S. and elsewhere have been exposed to ionizing radiation through employment at naval nuclear shipyards and reactor facilities, on nuclear submarines, and through participation as observers at above-ground nuclear tests in the 1950s. Early studies of workers at the Portsmouth Naval Shipyard in New Hampshire suggested approximately six-fold elevations in leukemia risk[61]; however, these findings, based on a proportional mortality analysis, have received much criticism due to lack of control for several sources of bias, including the healthy worker effect, and selection, misclassification, and recall biases.[36,67] A cohort of 76,160 U.S. male nuclear submariners employed between 1969 and 1982 was followed for mortality through 1982.[14] Cumulative dose among the cohort was very low, with a mean

of 5 mSv. No excess of leukemia was observed among these men, compared to the general U.S. population (n = 12, standardized mortality ratio [SMR] = 0.91, 95% CI: 0.47–1.60).

Studies of soldiers present at nuclear tests have shown conflicting results with respect to leukemia risk, with some studies showing no evidence of excess risk,[46,69,82] and others demonstrating excess risks of exposed compared to unexposed (or less-exposed) military personnel.[7,8,21] Most of these studies have poor (or no) dose estimates for the observers, making quantitative risk determination difficult.[43]

Nuclear Power Workers

Several studies have evaluated mortality among nuclear power workers (Table 1), and quantitative estimates per 10 mSv unit dose have also been calculated (Table 2). Jablon and Boice[44] observed just two leukemia deaths in a cohort of 8615 male workers monitored for exposure to external ionizing radiation, with a mean cumulative dose of 21 mSv. A study of 21,545 UK Atomic Energy Authority workers,[27] with a mean cumulative dose of 40 mSv, found no relation between external radiation dose and non-CLL leukemia risk. In a cohort study of 8977 workers at the Atomic Energy Commission of Canada Ltd, Gribbin and colleagues[37] found a dose-related increase in leukemia risk, with an estimated excess relative risk of 19% per 10 mSv.

U.S. Nuclear Weapons Workers

Occupational epidemiologic studies of the association between leukemia and ionizing radiation have been most numerous at Department of Energy (DOE) nuclear weapons facilities across the United States. Studies in DOE facilities are informative because high-quality radiation monitoring data exist at these sites, which facilitates quantitative estimation of risk. Risks have typically been expressed as ERR estimates per unit cumulative dose, usually modeled using Poisson regression maximum likelihood estimation techniques.[28,32]

The Hanford site is the most-studied U.S. nuclear weapons facility, having been the subject of at least ten mortality investigations since the late 1970s. An early study by Mancuso and colleagues[56] investigated the radiation doses associated with fatal leukemia and other lymphatic neoplasms (including multiple myeloma), compared to other cancer and non-cancer deaths, for Hanford workers followed through 1972. Cumulative doses were greater among workers dying of these neoplasms than other cancers (ratio of 2.05), or non-cancer deaths (ratio of 2.21). These ratio estimates are very imprecise due to the small number of lymphatic neoplasm deaths (i.e., 14 leukemias). After stratifying on age at death, the elevated dose ratios existed primarily for deaths that occurred among persons older than 70 years of age. The study has been criticized[1,33,41] because of the sensitivity of these results to a few cases with unusually high exposures; the lack of adjustment for attained age; and the unusual statistical analysis methods employed. A reanalysis of the cohort data[41] found no evidence for a dose-response relationship among the leukemia cases monitored for exposure to low-LET ionizing radiation (n = 8 total, 6 myeloid).

A series of analyses of Hanford mortality was conducted by Gilbert and colleagues.[31,33,34,79] These studies generally included workers hired before the mid-1970s, with additional mortality follow-up occurring at approximately 5-year intervals. In contrast to the findings of Mancuso and colleagues, no increase in leukemia rates was observed compared to the general U.S. population, nor was a significant dose-response trend in leukemia mortality noted after adjusting for age, sex, and calendar time for workers monitored for exposure to ionizing radiation. Quantitative ERR estimates per 10 mSv were consistently negative, although confidence intervals were

TABLE 1A. Design of Key Studies of Leukemia Mortality in Nuclear Workers Monitored for Exposure to Penetrating Ionizing Radiation.

