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Effects of Low Doses and Low Dose Rates of External Ionizing Radiation: Cancer Mortality among Nuclear Industry Workers in Three Countries

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Studies of the mortality among nuclear industry workforces have been carried out, and nationally combined analyses performed, in the U.S., the UK and Canada. This paper presents the results of internationally combined analyses of mortality data on 95,673 workers (85.4% men) monitored for external exposure to ionizing radiation and employed for 6 months or longer in the nuclear industry of one of the three countries. These analyses were undertaken to obtain a more precise direct assessment of the carcinogenic effects of protracted low-level exposure to external, predominantly γ, radiation. The combination of the data from the various studies increases the power to study associations between radiation and specific cancers. The combined analyses covered a total of 2,124,526 person-years (PY) at risk and 15,825 deaths, 3,976 of which were due to cancer. There was no evidence of an association between radiation dose and mortality from all causes or from all cancers. Mortality from leukemia, excluding chronic lymphocytic leukemia (CLL)—the cause of death most strongly and consistently related to radiation dose in studies of atomic bomb survivors and other populations exposed at high dose rates—was significantly associated with cumulative external radiation dose (one-sided P value = 0.046; 119 deaths). Among the 31 other specific types of cancer studied, a significant association was observed only for multiple myeloma (one-sided P value = 0.037; 44 deaths), and this was attributable primarily to the associations reported previously between this disease and radiation dose in the Hanford (U.S.) and Sellafield (UK) cohorts. The excess relative risk (ERR) estimates for all cancers excluding leukemia, and leukemia excluding CLL, the two main groupings of causes of death for which risk estimates have been derived from studies of atomic bomb survivors, were −0.07 per Sv [90% confidence interval (CI): −0.4, 0.3] and 2.18 per Sv (90% CI: 0.1, 5.7), respectively. These values correspond to a relative risk of 0.99 for all cancers excluding leukemia and 1.22 for leukemia excluding CLL for a cumulative protracted dose of 100 mSv compared to 0 mSv. These estimates, which did not differ significantly across cohorts or between men and women, are the most comprehensive and precise direct estimates of cancer risk associated with low-dose protracted exposures obtained to date. Although they are lower than the linear estimates obtained from studies of atomic bomb survivors, they are compatible with a range of possibilities, from a reduction of risk at low doses, to risks twice those on which current radiation protection recommendations are based. Overall, the results of this study do not suggest that current radiation risk estimates for cancer at low levels of exposure are appreciably in error.

INTRODUCTION

Current estimates of cancer risk associated with external exposure to low-linear energy transfer (LET)[2,3] ionizing

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[2]Low-LET radiations: γ and X rays in the range 100 to 2500 keV.

[3]Abbreviations used: AEA, Atomic Energy Authority; AECL, Atomic Energy of Canada Ltd.; AWE, Atomic Weapons Establishment; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DDREF, dose and dose-rate effectiveness factor; ERR, excess relative risk; IARC, International Agency for Research on Cancer; ICRP, International Commission on Radiological Protection; LET, linear energy transfer; ORNL, Oak Ridge National Laboratory; RERF, Radiation Effects Research Foundation; RR, relative risk; SES, socio-economic status; UNSCEAR, United Nations Scientific Committee on the Effects of Atomic Radiation.

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radiation are derived primarily from studies of the mortality of atomic bomb survivors in Hiroshima and Nagasaki and of patients irradiated for therapeutic purposes (*1–4*). Both these groups were exposed primarily at high dose rates. Radiation protection recommendations for environmental and occupational exposures have generally been based on the use of these estimates in conjunction with models to extrapolate the effects of such acute (or short-term) high-level exposures to the relatively low-dose, low-dose-rate exposures of environmental and occupational concern, and across populations with different baseline cancer risks (*4*). These models are, inevitably, subject to uncertainties.

A direct assessment of the carcinogenic effects of long-term, low-level radiation exposure in humans can be made from studies of cancer risk among workers in the nuclear industry.[4] Many of these workers have received low, above-background doses of ionizing radiation, predominantly from external γ-ray exposures, and their radiation doses have been carefully monitored over time through the use of personal dosimeters. Published studies have covered cohorts of nuclear industry workers in the United States of America (U.S.), United Kingdom (UK) and Canada[5] (*5–29*). Most of these studies have provided little evidence of dose-related increase in all-cancer mortality, although statistically significant associations between mortality from all cancers combined and cumulative radiation dose were observed in two studies: of Oak Ridge National Laboratory (ORNL) employees in the U.S. (*24*) and of the employees of the Atomic Weapons Establishment (AWE) in the UK (*16*). The statistical power of individual studies was low, however, and in most cohorts the confidence intervals of the 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. Analyses of specific types of cancer were also carried out in most studies; no consistent pattern of increase for any single cancer type was observed across all cohorts.

In 1988, the investigators responsible for the published studies agreed to conduct combined analyses of data from such studies through the International Agency for Research on Cancer (IARC) to maximize their informativeness. At that time, national analyses of data were already planned in the UK and the U.S., and these have been published (*30–32*). The objectives of the international combined analyses were: (1) to increase the precision of direct estimates of cancer risk in populations receiving protracted low-dose exposure to ionizing radiation and compare these estimates with those derived from high-dose studies;[6] (2) to increase the statistical power to study associations between radiation dose and single cancer types; and (3) to understand similarities and differences between studies.

The estimates of risk per unit radiation dose for all cancers excluding leukemia and leukemia excluding chronic lymphocytic leukemia (CLL) obtained from the international combined analyses have been published elsewhere (*33, 34*) and compared with estimates derived from analysis of data on atomic bomb survivors. The current paper presents a detailed comparison of the estimates for the combined worker population with risk estimates derived from high-dose-rate studies, comparisons of risk estimates across facilities, together with the results of analyses of cause-specific mortality and radiation dose.

MATERIALS AND METHODS

Selection of Cohorts for Inclusion

All cohort studies of nuclear industry workers which were published prior to 1989 were considered for inclusion in the combined analyses if they met the following criteria (*35*): (1) members of the cohort had potential for whole-body external exposure to ionizing radiation through employment in the nuclear industry; (2) monitoring of radiation exposure had been carried out routinely (by use of personal dosimeters) on workers likely to be exposed to ionizing radiation and records had been kept; (3) estimates of whole-body dose from external exposures were available for individual workers likely to be exposed on a yearly basis; (4) information on a minimum set of variables was available for all individuals in the cohort; (5) the mechanisms of follow-up were not selective (for example, restricted to current workers), and 90% or better ascertainment of vital status and of cause of death was possible; (6) information was available on monitoring policies and practices over time.

Ten cohorts met these criteria; one (*5*) was excluded because exposure was mainly internal and two (*6, 7*) because, for logistic reasons, the investigator could not participate in the combined analyses. The seven cohorts included in the combined analyses comprised employees at the Hanford site (*21, 27*), Oak Ridge National Laboratory (ORNL) (*17, 24*) and Rocky Flats nuclear weapons plant (*18*) in the U.S.; the Sellafield plant of British Nuclear Fuels (*11, 29*), the Atomic Energy Authority (AEA) (*9, 26*) and the Atomic Weapons Establishment (AWE) (*16*) in the UK; and Atomic Energy of Canada Ltd. (AECL) (*14, 29*). They included a total of almost 150,000 workers (mostly men) in the three countries with an average duration of follow-up of approximately 24 years. The types of activities carried out in the facilities included are shown in Table I.

The methods used to identify the members of the cohorts, to collect dosimetric information, to carry out mortality follow-up and to ascertain the cause of death of workers varied between (and sometimes within) countries. They are summarized elsewhere (*34*).

[4]Throughout the paper, the term "nuclear industry" is used to refer to facilities engaged in the production of nuclear power, the manufacture of nuclear weapons, the enrichment and processing of nuclear fuel, or reactor or weapons research. Uranium mining is not included.

[5]G. M. Matanoski, Health Effects of Low-level Radiation in Shipyard Workers. Report to DOE, 1991.

[6]Throughout this paper, the term "high-dose studies" is used, for simplicity, to refer to the studies currently used in formal radiation risk assessment, namely the atomic bomb survivors, and patients irradiated for therapeutic purposes. Not all subjects in these studies received high doses, but the exposure rates are assumed to be greater than would normally be experienced in the occupational and general environment.