Site	Study reference	Hire date and minimum work duration criteria	End of follow-up	Number of monitored workers	Average exposure (mSv)
Hanford	Gilbert & Marks 1979[33]	1944-65, 2 year	3/31/74	12,522*	4.8 (mean) 1.5 (med)
	Tolley et al 1983[79]	1944-78, 2 year	12/31/78	15,992*	NR‡
	Gilbert et al 1989[34]	1944-78, none	12/31/81	36,235	23 (mean)
	Gilbert et al 1993[35]	1944-78, 6 months	12/31/86	32,643	26 (mean)
Savannah River Site	Cragle et al 1988[17]	1952-74, 90 days	12/31/80	9860*,‡	NR‡
	Cragle et al 1999[18]	1952-74, 90 days	12/31/86	9757*	40 (mean) 7.2 (med)
ORNL	Wing et al 1991[87]	1943-72, 30 days	12/31/94	8318*	17 (mean) 1.4 (med)
LANL	Wiggs et al 1994[83]	1943-77, none	12/31/90	15,727*	NR‡
Mallinckrodt	Dupree-Ellis et al 2000[25]	1942-66, 30 days	12/31/93	2514*	48 (mean) 15 (med)
AECL	Gribbin et al 1993[37]	1956-80, none	12/31/85	8977*	15 (mean) 0 (med)
Hanford ORNL Rocky Flats	Gilbert et al. 1993[31]	1944-78, 6 months 1943-72, 6 months 1952-79, 6 months	12/31/86 12/31/84 12/31/83	36,972*	33 (mean) 22 (mean) 41 (mean)
Oak Ridge Sites (ORNL, Y12)	Frome et al 1997[29]	1943-85, 30 days	12/31/85	28,347*	13 (mean)
British AWE	Beral et al 1988[5]	1951-82, none	12/31/82	9389	7.8 (mean)
UKAEA	Fraser et al 1993[27]	1946-1979, none	12/31/86	21,545	40 (mean) 10 (median)
Sellafield plant	Douglas et al 1994[24]	1947-1975, none	12/31/88	10,276	128 (mean)
	Omar et al 1999[65]	1947-1975, none	12/31/92	10,382	130 (mean)
AWE, UKAEA, Sellafield	Carpenter et al 1995[12]	1946-1983 (variable), none	12/31/88	40,761	57 (mean)
UK NRRW	Kendall et al 1992[47]	Variable, none	12/31/88	95,217	34 (mean) <10 (med)
	Muirhead et al 1999[60]	Variable, none	12/31/92	124,743	31 (mean) <10 (med)
Combined Int'l Study**	IARC Study Group 1994[42]	1943-78, 0.5 year	1979-88	95,673*	40 (mean) <10 (med)
Mayak	Shilnikova et al. 2000[72]	1948-1972, none	12/31/94	18,829	870 (mean)

*White males only
AWE: Atomic Weapons Establishment, AEA: Atomic Energy Authority, NRRW: National Registry for Radiation Workers, ORNL: Oak Ridge National Laboratory
‡NR: radiation monitoring information not reported,
**Sites: Hanford, Rocky Flats, AWE, UKAEA, AECL

TABLE 1B. Results of Key Studies of Leukemia Mortality in Nuclear Workers Monitored for Exposure to Penetrating Ionizing Radiation.

Study	Leukemia grouping	Dose lag (yr)	N*	Measure of association	Result	Confounder adjustments
Hanford[33]	Myeloid leukemias (ICDA8 205)	2	5	Mantel trend (χ^2 1 df)	p=0.57	Age, CY†, occupation, employment status
Hanford[79]	Myeloid leukemias (ICDA8 205)	2	9‡	Mantel trend (χ^2 1 df)	p=0.21	Age, CY, occupation, employment status
Hanford[34]	Non-CLL leukemia§ (ICD8A 205-207)	2	29 ‡	Mantel trend (Z-score)	-0.84 (p>0.05)	Age, sex, CY
Hanford[35]	Non-CLL leukemia (ICDA8 205-207)	2	44 ‡	Score trend test	-0.85 (p>0.05)	Age, sex, CY, no. years monitored, SES
SRS[17]	Leukemia (ICDA8 204-207)	--	17	SMR (hourly, salaried workers)	1.63, 1.05 (p>0.05)	Age, sex, CY, employment duration
SRS[18]	Non-CLL leukemia**	2	20 ‡	χ^2 trend (1 df)	3.86 (pos. association p<0.05)	Age, sex, CY, paycode
ORNL[87]	Leukemia (ICDA8 204-207)	--	28	SMR vs US (95% CI)	1.63 (1.06-2.35)	Age, sex, CY
LANL[83]	All leukemia Myeloid leukemia Lymphocytic leuk.	2	26 15 4	Z-score trend	0.15 (p>.05) -0.99 (p>.05) 1.33 (p>.05)	Age, sex, CY
Mallinckrodt[25]	Leukemia (ICDA8 204-207)	--	11	SMR vs US (95% CI)	1.11 (0.57-1.89)	Age, sex, CY
Atomic Weapons Establishment[5]	Leukemia (ICD8 204-208)	2	4	χ^2 trend (1 df)	0.47 (neg. association, p>.05)	Age, sex, CY, social class
UK Atomic Energy Authority[27]	Non-CLL leuk-emia (ICD8 204-208, not 204.1)	2	24	χ^2 trend (1 df)	1.48 (neg. association, p>.05)	Age, sex, CY, site, social class
Sellafield[24]	Non-CLL leukemia (ICD8 204.0, 204.2-208.9)	0 2 10	12	Trend test for external dose (Z-score)	3.08 (p=.004) 2.75 (p=.009) 1.37 (p>.05)	Age, sex, CY, industrial (Y/N)
Sellafield[65]	Non-CLL leukemia (ICD8 204.0, 204.2-208.9)	0 2. 10	13 ‡	Trend test for external dose (Z-score)	2.77 (p=.006) 2.43 (p=.015) 1.00 (p>.05)	Age, sex, CY, industrial (Y/N)
Sellafield, AWE, UKAEA[12]	Non-CLL leukemia	0 2	49 ‡	Trend test for external dose (Z-score)	2.21 (p<.05) 2.38 (p<.01)	Age, sex, CY, site, social class
Mayak[72]	Non-CLL leukemia	2	55	Linear trend test	p<.001	Age, sex, hire date, facility, hire age

*Number of hematopoietic neoplasms, as defined in column 2.
†CY: Calendar year
‡Includes cases from previous study
§CLL: chronic lymphocytic leukemia
**Includes non-underlying causes of death

TABLE 2. Quantitative Risk Estimates for Leukemia from Epidemiologic Studies of Atomic Bomb Survivors and Workers Exposed to Penetrating Ionizing Radiation.

Study ref.	Site	Leukemia grouping	Dose lag (yrs)	N*	ERR per 10 mSv (95% CI)	Confounding factor adjustments
BEIR V[62]	A-bomb survivor study	All leuk. mortality	2	202	2.6% (0.8, 8.6)	Exp. age ≥ 20; Time since exp. ≤25 years
					1.3% (1, 13.3)	Exp. age ≥ 20; Time since exp. 25-30 years
					0.2% (.02, 2.6)	Exp. age ≥ 20; Time since exp. >30 years
Gilbert et al 1989[34]	Hanford	Non-CLL leuk. mortality	2	29	-2% (-2, 8)	Age, sex, CY
Gilbert et al 1993[35]	Hanford	Non-CLL leuk. mortality	2	44§	-1.1% (<0, 3)	Age, sex, CY, No. years monitored, SES
Cragle et al 1999[18]	SRS	Non-CLL leuk. mortality**	2	20	13.6% (0.61, 50.6)††	Age, sex, calendar year, paycode
Wing et al 1991[87]	ORNL	All leukemia mortality	10	30	9.1% (χ^2 =0.6, p=0.44)	Age, sex, birth year, age*birth year
Gilbert et al 1993[31]	Hanford ORNL, Rocky Flats	Non-CLL leuk. mortality	2	67‡	-1.0% (<0, 2.2)	Age, sex, CY, SES, facility
Frome et al 1997[29]	ORNL, Y12	All leuk. mortality	2	NR	0 (<0, 6.5)	Age, sex, CY, SES, facility, employment length, internal rad monitoring
Gribbin et al 1993[37]	AECL	Non-CLL leuk. mortality	2	4	19.0% (0.14-113) ††	Age, sex, CY, time since first employed
Fraser et al 1993[27]	UKAEA	Non-CLL leuk. mortality	2	24	-4.1% (-5.7-2.9)	Age, sex, CY, site, social class
Douglas et al 1994[24]	Sellafield	Non-CLL leuk. mortality	2	12	13.9% (1.94-70.5) ††	Age, sex, CY, industrial (Y/N)
Carpenter et al 1995[12]	Sellafield, AWE, UKAEA	Non-CLL leuk. mortality	2	49‡	4.2% (0.4-13)	Age, sex, CY, social class, site
Kendall et al 1992[47]	NRRW	Non-CLL leuk. mortality**	2	45‡	4.3% (0.40-13.6) ††	Age, sex, CY, industrial, 1st employer
Muirhead et al 1999[60]	NRRW	Non-CLL leuk. mortality**	2	91‡	2.6% (-0.03-7.2) ††	Age, sex, CY, industrial (Y/N/U), 1st employer
IARC Study Group 1994[42]	Comb. Internat.	Non-CLL leuk. mortality	2	119‡	2.6% (0.1, 7.0) ††	Age, sex, birth year, SES, facility
Shilnikova et al 2000[72]	Mayak	Non-CLL leuk. mortality	2	55	1.2% (0.5-2.8) ††,§§ 12.1%*** 0.4-0.8%†††	Age, sex, CY, hire date, facility, hire age

*Number of hematopoietic neoplasms, as defined in column 3.
‡Includes cases from previous study
**Includes non-underlying causes of death
AECL: Atomic Energy of Canada, Ltd
***3-5 years following exposure
NR = not reported
CY: Calendar year
CLL: chronic lymphocytic leukemia
††90% confidence interval
§§All years of follow-up combined
†††>5 years following exposure

wide. The Hanford data from the 1989 study[34] were reanalyzed by Kneale and Stewart[48] using a case-cohort risk set approach, and matching on sex, race, birth year, hire year, employment duration, offsite exposure status, discharge status, calendar year, discharge interval, and socioeconomic status. All lymphatic neoplasm (ICD8 200–209) deaths, both underlying and non-underlying, were evaluated; however, risk estimates were not reported separately from that for all "radiosensitive" cancers.