TABLE I
Type of Activities Carried Out in the Facilities Included in the Combined Analyses during the Study Period

Country	Facility	Predominant activity
U.S.	Hanford	Nuclear reactors, reprocessing, waste treatment, purification of plutonium
U.S.	Rocky Flats	Plutonium weapons
U.S.	ORNL[a]	Research and development plant, reactors
UK	Sellafield	Nuclear reactors, replacement, reprocessing, waste treatment, fast-reactor fuel fabrication
UK	AEA[a]	Research and development, reactor processing
UK	AWE[a]	Weapons research
Canada	AECL[a]	Nuclear reactor, research and related technologies

[a]ORNL = Oak Ridge National Laboratory; AEA = Atomic Energy Authority; AWE = Atomic Weapons Establishment; AECL = Atomic Energy of Canada Ltd.

Definition of the Study Population

For the combined analyses, the study population was restricted to the 95,673 workers who were monitored for external radiation by the use of personal dosimeters and who were employed in any of the participating facilities for at least 6 months. Workers with short durations of employment were excluded as it was thought they might not be comparable to longer-term workers in many aspects related to cancer risk. Nineteen workers who may have received a high-dose-rate exposure were also identified and excluded from the analyses. The specific criterion chosen for this exclusion was the fact of having had at least one annual dose of 250 mSv or more, the criterion in the U.S. for a radiation incident of medical significance (*36*).

Dosimetry

The recording of individual radiation dose was done to ensure compliance with radiation protection guidelines in force at the time and not for epidemiological purposes. The accuracy and precision of individual dose estimates therefore varied with time, place and radiation quality[7,8] (*37*).

A committee of persons experienced in dosimetry and radiation protection from each participating country (G. Cowper, Canada; J. Fix, U.S.; L. Salmon, UK) was set up to study historical dosimetric practices in the various facilities with the aims of (1) identifying sources of error and lack of comparability in individual dose estimates, (2) estimating the magnitude of these errors and (3) evaluating the extent to which recorded doses approximated doses to specific organs. Detailed results of this study are reported elsewhere[7] (*34*).

Overall, the majority of the doses to workers was predominantly from exposure to higher-energy (100 keV to 1 MeV) photons, and it was judged that the measurements across facilities and time were reasonably comparable. The bias in using recorded doses as estimates of organ doses was thought likely to be small, although recorded dose probably overestimated dose to the bone marrow slightly. A small minority of workers received a substantial portion (>10%) of their dose from exposure to photons of lower energies or neutrons or from intake of radionuclides. It has not been possible in general to estimate these doses adequately, but efforts were made to identify such workers and, to the extent possible, exclude them from selected subsidiary analyses, designated in the current paper as analyses based on "the restricted dosimetry population." Further details on the identification of these workers are given by Cardis and collaborators (*34*).

Statistical Methods

In general, the statistical methods used were similar to those which have been used for the national combined analyses (*30–32*) and involved internal comparisons of mortality within cohorts by level of external radiation doses. For each worker, cumulative dose and person-years at risk were accumulated over time from his or her date of entry in the study (defined as the later of date of start of employment plus 6 months and date of first monitoring) to his or her date of exit (defined as the earliest of date of death, date of loss to follow-up and date of end of follow-up in the appropriate cohort). Person-years at risk and deaths were stratified by levels of potential confounding variables (see below).

Observed (O) and expected (E) numbers of deaths were calculated by dose categories for 47 underlying causes of death defined in the Annex. The expected numbers of deaths were calculated assuming that, within a stratum defined by levels of the confounding variables, the mortality rate in each dose category was the same as that of the entire stratum, i.e., that the cause of death under study was not associated with exposure.

The score test statistic (*38*) based on the linear relative risk model was used to test for trends in mortality across 11 dose categories (<5, 5–, 10–, 20–, 50–, 100–, 150–, 200–, 300–, 400– and 500– mSv). As there was no reason to suspect that exposure to radiation would be associated with a decrease in risk of any specific type of cancer, one-sided tests are presented throughout. Because of the skewness of the dose distribution, use of the normal approximation may exaggerate statistical significance for diseases with small numbers of deaths. For this reason, for leukemia excluding CLL, multiple myeloma and all cases where the test statistic exceeded 1.28 (corresponding to a one-tailed P value of 0.10) and the number of deaths was less than 30, the P value presented was estimated using computer simulations (*39*) based on 5000 samples, rather than the normal approximation.

To allow for a possible latent period between an exposure and its consequences, cumulative doses were lagged by 2 years for leukemia and 10 years for other causes of death as follows: with a lag of x years, annual doses were included in the calculation of the cumulative dose at time t if they had been received in or before time $t - x$. Person-years were attributed to the category of dose accumulated by that time. Doses received off-site—i.e. in facilities other than those included in the combined analyses—were treated identically. In particular, a subject known to have received doses prior to entry in one of the study facilities entered the follow-up with the corresponding dose—when no lag was used—or with that dose cumulated up to x years previously when a lag of x years was used.

Estimates of excess relative risk (ERR) per Sv[9] were obtained using Poisson regression, based on a model in which the relative risk was assumed to be of the form $1 + \beta Z$, where Z is the cumulative dose in Sv. The relative risk (RR) at a given dose level d compared to zero

[7]J. Fix, L. Salmon, G. Cowper and E. Cardis, A retrospective evaluation of the dosimetry employed in a combined epidemiological analysis. Unpublished work.

[8]G. M. Kendall and L. Salmon, Records of UK exposure to ionizing radiation and their role in epidemiological studies. Unpublished work.

[9]Although it is recognized that very few workers received doses as large as 1 Sv, this unit was chosen for comparability to results reported for high-dose studies.

dose, a more commonly used risk measurement in epidemiology, can be obtained by multiplying the ERR by the dose d and adding 1. The 90% confidence intervals (90% CI) for the ERR were based on the score statistic using the expected information as described by Gilbert (*39*) and Gilbert *et al.* (*40*). For leukemia, confidence intervals were based on simulations as described by Gilbert (*39*). Model fitting was carried out using the computer software EPICURE. Tests of homogeneity of the ERR per Sv across a factor (such as facility) were obtained from the likelihood ratio test statistic resulting from the comparison of deviances of models with and without inclusion of the relevant factor. It is noted that the study had little power to detect heterogeneity of risk across facilities.

Two approaches were used for the formal comparison of risk estimates from the data for nuclear industry workers and from high-dose-rate studies. These comparisons were restricted to men because the number of exposed women in the workers cohorts was small.

First, risk estimates and confidence intervals from the data for the workers were compared to estimates of risk among male atomic bomb survivors exposed between the ages of 20 and 60 years derived at IARC using data supplied by the Radiation Effects Research Foundation (RERF). The constant linear relative risk model used for deriving estimates for the workers was applied to the RERF data, restricted to subjects with kerma dose below 4 Gy and attained age below 75 years, as was done in the analyses of the U.S. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation (BEIR V) (*1*). Analyses were adjusted for attained age (in 5-year intervals), calendar period (in 5-year intervals) and city, and based on nine dose categories (0–, 5–, 55–, 95–, 195–, 495–, 995–, 1995–, 2995– mSv). Estimates of bone marrow dose lagged by 2 years and of stomach dose lagged by 10 years were used, respectively, for estimating the risk of leukemia and that of all cancers excluding leukemia. The quality factor[10] for neutrons was taken to be 20, as in the BEIR V analyses (*1*).

Second, the models derived by the BEIR V Committee (*1*) for estimating risks of leukemia and respiratory, digestive and other cancers were applied to the data for the workers. Specifically, the annual doses of male workers were weighted, for each year of the follow-up, according to the age at which they were received and the time since the dose was received, using the BEIR V coefficients for men. The resulting risk estimates and confidence intervals were expressed as multiples of risk under the BEIR V model. Respiratory, digestive and other cancers were then analyzed simultaneously, stratifying on these three cancer groupings (*41*), to obtain an estimate of risk for all cancers excluding leukemia as a multiplier of the BEIR V estimate. For leukemia, only the linear term of the model was used because, although the preferred BEIR V model is linear-quadratic in dose, at low doses and dose rates the contribution of the quadratic term is negligible.

The magnitude of the estimates and confidence intervals for the workers was, in addition, compared to the estimates for men aged 20 and above at the time of exposure derived by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, ref. *2*) using a quality factor of one for neutrons, truncating doses at 6 Gy and stratifying age at exposure in three categories. The UNSCEAR coefficients served as a basis for the current recommendations of the International Commission on Radiological Protection (ICRP, ref. *4*).