A cohort study of white, male workers at the Savannah River nuclear fuels facility found elevated leukemia mortality compared to rates in the US, and in Georgia and South Carolina combined.[17] The SMRs for all leukemias combined ranged from 1.05 for salaried workers to 1.63 for hourly workers, and were highest for hourly workers hired before 1955, who worked between 5 and 15 years at the facility. A more recent study of this cohort[18] found a significant trend of increased leukemia mortality with increasing dose, and an elevated excess relative risk of 13.6% per 10 mSv cumulative dose for non-CLL leukemia.

One recent study[87] evaluated leukemia and other cancer mortality among 8318 white, male, radiation-monitored workers at the Oak Ridge National Laboratory (ORNL). The study found elevated SMRs (compared to the general U.S. population) for leukemia deaths among all workers (1.63, 95% CI: 1.06–2.35) and workers monitored for exposure to internal radiation (2.23, 95% CI: 1.27–3.62). Workers in the latter category were more likely to have received elevated external radiation doses: 50% of internally-monitored workers received cumulative doses of at least 50 mSv, compared to just 8% of those not monitored for internal exposures. Adjusting for age, birth year, and their interaction, leukemia rates increased in a dose-dependent manner, with an imprecisely estimated ERR of 6.9% (SE 10.9) and 9.2% (SE 11.1%) per 10 mSv cumulative dose when a 5-year or 10-year lag (respectively) was assumed.

The association between mortality from leukemia and exposure to external ionizing radiation was evaluated in 15,727 white, male workers at the Los Alamos National Laboratory (LANL).[83] A nonsignificant positive trend was observed for lymphocytic leukemia, but not for myeloid leukemia. In a recent study of the Mallinckrodt Chemical Works (a uranium processing facility in St. Louis, MO), Dupree-Ellis and colleagues[25] observed 11 leukemia deaths among 2514 white, male workers monitored for exposure to low-LET ionizing radiation. The leukemia SMR, adjusting for age and calendar period, was 1.11 with a wide 95% confidence interval. Excess relative risks per unit dose were not reported, despite the availability of low-LET dose data.

Combined U.S. Studies

Because of the limited statistical power of individual studies to observe radiation-related leukemia risks at the low cumulative doses experienced by nuclear worker populations, researchers have combined studies of several DOE cohorts. Analysis of a combined cohort of 44,943 workers at Hanford, ORNL, and Rocky Flats,[31] monitored for exposure to low-LET ionizing radiation, showed no dose-related increase in leukemia mortality risk. Results of this study were strongly influenced by the large Hanford cohort; however, risk estimates per unit dose were quite similar for Hanford and ORNL in this study. A second U.S. combined study, conducted among 28,347 white male workers at ORNL and Y-12, found no relation between external radiation and leukemia mortality.[29]

Nuclear Workers Outside the United States

There have been several important studies of leukemia and other cancer risks among British nuclear workers.[4,5] These cohorts are generally smaller than many U.S. cohorts; however, the average exposure for some UK cohorts is greater among workers

monitored for exposure to ionizing radiation. One large study[4] observed excess leukemia rates among 39,546 UK workers with an average exposure of 32.4 mSv. An early study of Sellafield workers,[75] with average cumulative doses of 124.0 mSv, also showed dose-related leukemia deaths among 14,327 workers. Later studies of the Sellafield cohort found non-CLL leukemia incidence and mortality to be significantly related to external, but not to internal, radiation exposures.[24,65] The estimated lenkemia mortality ERR per 10 mSv in this cohort was 13.9%, with a 90% confidence interval of 1.94–70.5.[24]

A later study[5] found only four leukemia cases among a combined group of 22,552 nuclear workers at five British atomic weapons facilities followed for an average of 18.3 years. All cases were workers who had received cumulative doses of less than 10 mSv. No lenkemias occurred among workers monitored for internal radiation exposure. A recent large study[12,13] found similar leukemia risks among three UK workforces (the Atomic Weapons Establishment, the Atomic Energy Authority, and the Sellafield plant of British Nuclear Fuels Ltd), compared to estimates derived from the Japanese A-bomb survivors.[62] The observed ERR per 10 mSv was 4.2% (95% CI: 0.4–13.4). The ratio of observed to predicted non-CLL leukemia risks per unit dose was 1.3 (90% CI: –0.2–4.5), suggesting good but imprecise agreement between risks derived from low-dose and higher-dose studies.

In the UK, the National Registry for Radiation Workers (NRRW) was established in 1976 to evaluate exposures and health risks among workers exposed to ionizing radiation. The NRRW encompasses a wide range of nuclear workers, from nuclear medicine production and energy workers, to nuclear weapons production and defense workers. Leukemia risks among workers in the NRRW have been evaluated in several studies.[47,53,60] The most recent analysis[60] comprises a large cohort of 124,743 workers at more than a dozen facilities throughout the UK. Compared to the U.S. DOE cohorts, the median ages of the UK registry worker cohorts are qnite low (i.e., the median years of birth ranged from 1949 to 1954). Measnred cumulative doses were low compared to earlier UK studies, at 30.5 mSv mean dose; however, there was wide variability by site, with the mean cumulative dose ranging from 5.3 mSv among radiobiology workers to 66.2 mSv among nuclear fuel workers.[60] The study estimated an ERR per 10 mSv of 2.55% for non-CLL leukemia. Of the leukemia subtypes, dose-related leukemia risk was greatest for CML, and was not evident for CLL.

Over the past decade, several important studies of leukemia and other cancers among nuclear weapons production workers in the former Soviet Union have been conducted. These cohorts tend to have much higher exposures than U.S. facilities, which may facilitate the detection of excess risk, if it exists. For example, of those hired between 1948 and 1953, 6.5% of reactor workers and 22.8% of radiochemical processors received annual doses of 1000 mGy or greater.[49]

No excess leukemia mortality risk was fonnd among reactor workers at the Mayak production site in the South Urals, compared to the general popnlation; however, workers at its radiochemical processing facility were found to have elevated leukemia risk.[49,50] These studies of workers in the former USSR are limited by small population sizes (e.g., n = 1839 at the reactor facility[50]), inadequate dose estimates, lack of dose-response assessment, and the lack of well-developed national disease rate tracking systems (for example, disease rates were not adjusted for calendar period in the SMR calculations). A more recent study of 15,601 Mayak workers[72] found strong evidence of a dose-response relationship between external radiation and non-CLL leukemia risk. Excess relative risks per Gy were strongly related to time since exposure, with peak ERR/Gy observed at 3–5 years following exposure, and ERR/Gy declining by a factor of 15 at 6 or more years following exposure.

Pooled and Combined (International) Studies

Researchers have combined results of international studies using two different approaches: meta-analysis of the existing literature, and pooled analysis of combined cohorts. Wilkinson and Dreyer[84] reviewed all reports of leukemia among low-LET radiation-monitored, white, male nuclear workers published through 1989. Their analysis included workers from Hanford, Rocky Flats, Portsmouth Naval Shipyard, and ORNL in the U.S., and the cohorts from the Atomic Energy Authority (AEA) and Atomic Weapons Establishment (AWE) studies in the UK. The researchers applied grouped statistical techniques to adjust externally pooled risk estimates (of exposures greater than 10 mSv compared to less than 10 mSv) for confounding by age and calendar year. Relative risk estimates (compared to the group exposed to < 10 mSv) were higher for the intermediate exposure group (10–50 mSv) than for the highest exposure group (> 50 mSv). The unadjusted risk estimates for these groups (and 95% CI) were 2.1 (1.4–3.3) and 1.4 (0.8–2.6), respectively. Estimates externally adjnsted for age and calendar year decreased slightly for both groups, to 1.8 and 1.2, respectively. This study was unable to account for differences in definitions of leukemias, or for differences in dosimetry practices, across populations.

A second combined international study, conducted by the International Agency for Research on Cancer (IARC), employed *de novo* analysis of individual data from six nuclear worker cohorts in the U.S., UK, and Canada.[10,42] The cohorts included Hanford, Rocky Flats, ORNL, AWE, AEA, and the Atomic Energy of Canada Ltd workers, followed to the mid-1980s. The researchers adjusted for age, calendar year, sex, socioeconomic status, and facility; therefore, the study represents a refinement over the meta-analysis of Wilkinson and Dreyer,[84] who had to indirectly adjust for the first three factors. The study estimated an ERR for non-CLL leukemia of 2.6% per 10 mSv (90% CI: 0.1–7.0), using whole-body doses adjusted to bone marrow. Quantitative risk estimates varied widely by site; however, these differences were not statistically significant because some facilities had very few leukemia deaths. Site-specific risk estimates reflected the findings of individual cohort studies.

High-LET Radiation Workers

Several studies, primarily of nuclear weapons workers in the U.S., UK, and former Soviet Union and uranium miners and millers, have evaluated leukemia and other cancers among workers exposed to plutonium, uranium, and other radionuclides. A combined study of 11 uranium miner and miller cohorts showed an increased leukemia SMR of 1.93 (95% CI: 1.19–2.95) for these workers compared to the general popnlation.[22] However, this increase was restricted to the period less than 10 years after starting work, and no dose-response relationship was observed for radium.

Most U.S. nuclear industry cohorts are small, with low and extremely skewed internal dose distributions, reducing their statistical power to detect effects. In addition, most U.S. cohorts of plutoninm or uranium exposed workers receive non-trivial low-LET radiation exposures as well. Workers exposed to radionuclides such as plutonium and uranium at the Rocky Flats, Oak Ridge Y-12, and LANL facilities of the DOE have been studied. Wilkinson and colleagues[85] reported a positive (but not statistically significant) association between myeloid leukemia and presence of a measurable body burden of plutonium in Rocky Flats workers. Checkoway and colleagues[15] observed four leukemia deaths among 6781 Oak Ridge Y-12 uranium-processing workers, monitored for exposure to uranium and low-LET radiation, who were followed for an average of 21 years. No association has been observed between internal radiation exposure and leukemia mortality in the LANL cohort.[83] Interpretation of these findings is problematic,

however, due to the small number of plutonium-exposed workers, especially at LANL, and the difficulty in estimating bone marrow doses for these populations.