Confounding Factors

All analyses were adjusted through stratification for sex, attained age (by 5-year intervals), calendar period (by 5-year categories), socio-economic status (SES) within facility (as information available differed between cohorts, see below) and study population (Hanford, ORNL, Rocky Flats, Sellafield, Dounreay,[11] South of England[11] and AECL).

Information on SES was obtained for all cohorts except AECL. For Hanford, job category data were used to define four socio-economic categories as described by Gilbert *et al.* (*27*). For ORNL, a variable was provided indicating whether a worker was paid hourly, weekly or monthly. For Rocky Flats, information on educational level was used to derive a three-level classification (no or some high school, high school graduate or some college, college graduate or higher). Sellafield workers were classified only as "industrial" and "non-industrial." For the rest of the UK, the British Registrar General's six-category social class classification was available; for the purpose of the analyses, these were combined to form four categories: I + II, III—manual, III—non-manual and IV + V.

Adjustment on facility or grouping of facilities (as in the UK) where a worker was employed was carried out to account for possible differences in cancer risk by geographic location or across workplaces. Workers known to have worked in more than one facility were assigned to the facility of last employment (*34*).

As only limited information was available on tobacco smoking or alcohol consumption in the participating cohorts, the relationships between radiation exposure and mortality from smoking-related cancers (*42*) and from non-malignant respiratory diseases excluding pneumonia were studied as indirect indicators of confounding by smoking, and that with death from liver cirrhosis as a possible indicator of confounding by alcohol consumption.

No information was available on radiation dose from natural background or medical exposures. The tacit assumption was made that, within a facility, non-occupational radiation dose level was independent of occupational dose level; thus non-occupational radiation dose was not considered to be a confounder of the association between occupational radiation dose and cancer risk. Differences in natural background radiation levels between geographical areas were taken into account by the adjustment on facility described above.

RESULTS

Characteristics of the study population are shown, by facility, in Table II. The mean cumulative radiation dose in the combined cohort was 40.2 mSv per worker and the collective dose was 3,843.2 Sv. The total number of person-years (PY) at risk was 2,124,526. A total of 15,825 deaths occurred during the study period. Women comprised less than 15% of the workers and their mean cumulative dose was low (6.2 mSv) compared to the men's (46.0 mSv). Overall, the distribution of doses was very skewed (Fig. 1); close to 60% of subjects had cumulative doses below 10 mSv, 80% below 50 mSv; less than 2% had doses greater than 400 mSv.

Observed and expected number of deaths by cumulative dose and trend test statistics for the 47 causes of death are presented in Table III. There was no evidence for an association between radiation dose and all-cause ($P = 0.23$) or all-

[10]Quality factor: weighting factor applied to an absorbed dose to take into account the type and energy of the radiation causing the dose.

[11]Note: In the data provided on UK workers, it was not possible to distinguish AEA and AWE workers. To adjust for possible environmental differences across the facilities of the UK AEA and AWE, however, information was provided to separate workers from Scotland (Dounreay) from those of the South of England.

TABLE II
Distribution of Workers, Person-Years and Collective Dose by Facility[a]

	Hanford	Rocky Flats	ORNL	Sellafield	UK other than Sellafield	AECL	Total
Number of workers	32,595	6,638	6,591	9,494	29,000	11,355	95,673
Men	24,628	6,638	6,591	8,802	26,495	8,591	81,745
Women	7,967	0	0	692	2,505	2,764	13,928
Recruitment period	1944–1978	1951–1979	1943–1972	1947–1976	1946–1982	1956–1980	
Follow-up period	1944–1986	1951–1979	1943–1984	1947–1988	1946–1988	1956–1985	
Number of deaths	6,445	587	1,246	2,027	4,629	891	15,825
Number of cancer deaths	1,508	109	304	544	1,272	239	3,976
Person-years	781,549	100,022	173,730	233,090	637,925	198,210	2,124,526
Collective dose (Sv)	877.2	241.8	141.4	1,309.6	958.6	314.6	3,843.2
Men	831.6	241.8	141.4	1,294.5	936.4	311.8	3,757.5
Women	45.6	0	0	15.1	22.3	2.8	85.8

[a]These results are restricted to monitored workers who were employed at least 6 months in any of the participating facilities and exclude workers having received a dose of 250 mSv or above in a single year.

cancer mortality ($P = 0.51$). Among non-cancer causes of death, mortality from circulatory diseases was significantly associated with radiation dose ($P = 0.045$). There was a weak negative relationship between radiation dose and mortality from respiratory diseases, excluding pneumonia, and from liver cirrhosis. These conditions were considered as indirect

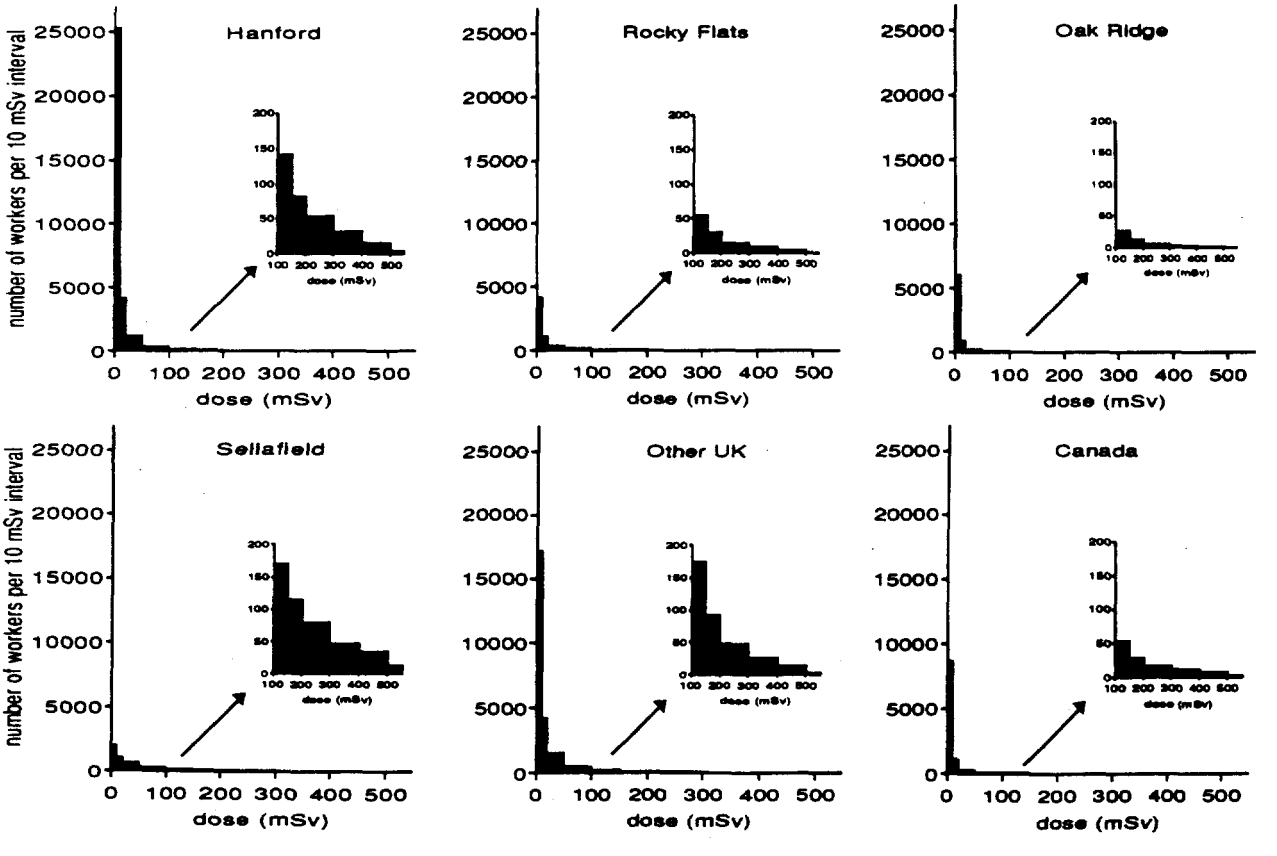

FIG. 1. Distribution of monitored workers by cumulative dose.

TABLE III

Observed and Expected Numbers of Deaths by Cause, All Facilities Combined, Adjusted for Sex, Age, Calendar Period, SES and Facility (Doses Are Lagged by 2 Years for Leukemia and 10 Years for Other Causes of Death)

	Cumulative dose (mSv)								
Causes of death	0– O/E	10– O/E	20– O/E	50– O/E	100– O/E	200– O/E	400– O/E	Total Deaths	Trend[a] (1-sided *P*)
All causes	9582/9506.3	1848/1915.8	1880/1909.9	989/986.5	702/719.2	586/549.2	238/238.2	15,825	0.75 (0.226)
All cancers	2317/2317.3	483/483.5	465/494.7	285/263.2	201/196.8	165/151.5	60/68.9	3,976	–0.02 (0.508)
All except leukemia	2234/2228.3	462/465.4	445/476.9	276/254.3	196/190.5	161/147.5	56/67.3	3,830	–0.28 (0.609)
Buccal and pharynx	51/42.3	10/8.0	0/7.0	3/3.9	1/3.1	2/2.7	1/0.9	68	–1.10 (0.864)
Esophagus	52/48.8	13/13.1	16/15.3	6/9.6	6/7.8	6/6.3	5/3.2	104	0.32 (0.375)
Stomach	158/155.1	34/31.7	29/35.2	24/20.9	13/15.3	11/11.1	6/5.7	275	–0.21 (0.582)
Small intestine	6/6.1	2/1.6	1/1.8	1/1.0	1/1.0	1/0.4	0/0.1	12	0.36 (0.360)
Colon	220/204.7	36/42.8	32/41.3	22/21.9	19/15.4	9/11.6	5/5.3	343	–0.83 (0.797)
Rectum	74/77.7	15/14.2	20/17.0	5/9.6	10/7.6	6/6.1	5/2.8	135	0.99 (0.161)
Liver	24/21.4	3/4.1	4/3.7	0/1.7	0/1.1	2/0.7	0/0.2	33	0.01 (0.495)
Biliary tract	23/21.4	3/3.8	4/3.2	0/1.4	1/0.8	0/0.4	0/0.1	31	–0.86 (0.806)
Pancreas	115/113.2	27/24.5	20/23.4	10/11.6	7/8.6	7/6.8	5/2.9	191	1.20 (0.115)
Nasal cavity	6/6.2	0/0.7	2/1.1	0/0.4	0/0.3	1/0.2	0/0.1	9	0.43 (0.334)
Larynx	24/21.8	3/4.0	2/4.2	3/1.8	1/1.3	0/0.8	1/0.1	34	1.17 (0.122)
Lung	676/689.4	144/154.2	154/161.2	111/87.6	75/67.0	64/54.0	14/24.6	1,238	–0.28 (0.610)
Pleura	4/8.1	3/2.5	5/3.4	3/2.1	3/1.6	2/1.4	0/1.0	20	–0.18 (0.571)
Bone	10/8.2	0/0.7	1/0.8	0/0.4	0/0.3	0/0.4	0/0.2	11	–1.21 (0.887)
Connective tissue	10/12.0	3/2.2	2/2.2	0/1.0	3/0.8	1/0.6	0/0.2	19	0.36 (0.358)
Melanoma	32/31.1	3/4.6	2/4.4	5/2.4	2/1.7	2/1.3	0/0.4	46	0.21 (0.416)
Female breast	69/71.3	8/5.9	2/3.9	4/1.6	1/1.1	0/0.2	0/0.0	84	0.50 (0.308)
Cervix uteri	7/8.4	1/0.8	2/0.5	0/0.2	0/0.0	0/0.0	0/0.0	10	0.63 (0.266)
Other uterus	7/7.7	1/0.7	1/1.4	1/0.2	0/0.0	0/0.0	0/0.0	10	1.71 (0.092)*
Ovary	18/19.5	2/2.2	3/1.3	0/0.6	1/0.3	0/0.1	0/0.0	24	0.49 (0.312)
Prostate	127/136.4	47/35.8	36/37.0	21/18.0	13/12.5	11/11.1	1/5.2	256	–1.68 (0.953)
Testis	14/14.6	1/1.4	2/1.4	1/0.7	1/0.5	0/0.3	0/0.1	19	–0.26 (0.604)
Bladder	51/53.4	17/13.2	16/14.4	5/8.1	5/6.7	6/5.4	4/3.0	104	0.62 (0.266)
Kidney	54/50.7	7/10.4	11/11.2	7/5.9	6/4.6	3/3.4	0/1.7	88	–1.03 (0.848)
Brain and CNS	73/75.1	12/14.5	19/14.3	9/7.7	4/5.5	4/3.6	1/1.3	122	–0.24 (0.593)
Thyroid	10/8.4	2/1.3	1/2.3	1/1.3	0/0.8	0/0.6	1/0.3	15	0.58 (0.281)
Ill-defined and secondary	151/145.8	32/34.5	33/33.9	13/16.7	12/12.8	11/9.4	5/4.0	257	0.63 (0.263)
Non-Hodgkin's lymphoma	76/81.6	24/16.9	13/16.3	11/8.5	5/6.2	6/4.1	0/1.5	135	–0.25 (0.600)
Hodgkin's disease	32/31.4	2/3.8	4/3.4	0/1.8	3/1.2	2/1.0	0/0.5	43	0.28 (0.390)
Multiple myeloma	28/26.6	3/5.2	1/4.7	5/2.7	3/2.1	2/1.9	2/0.8	44	1.87 (0.037)*
All leukemia	72/75.7	23/21.2	20/21.8	12/11.3	9/7.8	4/5.5	6/2.6	146	1.43 (0.076)*
All except CLL	60/62.0	19/17.2	14/17.4	8/9.0	8/6.4	4/4.7	6/2.3	119	1.85 (0.046)*
CLL	12/13.7	4/4.0	6/4.4	4/2.2	1/1.5	0/0.9	0/0.3	27	–0.74 (0.771)
Acute leukemias	33/31.3	7/9.0	11/9.9	3/5.3	3/3.6	4/2.6	2/1.3	63	0.82 (0.206)
Other cancers	32/29.8	4/6.2	7/6.0	5/3.0	0/2.5	2/1.7	0/0.9	50	–0.87 (0.808)
Smoking-related	969/968.9	214/217.0	208/225.4	138/122.6	95/94.5	85/75.9	30/34.7	1,739	0.29 (0.386)
Non-smoking-related	1348/1348.4	269/266.5	257/269.3	147/140.7	106/102.4	80/75.6	30/34.2	2,237	–0.32 (0.624)
All non-cancer causes	7265/7189.0	1365/1432.3	1415/1415.2	704/723.2	501/522.4	421/397.6	178/169.3	11,849	0.90 (0.184)
Non-malignant tumors	24/23.1	3/4.4	6/4.8	1/2.5	3/1.7	1/1.1	0/0.4	38	–0.26 (0.601)
Circulatory diseases	4689/4626.5	908/975.7	954/975.4	487/504.4	372/366.6	313/282.6	132/123.9	7,855	1.69 (0.045)
Respiratory diseases	421/447.3	117/106.0	129/102.5	53/49.6	25/37.1	30/30.7	12/13.8	787	–0.82 (0.795)
Liver cirrhosis	120/116.3	19/21.6	18/17.6	10/8.4	5/6.2	4/4.5	0/1.4	176	–1.29 (0.902)
External causes	880/880.0	99/97.9	91/92.3	53/46.2	33/31.7	14/19.6	3/5.3	1,173	–1.29 (0.901)
Unknown	95/84.0	23/19.8	11/16.3	2/7.1	3/5.1	2/3.7	1/1.1	137	–1.76 (0.961)

[a]Trend test based on 11 dose categories; can be compared to a standard normal distribution. However, statistical significance may be exaggerated for diseases with a small number of deaths; *denotes simulated *P* values (see Methods).

TABLE IV
Excess Relative Risk (ERR) Estimates per Sv, 90% Confidence Intervals (CI) and Relative Risk (RR) Estimates at 100 mSv for All Cancers and Leukemias

Type of cancer	Number of deaths	ERR per Sv	90% CI	RR for 100 mSv vs 0 mSv[a]
All cancers	3976	–0.02	(–0.34, 0.35)	1.00
Except leukemia	3830	–0.07	(–0.39, 0.30)	0.99
All leukemia	146	1.55	(–0.21, 4.7)[b]	1.16
Except CLL[c]	119	2.18	(0.13, 5.7)[b]	1.22
ALL[c]	11	–0.89	(<0,[d] 7.3)[b]	0.91
CLL[c]	27	–0.95	(<0,[d] 9.4)[b]	0.91
AML[c]	32	3.38	(<0,[d] 14.9)[b]	1.34
CML[c]	28	11.00	(2.9,30.9)[b]	2.10

[a]See Methods.
[b]Simulated confidence intervals (see Methods).
[c]ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia.
[d]Lower bound would lead to negative relative risks in the low-dose range (<500 mSv).

indicators of possible differences in smoking and alcohol consumption across dose groups. There was, in addition, little evidence of an association between cumulative dose and mortality from smoking-related cancers as a group [defined as cancers of the oral cavity and pharynx, esophagus, pancreas, larynx, lung, bladder and renal pelvis (*42*)] ($P = 0.39$).