Two studies in the UK found no significantly positive relation between internal plutonium dose and leukemia[13,65]; however, the latter study was based on just six non-CLL leukemia deaths. Plutonium workers at the Russian Mayak facility experienced excess leukemia risks (SMR = 2.06 and 2.31, respectively, for males and females) compared to a control group; however these estimates had very wide confidence intervals.[50] This study did not incorporate dose-response analysis or control for exposure to external radiation exposures (which averaged 1.32 Gy for males and 1.15 Gy for females), and used a control group that appeared very highly exposed to external radiation (e.g., the average cumulative dose for males was reported as 27 Gy).

Airplane Crews

Most studies of cancer among airplane crews exposed to cosmic radiation (primarily neutrons) have not found excess leukemia risk.[6] Findings of two studies of Canadian and Danish cohorts suggested increased incidence of AML, but these studies are based on six and four cases, respectively.[3,39] Annual exposures among aircrews are estimated to average from 0.2 to 5 mSv, depending on altitude and latitude,[64] with estimated average and maximum lifetime doses of 30 and 46 mSv, respectively.[43]

CURRENT STUDIES OF LEUKEMIA IN NUCLEAR WORKERS

Researchers at both the National Institute for Occupational Safety and Health (NIOSH) and IARC have multi-site studies underway to evaluate the relation between external radiation exposure and leukemia mortality among nuclear workers.[11,63] The NIOSH study is a nested case-control study within a combined cohort from four previously studied DOE sites and one naval shipyard. Cases and controls are drawn from a cohort restricted to those who worked at least 30 days and were monitored for external radiation, with added mortality follow-up for most cohorts. The NIOSH study includes women and non-whites, unlike many of the previous studies. With more than 250 leukemia cases, including over 200 non-CLL leukemias (Table 3), sufficient power to detect moderate excess relative risk should be present. Possible confounding by pluto-

TABLE 3. NIOSH Leukemia Case-Control Study Features.

Site	Cohort size*	Number of cases†	Number of non-CLL cases†,‡	Number of study subjects†	Median duration (yr) of employment	Median cumulative exposure (mSv)
Hanford	36,384	93	81	485	9.8	6.6
ORNL	19,815	52	40	238	2.6	3.5
Savannah River	12,886	42	31	201	13.5	5.9
Los Alamos NL	12,179	23	19	106	7.2	6.0
Zia	5686	14	13	62	9.5	4.5
Portsmouth Naval Shipyard	9662	33	30	177	27.2	3.7
Total cohort	94,517	257	214	1269		5.7

Note: Workers are classified according to the first site at which they were employed.
*Each group includes workers at multiple sites
†Workers grouped according to site first employed
‡Leukemia cases, excluding chronic lymphocytic leukemia (204.1, ICD rev. 8 and 9)

nium, smoking, or chemical exposures will also be evaluated. The IARC study is a combined cohort study that evaluates mortality among several hundred thousand male and female workers worldwide, who were monitored for exposure to ionizing radiation. Leukemia will be evaluated with other cancer and non-cancer causes of death. Improved exposure assessment techniques, added mortality follow-up, and the inclusion of new cohorts are some of the study improvements over the previous IARC study.[11]

LIMITATIONS OF EPIDEMIOLOGIC STUDIES

Variable Sensitivity of Leukemia Subtypes to Ionizing Radiation. The diagnostic criteria for leukemia subtypes have evolved rapidly over the past two decades[26] due to recent advances in histochemistry and cytogenetics. Epidemiologic studies have provided evidence that the etiologies of these subtypes may differ, in addition to their known differences in clinical presentation and prognosis.[26,52] While the epidemiologic evidence for the varying sensitivity of these subtypes to radiation has not kept pace with these diagnostic advances, a recent combined analysis of three high-dose studies, including the atomic bomb survivors, suggests that substantial differences exist in dose-response curves among leukemia subtypes (CML, AML, and ALL), which outweigh population differences in dose-response models.[54] Interpretation of this finding in the context of nuclear worker studies is made difficult by the lack of consistency among researchers in categorizing leukemias in analysis (e.g., Table 1B).

Despite these limitations, there is substantial evidence that low-LET ionizing radiation exposure is associated with AML, ALL, CML, and certain subtypes of CLL (e.g., hairy cell leukemia[77]), while the majority of CLL subtypes appear not to be related to ionizing radiation exposures.[19,20,62] Studies among nuclear workers have generally confirmed these observations.[24,60] Although chronic, acute, myelogenous, and lymphocytic distinctions have been supported within the ICD coding system since 1965, some death certificates still do not distinguish among leukemia subtypes, making epidemiologic analyses imprecise.

Inadequate Power, Low Range, and Heterogeneity of Exposures. Studies of U.S. nuclear workers have been criticized for several reasons. DOE cohort studies are expected to have relatively low power to detect radiation-related risks. This is primarily because of the low number of expected leukemia deaths among even highly exposed individuals (assuming applicability of extrapolations in radiation-related risk observed among other populations). Generally low cumulative doses (and extremely right-skewed dose distributions) combined with limited cohort sizes have made dose-response assessment very difficult, and has led to the use of combined cohort analyses.