Among individual cancer types, mortality from leukemia excluding CLL was significantly related to radiation dose ($P = 0.046$), as was mortality from multiple myeloma ($P = 0.037$).

Table IV shows estimates of excess relative risk per Sv and of relative risk for 100 mSv compared to 0 mSv for mortality from all cancers and from leukemia and leukemia subtypes. The ERR of 1.22 per Sv for leukemia excluding CLL would correspond to an excess of 9.7 leukemia deaths (8% of all such deaths) attributed to radiation in this cohort if the observed association were causal. The ERR per Sv was greatest for myeloid leukemias, in particular chronic myeloid leukemia (CML), but the confidence intervals for each subtype overlapped.

The ERRs for all cancers excluding leukemia and leukemia excluding CLL are presented separately by sex and by facility in Table V. The ERRs for men were very similar to those observed for the entire population. The point estimates for women differed from those for men, but the confidence intervals were wide and the formal test for homogeneity provided no evidence of a difference in risk between men and women.

The ERR for all cancers except leukemia ranged from –1.63 per Sv (90% CI <0, 0.5) at Rocky Flats to 1.66 per Sv (0.04, 4.4) at ORNL. The confidence intervals were wide, however, and the test for homogeneity indicated that these differences could be due to chance fluctuation. For leukemia excluding CLL, the ERRs ranged from –1.06 to 48.4 per Sv across facilities. Here again, the confidence intervals were wide and there was only weak evidence for differences in risk across facilities ($P = 0.08$).

Table VI summarizes the results of comparisons with estimates derived from high-dose studies based on the approaches outlined above. All estimates from high-dose studies are based primarily on the follow-up of the atomic bomb survivors. For all cancers excluding leukemia, the

TABLE V
Number of Deaths and Excess Relative Risk (ERR) Estimates per Sv and 90% Confidence Intervals (CI) for All Cancers (Excluding Leukemia) and Leukemia (Excluding CLL) by Sex and Facility

Subpopulation	All cancers excluding leukemia			Leukemia excluding CLL		
	Number of deaths	ERR per Sv	90% CI	Number of deaths	ERR per Sv	90% CI
Sex						
Male	3522	–0.07	(–0.4, 0.3)	109	2.21	(0.1, 5.8)[a]
Female	308	0.97	(<0.9,[b] 8.2)	10	–2.67	(<0,[b] 127)[a]
χ^2 for homogeneity (1 *df*)		0.11	$P = 0.74$		0.07	$P = 0.79$
Facility						
Hanford	1452	–0.22	(<0,[b] 0.6)	47	–0.90	(<0,[b] 2.9)[a]
Rocky Flats	104	–1.63	(<0,[b] 0.5)	4	4.08	(<–0.0, 54.2)[a]
ORNL	280	1.66	(0.04, 4.4)	18	–1.06	(<0,[b] 4.8)[a]
Sellafield	533	–0.03	(<0,[b] 0.5)	10	43.50	(3.1, >100)[a]
Other UK	1227	–0.40	(<0,[b] 0.7)	35	1.50	(<0,[b] 14.3)[a]
Canada	234	0.13	(<0,[b] 2.1)	5	48.40	(2.8, >100)[a]
χ^2 for homogeneity (5 *df*)		4.86	$P = 0.43$		9.91	$P = 0.08$

[a]Simulated confidence intervals (see Methods).
[b]Lower bound would lead to negative relative risks in the low-dose range (<500 mSv).

TABLE VIII

Excess Relative Risk (ERR) Estimates per Sv and Confidence Intervals (CI) for All Cancers Excluding Leukemia and Leukemia Excluding CLL by Attained Age, Age at Exposure, Time since Exposure and Different Lags

Characteristics	All cancers excluding leukemia		Leukemia excluding CLL	
	ERR per Sv	90% CI	ERR per Sv	90% CI
Standard	-0.09	(-0.4, 0.3)	2.18	(0.1, 5.7)
Attained age				
<65	0.07	(-0.5, 0.7)	0.35	(<0.[a] 3.6)
65–75	-0.03	(-0.8, 0.3)	7.26	(<0.[a] 18.4)
75+	0.22	(-1.0, 1.4)	5.51	(<0.[a] 22.6)
χ^2 for homogeneity (2 *df*)	0.84	$P = 0.66$	2.61	$P = 0.27$
Age at exposure				
<35	0.43	(-1.1, 1.9)	-1.86	(<0.[a] 10.5)
35–50	-0.35	(-0.1, 3.0)	3.37	(<0.[a] 5.7)
50+	0.17	(-0.6, 1.0)	2.20	(<0.[a] 8.3)
χ^2 for homogeneity (2 *df*)	0.89	$P = 0.64$	0.19	$P = 0.91$
Time since exposure (years)				
<10+	n.a.[b]		1.82	(<0.[a] 8.9)
10–20	-0.48	(-1.16, 0.20)	-1.35	(<0.[a] 4.1)
20+	0.36	(-0.44, 1.16)	3.48	(<0.[a] 11.1)
χ^2 for homogeneity	1.60	(1 *df*) $P = 0.21$	1.48	(2 *df*) $P = 0.48$
Lags for dose (years)				
0	-0.21	(-0.4, 0.1)[c]	1.89	(0.0, 5.2)[d]
5	-0.13	(-0.4, 0.2)[c]	2.08	(0.0, 5.7)[c]
10	-0.07	(-0.3, 0.3)[c]	2.18	(0.1, 5.7)[c]
15	-0.04	(-0.5, 0.5)[c]	3.36	(0.6, 8.6)[c]
20	0.14	(-0.5, 0.9)[c]	5.13	(0.9, 13.2)[c]

[a]Lower bound would lead to negative relative risks in the low-dose range (<500 mSv).
[b]Not applicable: analyses for all cancers are lagged by 10 years.
[c]Score-based 90% confidence intervals.
[d]Simulated 90% confidence intervals.

entirely the possibility of residual confounding by SES or by a variety of lifestyle factors associated with cancer risk, and for which the SES variable may be an imperfect measure. The ERR for leukemia excluding CLL was little changed by adjustment for SES, whereas that for all cancer excluding leukemia was decreased. The leukemia risk estimate therefore appears to be less sensitive to confounding by SES.

As in most occupational cohort studies, information on lifestyle factors such as smoking habits, diet and occupational exposures could not be obtained retrospectively for all members of the cohorts. There was little indirect evidence, however, for an association between cumulative dose and mortality from smoking-related cancers, respiratory diseases or liver cirrhosis; it is thus unlikely that smoking or alcohol consumption is strongly correlated with radiation dose and that adjustment for these factors would greatly affect the conclusions of the study. This is supported, for tobacco, by the observation that the risk estimates for all cancers excluding leukemia and all cancers excluding both leukemia and lung were nearly identical (*34*) and by the results of two studies (*44*, *45*) carried out, respectively, within the Hanford and the UK AEA cohorts which showed little evidence for an association between smoking and occupational radiation dose.

A positive association between radiation dose and mortality from circulatory disease was observed in the three cohorts where information on SES was least detailed (Rocky Flats, Sellafield, AECL). It may therefore reflect residual confounding by lifestyle factors for which the SES variable is an inadequate proxy. Alternatively, given the large number of associations tested, this could be a chance finding. It should be noted, however, that such an association has also been seen in studies of atomic bomb survivors (*46*) and U.S. radiologists (*47*).

There was little evidence of an increase in the ERR for all cancers excluding leukemia with attained age, as was reported in recent analyses of the U.S. data alone (*31*).