Uncertainties in exposure estimates for nuclear workers have been criticized as well. Although dose estimates for low-LET ionizing radiation are far superior to exposure estimates for most carcinogens, their presumed precision belies considerable uncertainty in measurement. For example, measured whole-body doses were found to overestimate bone marrow doses by 20%.[42] Individual dose estimates are likely to be uncertain at low levels, because of the preponderance of dose imputation near the detection limit of dosimeters.[84] Some researchers[60] have evaluated uncertainty in the dose-response relationship due to near-detection limit dose estimation. Uncertain exposures to neutron, beta, and internal radiation across the nuclear workforce may be problematic, although analyses conducted in the IARC combined international study suggest these have little biasing effect on risk estimates.[10]

Potential Confounding Factors in Epidemiologic Studies. These factors include chemical exposures and personal attributes. Since the first studies were published of leukemia among U.S. nuclear workers, the possibility of confounding of the relation between ionizing radiation exposure and leukemia has been of concern.[1]

Research in the Hanford cohort suggests very little change in risk estimates per unit dose after controlling for known and suspected confounding by duration of exposure, job category, year of hire, years since termination, or monitoring for internal radiation exposures.[34] However, in other cohorts, leukemia risk estimates vary substantially by period of hire and job type (e.g., hourly vs. salaried and early vs. later hires[17]).

By far the **most important confounding factor** in studies of the association between ionizing radiation and leukemia is **age.** Incidence rates are 50- to 100-fold higher in the 9th than in the 4th decade of life for the chronic leukemias.[58] Males consistently show higher leukemia incidence rates than females. Observed rate ratio (M:F) ranges in the U.S. for the chronic and acute leukemias are 1.6–2.0 and 1.2–2.0, respectively.[66] Racial and ethnic differences are of smaller magnitude. AML incidence rates have changed little in the U.S. between 1973 and 1990, while CML and CLL incidence rates declined and ALL incidence increased over the same period.[38]

One well-known limitation that affected many early epidemiologic studies among nuclear workers is the lack of control for the **healthy worker effect.** This form of selection bias has several well-studied components,[2] including the initial selection of a robust workforce from the general population, the fact that longer-term workers generally have better health than short-term workers (the healthy worker *survivor* effect), and uncontrolled effects of geographic variability in mortality rates. The bias resulting from the healthy worker effect is well-understood, and the most common control mechanism is the use of internal analyses to compare mortality rates among those differentially exposed. However, bias resulting from the healthy worker survivor effect, which may mitigate against the ability to detect a dose-response relationship, is less frequently evaluated in studies of nuclear workers. Adjustments include restricting cohorts to workers with longer employment duration, or crudely stratifying by employment duration. Several researchers have suggested that an additional aspect of the healthy worker effect occurs within nuclear worker cohorts, as less-healthy workers are less likely to pass stringent health requirements for working with radioactive materials.[5,75,86] This hypothesis, supported by the observation that SMRs are frequently lower for workers monitored for exposure to ionizing radiation than for non-monitored workers,[12,34,35,67,86] implies that internal comparisons of leukemia mortality may be biased toward the null if non-monitored workers are used as a reference group. It is not clear if this bias exists for hematopoietic neoplasms.

Confounding by simultaneous exposure to chemical carcinogens, work-related medical radiation exposures, or unmeasured internal radionuclides has been repeatedly mentioned as a potential biasing factor in these studies.[1,9,24,60,80,87] While some researchers have controlled for exposure to internal radiation sources in the analysis of the relation between external radiation and leukemia,[65] no studies have attempted to control for suspect chemical leukemogens, such as benzene or other solvents, or nonionizing radiation, due to the complexity of the exposure assessment for a large cohort study and the lack of available exposure records. Studies of the association between chemical exposure and leukemia risk among DOE workers are rare; one recent study[68] found an association between exposure to cutting fluids and all lymphopoietic neoplasms at the Fernald uranium processing facility.

CONTROVERSY

It has been asserted that cohorts of U.S. workers are too small, and cumulative dose distributions too low and right-skewed, to be of use in deriviug quantitative estimates of risk.[30,43] The debate about the value of **low-dose epidemiology** is not novel, but is currently occurring throughout the field of epidemiology.[40,71] This article has identified the major issues regarding the minimal power of worker studies to detect

the low-level health effects predicted by studies of A-bomb survivors or medically-exposed cohorts. Some have also suggested that results of occupational cohort studies are too likely to be biased by unmeasured confounding to be reliable substitutes for high-to-low-dose risk estimation for ionizing radiation.[43] As discussed on the previous pages ("Limitations"), potential confounding from the healthy worker effect, sex, race, temporal leukemia trends, smoking history, education levels or access to health care, concomitant work-related medical x-ray, and chemical or nonionizing radiation exposures have all been perceived as barriers to correctly estimating the radiation-leukemia dose-response relationship for nuclear workers.