Leukemia Risk

The combined analyses of the data for the workers demonstrated a significant ($P = 0.046$) association between

TABLE VII

Number of Deaths and Excess Relative Risk (ERR) Estimates per Sv and 90% Confidence Intervals (CI) for all Cancers (Excluding Leukemia) and Leukemia (Excluding CLL) Using Alternative Analytical Strategies

Subpopulation	All cancers excluding leukemia			Leukemia excluding CLL		
	Number of deaths	ERR per Sv	90% CI	Number of deaths	ERR per Sv	90% CI
Standard	3830	–0.07	(–0.4, 0.3)	119	2.18	(0.1, 5.7)[a]
Study populations						
Total workers[b]	6444	–0.05	(–0.4, 0.3)	187	2.26	(0.3, 5.6)[a]
All monitored[c]	4180	–0.08	(–0.4, 0.3)	133	2.09	(0.1, 5.2)[a]
Restricted dosimetry[d]	3455	–0.04	(–0.5, 0.5)	108	2.05	(–0.1, 6.4)[a]
Including associated causes[e]	4113	0.01	(–0.3, 0.4)	127	1.78	(–0.1, 5.1)[a]
Effect of SES						
No adjustment	3830	0.20	(–0.2, 0.6)	119	2.28	(0.2, 5.7)[a]
Effect of duration of employment						
Adjusted—all facilities	3830	0.08	(–0.3, 0.5)	119	1.72	(–0.3, 5.5)[a]
Adjusted—Hanford	3830	0.03	(–0.3, 0.4)	119	3.63	(0.8, 8.7)[a]

[a]Simulated confidence intervals (see Methods).
[b]Including non-monitored workers in the zero-dose category.
[c]Including monitored workers employed less than 6 months.
[d]Excluding workers judged to have potential for substantial dose from neutrons and/or internal exposures (see Methods).
[e]Including cancer deaths listed on the death certificate as either underlying or associated causes of death.

populations with low-level protracted exposure to mainly γ radiation. By contrast, the estimates obtained from the atomic bomb survivors are influenced by subjects receiving doses of 500 mSv or more and relate to acute exposure over a very short time. Our analyses imply that the estimates obtained from studies of high-dose-rate exposures are unlikely to underestimate substantially the actual risk at low doses and low dose rates. A significant increase in leukemia risk was observed in this study, at relatively low dose levels; the risk estimate was intermediate between the linear and linear-quadratic estimates from studies of atomic bomb survivors.

Uncertainties

Several points must be kept in mind when making comparisons of these worker-based risk estimates and confidence bounds with those based on studies of high-dose-rate exposures. The most important are possible biases and uncertainties in dose estimates, errors in outcome data and inadequate adjustment for confounders.

The risk estimates obtained for the "restricted dosimetry population," i.e. excluding workers who could be identified as having received substantial doses from radiation other than high-energy photons (Table VII), did not differ substantially from those based on the standard approach, although the uncertainty in the risk estimates increased slightly.

Although it appears that, for the majority of workers in these facilities, the dose estimates were compatible with 1 cm depth dose [the quantity currently recommended by ICRU (*43*) for radiation protection], in most cases available dose estimates overestimated organ doses by several percent. The Dosimetry Committee judged that bone marrow doses were overestimated by about 20%, implying that the present leukemia risk estimate and confidence limits may be underestimated by 20%. Random errors in dose estimates are likely to further bias the risk estimates downward, compared to estimates from high-dose studies which have been based on organ doses.

Some workers in the UK and the U.S. were known to have been employed in more than one study facility within those countries. Efforts were made to reconstruct their detailed employment and exposure history, particularly in the UK (*32*). Doses incurred after termination of employment in one of the study facilities were not generally available, however, and it is difficult to assess the impact of these missing doses.

The ascertainment of vital status was 92–100% complete, and ascertainment of cause of death was 98–100%, which was required to meet the criterion for inclusion in the combined analysis. Any misclassification of vital status or of underlying cause of death is unlikely to have been related to radiation dose and, if present, would tend to result in a small bias of estimates toward the null.

In this study, adjustment for SES had a strong effect on the risk estimate for all cancers excluding leukemia. As the type and detail of information available from each facility varied substantially and as no information was available for AECL workers, it is not possible to exclude

TABLE VI
Comparison of Excess Relative Risk (ERR) Estimates per Sv[a] (and 90% Confidence Intervals) between Nuclear Workers, Atomic Bomb Survivors and Other Published Estimates of Risk from High-Dose Studies; Men Only

Population	All cancers excluding leukemia		Leukemia excluding CLL	
	ERR per Sv	90% CI	ERR per Sv	90% CI
Nuclear workers data[b]	–0.07	(–0.39, 0.30)	2.18	(0.13, 5.7)[c]
A-bomb,[d] linear	0.18	(0.05, 0.34)	3.67	(2.0, 6.5)
A-bomb,[d] L-Q[e]	—	—	1.42	(<0, 6.5)
UNSCEAR	0.24	—	3.7	—
	Multiplier[f]	90% CI	Multiplier	90% CI
BEIR V	–0.17	(–0.76, 0.57)	0.71	(–0.04, 2.0)
A-bomb, linear	–0.39	(–2.2, 1.7)	0.59	(0.04, 1.6)

[a]Estimates of organ dose and 1 cm depth dose were used respectively in analyses of the data for atomic bomb survivors and nuclear industry workers.

[b]Adjusted for age, SES, facility and calendar time.

[c]Simulated confidence interval.

[d]A-bomb: data for atomic bomb survivors; adjusted for age, city and calendar time.

[e]Based on the linear term of a linear-quadratic (L-Q) dose–response model in the data for atomic bomb survivors.

[f]ERR in nuclear workers expressed as a multiple of the high-dose ERR; for example, the leukemia risk estimate is 0.71 times the BEIR V estimate with confidence interval ranging from –0.04 times to twice the BEIR V estimate.

excess relative risk obtained for male nuclear workers was less than that estimated at IARC from data for the atomic bomb survivors. The confidence interval was wide, however, and ranged from –2.2 to 1.7 times the estimate for the atomic bomb survivors. The ERR for male workers was estimated to be –0.17 times the BEIR V estimate with a confidence interval ranging from –0.8 to 0.6 times the BEIR V estimate. It was also less than the UNSCEAR estimate.

The risk estimate for leukemia excluding CLL obtained from the data for nuclear workers was greater than the estimate based on a linear-quadratic model and less than that based on a linear relative risk model obtained by reanalyzing data for male atomic bomb survivors at IARC (Table VI). The confidence interval for the estimate for the workers was relatively wide, however, and ranged from 0.04 to 1.6 times the linear estimate for the atomic bomb survivors. The ERR for male workers was estimated to be about 0.7 times the BEIR V estimate with a confidence interval ranging from –0.04 times to twice the BEIR V estimate. It was also less than the UNSCEAR estimate.

Table VII presents the results of additional analyses designed to assess the impact of the choice of analytical strategy on estimates for the workers. They include (a) analyses based on all workers whether they were monitored or not, all monitored workers (including those employed less than 6 months), and all workers in the restricted dosimetry population (see Methods, above); (b) analyses in which cancer was treated as the cause of death if it was either the underlying or an associated cause of death; and (c) analyses using different treatments of potential confounding factors.

Except in the following cases, the variations in analytical approaches presented in Table VII had little effect on the risk estimates. When cancer as an associated cause of death was included, the ERR for all cancers excluding leukemia increased from –0.07 to 0.01 per Sv (90% CI: –0.3, 0.4). For leukemia excluding CLL, the effect was to reduce the ERR from 2.21 to 1.78 per Sv (90% CI: –0.1, 5.1). Adjustment for duration of employment at Hanford only (the only facility where an association between all-cancer mortality and duration of employment was demonstrated) or in all facilities increased the ERR for all cancers excluding leukemia to 0.03 and 0.08 per Sv, respectively. For leukemia excluding CLL, adjustment at Hanford increased the estimate to 3.63 per Sv (90% CI: 0.8, 8.7), while adjustment in all facilities reduced it to 1.72 per Sv (90% CI: <0, 5.5). Not adjusting for SES in any facility increased the ERR for all cancers excluding leukemia to 0.2 per Sv (90% CI: –0.2, 0.6) and had little effect on the ERR for leukemia excluding CLL.

Analyses aimed at assessing the influence of potential effect modifiers (attained age, age at exposure and time since exposure) and analyses using alternative lag periods (0, 5, 10, 15 and 20 years) are presented in Table VIII. Attained age, age at exposure and time since exposure had little effect on the ERR for all cancers excluding leukemia or for leukemia excluding CLL.