One goal of quantitative dose-response assessment is to estimate risks in the range of exposure that is relevant to exposed populations. Since nuclear workers comprise a large percentage of persons exposed to man-made ionizing radiation,[43] derivation of quantitative estimates from this population is highly relevant for the development of dose-related risks. It is also worthwhile, where feasible, to estimate risks in the context in which they are experienced, rather than to rely on extrapolation from high-exposure risk estimates. Thus, well-designed studies of workforces exposed to both radiation and chemical leukemogens should provide relevant information about the dose-response relationship as experienced by nuclear workers.

Epidemiologic studies of nuclear workers must estimate risks very precisely to be meaningful, as the expected relative risks are very low at the median exposure in most nuclear worker cohorts (e.g., 1.02–1.10).[30] Combining cohorts circumvents some of the limitations of nuclear worker studies, especially for understudied populations (e.g., women and racial minorities), but introduces difficulties in comparability of populations, and in the availability of comparable data for assessment of both radiation exposures and non-radiologic confounding factors. Selection of the appropriate study design is critical to maximize the effectiveness of these combined studies. Case-control studies permit in-depth exposure assessment for radiologic and non-radiologic workplace hazards, as well as personal factors, such as smoking history, that may confound the relation between radiation exposure and leukemia risk. By selecting a large number of controls per case and using efficient exposure, epidemiologic, and statistical methods, the ability to observe a precise and unbiased estimate of the risks per unit dose should exceed that possible with a cohort analysis.

Some important aspects of the dose-response relationship must be evaluated in new studies. For example, one of the most important observations of leukemia risk in the A-bomb and medically exposed cohort studies is the decreasing or wavelike pattern in ERR following exposure, with peaks observed approximately 5–15 years after exposure.[54,62] Few studies of workers, however, have evaluated the temporal dynamics of radiation-related risks following exposure, instead simply adjusting for time since exposure,[37] or ignoring it in the analysis. This approach has been due primarily to the lack of sufficient numbers of cases to support fine stratification by time since exposure, and difficulties associated with the longer periods of exposure for most workers. Recent studies of early Mayak workers, who received exceptionally high doses during a short time period, confirm the temporal association found in the A-bomb cohort. ERR per Sv were approximately 15-fold higher after 3–5 years than 6 or more years following exposure.[50,72] This important analysis reveals a peak in risk that was unobservable in the A-bomb cohort, since follow-up did not begin until 5 years after exposure. This finding also illustrates that merely increasing the period of follow-up beyond peak exposure may dilute the highest excess risks experienced by a cohort. For U.S. workers, it is likely that similar temporal effects, which may provide very important information for regulatory purposes, can only be evaluated in large (combined) cohort studies.

PUBLIC HEALTH IMPACT OF STUDIES OF LEUKEMIA IN NUCLEAR WORKERS

Improved understanding of the effects of low-dose radiation on leukemia risk will most benefit those who may still be exposed to radiation at work. Because of the diverse regulatory climate in the U.S. and the lack of a central radiation exposure registry, it is difficult to estimate the number of workers currently exposed to external radiation. For example, the Nuclear Regulatory Commission (NRC), the DOE, and individual states have distinct responsibilities for different large sectors. The NRC covers power plants, fuel fabricators, and radiopharmaceutical producers, but the states have jurisdiction for x-ray exposures in medical and dental care. In general, the states do not require reporting of exposure results or summaries, and confine their involvement to equipment licensing and inspection. The DOE reports on its industrial complex (including cleanup workers) and National Laboratories, where about 24,000 workers overall had detectable exposures in 1995. Exposure distributions among medical personnel are not well known; however, the Environmental Protection Agency has estimated that 42% of workers receiving a measurable radiation exposure in 1980 were employed in the fields of medicine or dentistry.[51]

The NRC and DOE now compile annual exposure data in a two-part registry known as the **Radiation Exposure Information and Reporting System.**[78] Both agencies produce summary documents each year, but because of uncertainties about job tenure, it is difficult to use them to estimate how many workers may accumulate elevated total exposures. Distributions of cumulative exposures have been described for many groups of radiation workers, such as those hired at DOE facilities prior to the 1980s (Table 1A). In these groups the median cumulative exposures varied (2–9 mSv), with 4–14% exceeding a cumulative exposure of 50 mSv. Similar estimates are difficult to obtain for groups such as nuclear power workers, since the NRC data only completely covers terminated workers. One feasibility study estimated that 13% of these nuclear power workers have a cumulative exposure exceeding 50 mSv.[73] More complete information about radiation exposures is needed to fully evaluate the occupational health impact of low-dose occupational exposure and leukemia.

CONCLUSIONS

Strong evidence exists that nuclear workers worldwide have experienced slight but meaningful elevations in leukemia mortality that can be related to increases in low-LET radiation dose. Individual studies of nuclear worker populations have limited statistical precision because of the small numbers of subjects and generally low worker exposures. Quantitative estimates of risk per unit of dose vary widely across cohort studies, and are sensitive to changes in study design. Combined-site studies that apply consistent epidemiologic and exposure assessment techniques, with increased follow-up of worker populations, should provide the most precise estimates of the dose-related risks of leukemia in workers exposed to low-LET ionizing radiation.

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