As the lag period used went from zero to 20 years, the lagged cumulative dose decreased and the ERR for all cancers excluding leukemia increased monotonically from –0.21 per Sv (90% CI: –0.4 to 0.1) to 0.14 per Sv (90% CI: –0.5, 0.9) (Table VIII). The ERR for leukemia excluding CLL also increased from 1.89 per Sv (90% CI: 0.0, 5.2) to 5.13 per Sv (90% CI: 0.9, 13.2).

DISCUSSION

This study combined mortality data from seven previously published studies of nuclear industry workers in three countries. The studies selected for inclusion in these analyses met a series of stringent quality criteria defined by the Study Group in the planning phase of the study. In addition, efforts were made to ensure comparability of available radiation dose estimates across facilities and over time.

The estimates presented here are the most precise and comprehensive yet to have been obtained directly from

mortality from leukemia excluding CLL and radiation dose in a population receiving protracted low-dose-rate exposures. The ERR for mortality from that disease was 2.18 per Sv (90% CI: 0.1, 5.7). Out of 119 leukemia deaths observed in the combined data set, however, six occurred in the 400 mSv and above category, a dose range comparable to the lowest dose range in which excesses were demonstrated in the atomic bomb survivor population. When analyses were restricted to cumulative doses below 400 mSv and below 200 mSv, to assess the influence of death in the higher-dose categories on the dose–response relationship, the association was no longer statistically significant but the estimates of the slope parameter were compatible with that based on the full data set (*34*).

Although positive associations were seen between radiation dose and leukemia mortality in four of the six facilities or groupings of facilities (they were significant in two), the risk estimate largely reflects the association in the Sellafield cohort. Activities at the Sellafield plant included reprocessing of nuclear fuel: the possibility that chemical exposures could have confounded the association between radiation exposure and leukemia risk cannot be excluded (*32*).

The observed association between radiation dose and mortality from leukemia excluding CLL appeared to be restricted to myeloid leukemia, particularly CML, although one could not exclude the possibility that the risk of acute myeloid leukemia was of the same order as that of CML. This finding is consistent with the results of a recent reanalysis of the data from the National Registry of Radiation Workers (NRRW) in the UK (*48*); most of the NRRW cases, however, were included in the combined data set.

While the risk estimate for leukemia excluding CLL derived from the data for the workers was less than both the linear estimate derived at IARC using data for male atomic bomb survivors exposed as adults and the UNSCEAR estimate, the 90% confidence interval was wide, and the possibility of a lower risk or that of a risk up to 1.6 times the linear estimates obtained from high-dose data (and up to four times the linear-quadratic estimate) could not be excluded. The risk for leukemia excluding CLL was also estimated to be less than the BEIR V estimate with a confidence interval ranging from less than zero to two times that estimate. As the BEIR V model for leukemia includes both a linear and a quadratic term in dose, however, the BEIR V estimate of risk at low doses and dose rates is about one-half that which would have been obtained with a linear model. Hence the estimate for the workers is compatible with risks of the order of the estimate which would be obtained using a BEIR V type linear model but not much higher.

The apparent discrepancy between the comparisons based on the analyses of the data for atomic bomb survivors and those based on the BEIR V model is explained by the different weight given to doses received in different periods by the two models. The constant linear relative risk model used for these analyses gives equal weight to all doses received in the past. As discussed in greater detail in ref. (*34*), the BEIR V model reduces the weight by half for doses received 26–30 years in the past and to close to zero for doses received 31 years or more previously. Four of the high-dose (400 mSv and above) leukemia deaths had their cumulative dose reduced by this approach.

The coefficients of the BEIR V leukemia model were estimated from analyses of data on atomic bomb survivors and ankylosing spondylitis patients. The uncertainty in these is relatively large. For example, the BEIR V model for leukemia predicts that the risk varies with time since exposure. An analysis of risk by time since exposure (2–25, 26–30, 31+ years) using the data for the nuclear workers provided no evidence of a reduction of risk after 25 or 30 years (χ^2 test for homogeneity: 0.84, 2 *df*; $P = 0.66$); the power to test such an effect in the data for the nuclear workers was, however, extremely low.

When a factor of 1.2 was applied to the risk estimate, as suggested by the Dosimetry Subcommittee to adjust for the probable overestimation of the dose to the bone marrow, the ERR for leukemia excluding CLL became 2.6 per Sv and was compatible with risks up to 2.4 times that of BEIR V and twice the linear estimate based on male atomic bomb survivors exposed between the ages of 20 and 60.

All Cancers Excluding Leukemia

The combined analyses of the data for the workers did not provide evidence for an association between all-cancer mortality and radiation dose ($P = 0.51$). The estimated ERR for all cancers excluding leukemia was lower than both the estimate derived at IARC from the data for atomic bomb survivors and the BEIR V estimate. The confidence interval was wide, however, and the possibility of a risk up to 1.7 times the linear estimates obtained from data for atomic bomb survivors, or up to 0.6 times the BEIR V estimate, could not be excluded (Table VI). This apparent discrepancy in upper confidence limits arises mainly from the fact that the BEIR V models, based on observed patterns of risk over time in a number of studies of high-dose exposures, give different weights to doses received at different ages and in different time-since-exposure intervals (*34*).

There is uncertainty concerning the appropriateness of the BEIR V time- and age-specific coefficients for cancers other than leukemia; indeed, recent analyses of the data for the atomic bomb survivors have shown little effect of time since exposure on the risk estimates for respiratory cancer and little indication of differences in the temporal behavior of risk between the BEIR V groupings for respiratory, digestive and other cancers (*41*). The comparisons with the

BEIR V Committee estimates for all cancers excluding leukemia should therefore be interpreted with caution.

Overall, the results of our analyses for all cancers excluding leukemia provide evidence that the estimates obtained from studies of high-dose exposures are unlikely to underestimate the actual risk after protracted low doses substantially. The estimates for the nuclear workers are compatible with risks up to the order of the BEIR V estimate and twice the estimates based on male atomic bomb survivors exposed between the ages of 20 and 60.

The follow-up of the UK AWE study (*16*) and recent updated analyses of the ORNL study (*24*) have provided excess relative risk estimates for all cancers which were several times greater than that estimated in the study of the atomic bomb survivors. In our analyses, the ERR for all cancers excluding leukemia in Oak Ridge workers was 1.66 per Sv, higher than for workers in other facilities [but lower than that reported by Wing and colleagues (*24*) for reasons explained by Gilbert and collaborators in ref. (*21*)], although the formal test of consistency provided no evidence that the ORNL estimate fell outside the expected range of random variation. As the data for the AWE supplied to IARC had been combined with the data from AEA facilities, it was not possible to calculate a separate estimate for that cohort. Overall, however, there was no evidence of non-homogeneity of risk across facilities.

Single Cancer Types

Most of the 36 cancer types or groupings of cancers studied showed little or no association with radiation exposure. This could, however, have resulted from lack of power of the combined analyses for detecting such risks. As discussed above, the estimate of risk for all cancers excluding leukemia was consistent with risks larger than those based on high-dose data. Although risk estimates and confidence intervals are not presented for most individual cancer types, in most cases, these confidence intervals were much wider than those for all cancers excluding leukemia and were therefore compatible not only with no risk but also with fairly large positive risks.

1. Multiple Myeloma

Apart from leukemia excluding CLL, multiple myeloma was the only type of cancer to exhibit a statistically significant association with radiation dose in the combined data set (one-sided P value: 0.037). Evidence exists for radiation-induced multiple myeloma from other studies, yet it is not consistent (*1*, *49*). In particular, although a dose-related increase in multiple myeloma mortality has been observed systematically among survivors of the atomic bombings in Hiroshima and Nagasaki since the late 1960s (*46*, *50*), recent analyses of data for the incidence of multiple myeloma, after an extensive review of cases of hematological malignancies, did not provide evidence of an association with radiation dose in that population (*51*).

Among nuclear industry workers, statistically significant associations between multiple myeloma mortality and radiation dose have been reported previously for workers at Hanford (*21*) and Sellafield (*11*), the two facilities included in the current combined analyses where reprocessing of nuclear fuel is carried out. In the most recent analyses of the Hanford data (*27*), however, this association was not statistically significant ($P = 0.10$).

In the combined data set, the association was statistically significant ($P = 0.037$), largely reflecting the associations in the Hanford and Sellafield cohorts reported previously. Although there was no evidence of inconsistency between facilities, tests of consistency have very limited power since multiple myeloma is a relatively rare type of cancer. A causal association between multiple myeloma and radiation dose is not inconsistent with the evidence from other studies. Since a large number of associations was studied in this report, however, a P value of 0.037 is not particularly unusual and chance is a possible explanation for the observed association.

The ERR for multiple myeloma was 4.2 per Sv (90% CI: 0.3 to 14.4) in the combined data set, larger than the estimate for leukemia and much larger than the estimate for all cancers excluding leukemia. This cancer type was, however, selected for risk estimation because it was the only one (apart from leukemia excluding CLL) which was significantly associated with radiation dose. The risk estimate, like all similarly chosen estimates, may therefore be biased upward.

Since multiple myeloma is a disease with a late age at onset, there is concern that it is underdiagnosed and thus unrecorded on death certificates. Further independent studies, and in particular studies of cancer incidence rather than mortality, with histological review of hematological malignancies, are needed to clarify the association between radiation and risk of multiple myeloma.

2. Prostate Cancer

Two studies in the UK (data from which are included in South England facilities) have reported statistical associations between radiation dose and mortality from cancer of the prostate (*9*, *16*). Updated analyses of mortality in the UK AEA cohort found that the association between cancer of the prostate and external radiation dose was largely confined to workers who had also been monitored for radionuclide exposure (*26*). These results were confirmed by a subsequent case-control study of prostate cancer in the AEA workforce (*52*), in which the authors concluded that the association with external dose was largely a result of the correlation between external doses and radionuclide contamination. That populations receiving high doses of external radiations have shown no evidence of an increased risk of prostate cancer (*46*) provides further support for this conclusion.

In the present combined analyses, no association was seen for cancer of the prostate in the combined data set or in any single facility, although the AEA could not be examined separately. There is therefore little evidence for an association between protracted external low doses of radiation and increased mortality from this disease. The possibility that an association exists between radionuclide exposure and mortality from cancer of the prostate could not, however, be tested in this study.

Implications for Radiation Protection

A primary objective of studies of cancer risk among nuclear industry workers is the assessment of the adequacy of existing protection standards. These are based on risk estimates derived from analyses of the mortality of atomic bomb survivors and studies of other high-dose exposures.

In its most recent recommendations, the ICRP (*4*) states that, based on consideration of experimental data, a dose and dose-rate effectiveness factor (DDREF) of two should be applied to estimates from these studies to set protection standards for low-dose protracted exposures. BEIR V used a linear-quadratic model for estimating leukemia risk and also made a recommendation that risks should be reduced to account for lower-dose-rate exposures (*1*). There is therefore particular interest in using data for populations receiving such exposures, in particular nuclear industry workers, to assess the appropriateness of this DDREF. The risk estimates presented in this paper for leukemia excluding CLL and all cancers excluding leukemia are compatible with a range of risks, ranging from close to zero to a risk approximately twice the linear estimates from analyses of atomic bomb survivors. If we assumed that the difference between the risk estimates derived from the nuclear workers and the studies of the atomic bomb survivors was entirely attributable to the effect of dose and dose rate, we could infer (by dividing the estimate for the atomic bomb survivors in Table VI by the estimate for the workers and its confidence limits) that the DDREF for leukemia excluding CLL is of the order of 1.7 with a lower limit of 0.6 and an upper limit of 28. There may be other differences, however, including differences in dose and outcome assessment, as well as in the distribution of host factors and environmental exposures, which could modify the association between radiation dose and leukemia risk. Furthermore, the confidence intervals presented describe only part of the uncertainty of the risk estimates. These are therefore not sufficiently precise to test the need for a DDREF or for estimating its magnitude.

The upper confidence bounds presented in this paper are of particular interest because it has been said that the extrapolation process used to assess cancer risk after low-dose protracted exposure may seriously underestimate this risk, possibly by an order of magnitude or more (*53*). These analyses indicate that if there has been underestimation, it is unlikely to have been by more than a factor of about two.

Another question of importance in radiation risk assessment is the choice of model to extrapolate risk estimates across populations with different background incidence and mortality rates of cancer. Comparisons of risk for specific cancer types (particularly lung and stomach, the incidence of which varies greatly between Japan and North America and Europe) could provide some information about this issue. At present, however, site-specific estimates of risk among nuclear industry workers are too uncertain for such comparisons to be meaningful. In general, however, the problem of extrapolating risks across populations would appear to be greater for specific cancer types than for all cancers combined, for which the baseline mortality rates vary less between industrialized countries.

The problem of predicting absolute risk has not been addressed directly in these analyses. One of the most important steps in obtaining such estimates, namely extrapolation from high to low doses and dose rates, has been discussed briefly above, as has that of extrapolating from one population to another. Additional factors to be taken into account include projection of risk over time and modifying effects of sex and age at exposure. Even for exposure received at high doses and dose rates, there is uncertainty concerning the appropriate methods for handling these issues. The data for the workers do not provide information regarding these issues and, at present, no information is available to judge whether the modifying effects of time since exposure, age at exposure and sex are similar after low-dose protracted exposures to those observed in studies of high-dose exposures.

CONCLUSIONS

Combining data from seven cohorts in three countries has provided the opportunity to obtain the most comprehensive and precise direct estimates to date of the carcinogenic effect of low-LET radiation at low doses and low dose rates. Overall, the estimates resulting from these analyses were consistent across studies, as well as with those derived from high-dose, high-dose-rate studies. A significant increase in leukemia (in particular myeloid leukemia) risk was demonstrated by the combined analyses at relatively low dose levels. The study has also provided the opportunity to examine some of the previously reported associations between low doses of ionizing radiation and mortality from specific cancer types: we have found a dose-related increase in mortality from multiple myeloma that largely reflected the experience at two facilities. Additional follow-up of these cohorts, as well as studies of additional groups of workers, will be useful to reduce the uncertainty further.

Annex
List of ICD Codes for Causes of Death Studied

		ICD8[a]	ICD9[b]
1.	All causes	000–999	000–999
2.	Unknown	—[c]	—[c]
3.	All cancers	140–207	140–208
4.	All except leukemia	(3)–(35)	(3)–(35)
5.	Buccal and pharynx	140–149	140–149
6.	Esophagus	150	150
7.	Stomach	151	151
8.	Small intestine	152	152
9.	Colon	153	153
10.	Rectum	154	154
11.	Liver	155.0–155.1	155.0–155.1
12.	Biliary tract	156	156
13.	Pancreas	157	157
14.	Nasal cavity	160	160
15.	Larynx	161	161
16.	Lung	162	162
17.	Pleura	163.0	163
18.	Bone	170	170
19.	Connective tissue	171	171
20.	Melanoma	172	172
21.	Female breast	174	174
22.	Cervix uteri	180	180
23.	Other uterus	181.182	179, 181, 182
24.	Ovary	183.0	183.0
25.	Prostate	185	185
26.	Testis	186	186
27.	Bladder	188	188
28.	Kidney	189.0, 189.1	189.0, 189.1
29.	Brain and CNS	191–192, 237.5–237.9, 239.6	191–192, 238
30.	Thyroid	193	193
31.	Ill defined and secondary	195–199	195–199
32.	Non-Hodgkin's lymphoma	200, 202	200, 202
33.	Hodgkin's disease	201	201
34.	Multiple myeloma	203	203
35.	All leukemias	204–207	204–208
36.	Leukemia excluding CLL	(35)–(37)	(35)–(37)
37.	CLL	204.1, 204.9	204.1, 204.9
38.	Acute leukemias	204.0, 205.0, 206.0, 207.0	204.0, 205.0, 206.0, 207.0, 208.0
39.	Other cancers	(3)–(5–35)	(3)–(5–35)
40.	Smoking-related cancers	140–150, 161–162, 157, 188, 189.1	140–150, 161–162, 157, 188, 189.1
41.	Non-smoking cancers	(3)–(40)	(3)–(40)
42.	All non-cancers	(1)–(3)	(1)–(3)
43.	Non-malignant tumors	210–239	210–229, 230.0–238.3, 238.5–239.9
44.	Circulatory diseases	390–458	390–459
45.	Respiratory diseases	460–479, 490.0–519.9	460–479, 487.1–519.9
46.	Liver cirrhosis	571	571.2, 571.5, 571.6
47.	External causes	800–999	800–999

[a] *International Classification of Diseases*, 8th ed.
[b] *International Classification of Diseases*, 9th ed.
[c] Varies with facility.

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